Evaluation of Effectiveness and Safety of Acupuncture in the Treatment of Migraine: A Systematic Review and A Randomised Controlled Trial

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(A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy)

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

Yanyi Wang ___________________________

Date ____________________________
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Publications

Published manuscripts


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## Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>AACMA</td>
<td>Australia Acupuncture &amp; Chinese Medicine Association</td>
</tr>
<tr>
<td>AC</td>
<td>Allocation Concealment</td>
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<tr>
<td>Acu</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>ADS</td>
<td>Depression Scale (Allgemeine Depressionsskala)</td>
</tr>
<tr>
<td>AEs</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>AHS</td>
<td>American Headache Society</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and Alternative Medicine</td>
</tr>
<tr>
<td>CF</td>
<td>Consent Form</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CM</td>
<td>Chinese Medicine</td>
</tr>
<tr>
<td>CTN</td>
<td>Clinical Trial Notification</td>
</tr>
<tr>
<td>DNIC</td>
<td>Diffuse Noxious Inhibitory Control</td>
</tr>
<tr>
<td>EF</td>
<td>Emotional Function in Migraine Specific Quality of Life questionnaire</td>
</tr>
<tr>
<td>EIF</td>
<td>Expression of Interest Form</td>
</tr>
<tr>
<td>FR</td>
<td>Function-Restrictive in Migraine Specific Quality of Life questionnaire</td>
</tr>
<tr>
<td>FP</td>
<td>Function-Preventive in Migraine Specific Quality of Life questionnaire</td>
</tr>
<tr>
<td>GLM</td>
<td>General Linear Model</td>
</tr>
<tr>
<td>IHS</td>
<td>International Headache Society</td>
</tr>
<tr>
<td>IMMPACT</td>
<td>Initiative on Methods, Measurement and Pain Assessment in Clinical Trials</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>IVS</td>
<td>Internal Validity Scale</td>
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MI Migraine Index
MPQ McGill pain questionnaire
MQS Medication Quantification Scale
MSQOL Migraine Specific Quality of Life
NIH National Institutes of Health
NSAID Non-Steroidal Anti-Inflammatory Drugs
NWC The Number of Words Chosen
OPVS Oxford Pain Validity Scale
PDR Physicians Desk Reference
PDI Pain Disability Index
PLS Plain Language Statement
PP Per Protocol
PPT Pressure Pain Threshold
PRI Pain Rating Index
PRI-S Sensory Components of Pain Rating Index
PRI-A Affective Components of Pain Rating Index
PRI-E Evaluative Components of Pain Rating Index
PRI-M Miscellaneous Components of Pain Rating Index
PWM Placebo Western Medication
QOL Quality of Life
RA Real Acupuncture
RCTs Randomised Controlled Trials
RR Relevant Risk
SA Sham Acupuncture
SD Standard Division
SEM Standard Error of the Mean
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SES</td>
<td>Assessing Emotional Scale</td>
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<tr>
<td>SMD</td>
<td>Standardized Mean Difference</td>
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<tr>
<td>SRs</td>
<td>Systematic Reviews</td>
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<tr>
<td>STRICTA</td>
<td>Standards for Reporting Interventions in Controlled Trials of Acupuncture</td>
</tr>
<tr>
<td>TCM</td>
<td>Traditional Chinese Medicine</td>
</tr>
<tr>
<td>TENS</td>
<td>Transcutaneous Electrical Nerve Stimulation</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>UC</td>
<td>Usual Care</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scales</td>
</tr>
<tr>
<td>WL</td>
<td>Waiting List</td>
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<tr>
<td>WM</td>
<td>Western Medication</td>
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<tr>
<td>WMD</td>
<td>Weighted Mean Difference</td>
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SUMMARY

Migraine is characterised by pulsating, unilateral headache that is worsened by movement. It is often accompanied by altered sensitivity to light and sound and gastrointestinal symptoms (nausea, vomiting). This common disabling condition, affecting 10-15% of the population in Australia, the United States of America and Germany, is associated with loss of productivity and increased family and economic burden. The causes of migraine headache are yet to be fully elucidated. The neurovascular theory and altered central modulation, involving the trigeminal nerve and higher brain centres, explain the pain and other symptoms, and have guided the symptomatic management for abolishing acute attacks and for prevention. These medications, including non-steroid anti-inflammatory drugs, ergots, tripan, antidepressants and anticonvulsants, are effective, however are associated with a range of unwanted side effects.

Globally, the increasing use of complementary and alternative therapies including acupuncture has generated broad interest from academia, governments, healthcare professionals and the community. The recent advancement on the understanding of the neurophysiologic actions of acupuncture, such as its anti-inflammation and central pain modulation effects, has provided the base for its increased use for pain management. There has been a number of randomised controlled trials (RCTs) that evaluated the benefits of acupuncture for migraine over the last two decades. These studies, originated from different countries, have produced conflicting evidence due to a range of methodological and reporting deficiencies, including, but not limited to, small sample size and inappropriate outcome measures. Furthermore, systematic reviews on acupuncture for headache failed to adequately represent non-English studies such as those were conducted in China, where acupuncture was originated and widely used.
The objectives of this study were to: 1) systematically review the current state of evidence from English and East Asian literature of acupuncture for migraine; and, 2) design and conduct a RCT that addresses the key identified methodological problems from the systematic review (SR), to determine the short- and long-term effect and safety of acupuncture for patients with migraine.

To address Objective 1, two SRs were conducted guided by the “Cochrane Handbook for Systematic Reviews of Interventions”. Major English and Chinese, Japanese and Korean databases were searched and studies were selected and assessed using pre-defined criteria. Fifteen English and 17 Chinese studies were selected for the English and East Asian review, respectively. Overall, findings of these two reviews supported the value of acupuncture in the treatment and prevention of migraine when compared with western medications (English studies: RR 1.19; 95% CI 0.98 to 1.46; Chinese studies: RR 1.55; 95% CI 1.27 to 1.88). However, there was insufficient data for a meta-analysis to determine the effectiveness of acupuncture when compared with no treatment. Furthermore, conflicting findings were reported with respect to the specific effect of acupuncture for migraine in studies that compared real and “sham/placebo” acupuncture (English studies: RR 1.07, 95% CI 0.93 to 1.25).

When compared with the studies published in English, Chinese studies appeared to have a higher frequency of acupuncture treatment, lower methodological quality, and more commonly use pharmacotherapy as a comparator (See Publication 1).

The SRs also revealed that there was limited evaluation of acupuncture for frequent migraine, a more debilitating form of headache.
To address Objective 2, a randomised, sham acupuncture controlled trial was conducted for frequent migraine incorporating the Chinese medicine differentiation diagnosis for acupoint selection. Nested in this trial was an evaluation of, the effect of acupuncture on cranial pressure pain threshold (PPT) and its relationship with features of migraines, such as migraine attacks and intensity.

Fifty participants met the selection criteria were randomly allocated to receive real (RA, 26 subjects) and sham (SA, 24 subjects) acupuncture for a total of 16 sessions over 20 weeks in a gradually decreasing frequency. Formula and supplementary acupoints were used. The same registered acupuncturist, not involved in outcome assessment, performed all RA and SA treatments. Participants were blinded from treatment allocation. Upon completion of the treatment period, participants were followed up for further assessment at three months and one year. Intention to treat analysis was employed to deal with missing data and dropouts (2, 1 and 22 drop-out/s at the end the treatment, three months and one-year follow-up periods, respectively).

At baseline (four weeks), the two groups were comparable with respect to demographic data and migraine characteristics. At the end of the treatment period (20th week), the mean (SD) migraine attack days per four weeks decreased from 11.81 (5.76) to 5.17 (5.02) in the RA group and from 12.41 (6.4) to 10.08 (7.11) in SA (Group difference: \( p = .008 \)). Intensity of migraine assessed using a Six-point Likert scale was lower in the RA (2.18 ±1.05) than that in the SA group (2.93 ± 0.61, \( p = 0.004 \)). However, there was no statistically significant difference between the two groups with respect to Migraine Specific Quality of Life (MSQOL). Medication consumption was reduced in the RA group. Group differences were shown at the end of the three-month follow up, but not at the one-year follow up. No severe adverse event was reported. Blinding was successful through the credibility test.
At the end of the treatment period, there was significant group difference in the percentile change of PPTs detected at the bilateral points of TaiYang (Ex-HN5) which is located on the temporal areas (228.48% vs. -0.66 % in the left and 92.69% vs. -2.52% in the right).

The major limitation of this RCT was a smaller than anticipated sample size due to difficulties experienced for subject recruitment. The strict inclusion and exclusion criteria with the long treatment and follow-up periods might have contributed to this outcome. Other challenges such as participants’ experience in the trial (See Publication 2) and types of controls were discussed.

In conclusion, this study demonstrates that acupuncture is a potentially effective and safe option for adult patients with frequent migraine headache with the effects lasting up to three months after the termination of the treatment. Further studies are needed to confirm these therapeutic benefits with adequate sample sizes, preferably in a multi-centric setting. Future studies also need to investigate the anti-migraine mechanisms of acupuncture.
CHAPTER ONE: INTRODUCTION

Migraine, a chronic neurovascular disorder, is characterized by recurring severe headaches and a series of autonomic and neurological symptoms such as vomiting, nausea, light sensitivity and sound sensitivity (Ferrari, 1998). The prevalence of migraine is high, involving 16% of the Australian population (Heywood et al., 1998), 13% of the population in the United States of America (Lipton et al., 2000b), 11% of the population in Germany (Göbel et al., 1994), and 8.4% to 12.7% of the population in different Asian countries and areas including China, Japan, Korean and Malaysia (Wang, 2003). Furthermore, migraine is ranked as the 19th disease worldwide to cause disability (Headache Classification Subcommittee of the International Headache Society, 2004), affecting a high percentage of adults in the productive phase of their life. Migraine is therefore associated with a loss of daily activity. Migraine results in high social and economic costs (Pradalier et al., 2004, Bigal et al., 2003).

Due to the complexity and unclear mechanisms of migraine, no “cure” approach exists. To date, the pharmacologic management used in the treatment of migraine can be divided into two groups: agents that abolish the acute migraine, including normal analgesic and specific drugs like ergotamine; and prophylactic drugs that are taken regularly, such as methysergide. The principle of pharmacologic management of acute pain is to use safe, effective and inexpensive medication as first line agents. If the initial agent does not work a more expensive second-line migraine-specific medication is then used. For patients who experience two or more attacks per month or have contraindications to, or fail to respond to, acute treatment, preventive therapy is employed (Snow et al., 2002). Although these pharmacologic products provide some relief to migraine sufferers, they are not without risks. Risks of using the pharmacologic products can include low blood pressure, decreased libido, nausea, depression, sedation, dry mouth, sleepiness, increased appetite, weight gain and kidney damage. Due to these possible side effects, a relevant proportion of patients prefer non-pharmacologic or
complementary therapies for migraine which can address the limitations associated with existing medical approaches.

According to the Guidelines of the Non-Pharmacologic Management of Migraine in Clinical Practice (Pryse-Phillips et al., 1998), a range of approaches can be used for managing migraine. Acupuncture is one such therapy increasingly used by patients and physicians (Larner, 2005). A recent study reported that migraine patients were likely to incorporate complementary and alternative medicine (CAM) into their treatment plans and the percentages of CAM users in chronic migraineurs and episodic migraineurs were 50% and 27% respectively (Rossi et al., 2005). In 1998, the National Institutes of Health in America (NIH) stated that acupuncture could be a useful adjunct treatment or an acceptable alternative for several health conditions, including headache (NIH Consensus Conference, 1998). The conclusion of the NIH has been endorsed by the World Health Organisation (WHO)(2003).

Acupuncture is a technique of traditional Chinese medicine (TCM) and is based on the meridian theory. Acupuncture has been used in China to deal with illnesses for thousands of years. Having originated in China, acupuncture is now widely practiced by traditionally trained acupuncturists, medical doctors and physiotherapists in Western countries. According to TCM principles, the fundamental purpose of acupuncture treatment is to balance the state of a patients’ blood and Qi. Since the 1970’s, a series of studies have been conducted to explore the possible mechanisms of action for acupuncture, such as it acting through the diffuse noxious inhibitory control system (Carlsson, 2002); producing endogenous opioid peptides (McLennan et al., 1977, Han et al., 1979); and its anti-inflammation effect (Lao et al., 2004, Lao et al., 2001). However, despite these studies, how acupuncture works is still not known.
Clinical trials have shown that acupuncture is an effective alternative treatment for tension-type headache (Endres et al., 2007a, Xue et al., 2004, Melchart et al., 2005), and chronic headache (Vickers et al., 2004a). To date, there have been a number of systematic reviews on the use of acupuncture for chronic pain in general (ter Riet et al., 1990, Patel et al., 1989); headaches as a whole (Manias et al., 2000, Melchart et al., 1999); idiopathic headache (Melchart et al., 2001) and migraine in particular (Scott and Deare, 2006, Griggs and Jensen, 2006b) as well as tension-type headache (Davis et al., 2008).

However, there are a number of major issues associated with current migraine literature. Firstly, the results appear conflicting: Pintov (1997) supported the effectiveness of acupuncture in migraine patients when compared with sham acupuncture. However, Linde and her colleagues (2004) found no difference in effectiveness between real and sham acupuncture in treating migraines.

Secondly, evidence from East Asian studies is significantly lacking in reviews published in English; this is most likely due to language barriers. For example, in the two available SRs on migraine (Scott and Deare, 2006) and headache as a whole (Melchart et al., 2001), only one Chinese study was included. East Asia is one of the regions where acupuncture is most widely used, especially China, where acupuncture is considered the mainstream medicine. Due to the widespread use of acupuncture in East Asia, data from these areas is extremely important in determining the effectiveness and safety of acupuncture for migraine.

Thirdly, the quality of these trials is often low. According to Jadad scoring, a score of 3 or more (which equates to 60% or more of the maximum possible score) in a study is indicative of high quality. However, the median of Jadad scoring in the two SRs (Melchart et al., 2001, Scott and Deare, 2006) were 1.5 and 2.3 respectively, indicating poor quality. Furthermore,
less than half of the studies in Scott and Deare’s SR selected the acupoints according to Chinese medicine individual syndrome differentiation; this is against the principles of Chinese medicine. It is also unknown whether East Asian literatures suffer from the same flaws.

Fourthly, the outcome measures often rely on patient’s reporting. Other measures such as medication consumption, recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin et al., 2005) and IHS (2000), need to be assessed. Pressure pain threshold (PPT), reflecting the individual’s sensitivity to pain, is often assessed with an algometry and is widely used in pain studies. Although lower PPTs have been observed in tension-type headache sufferers (Schoenen et al., 1991, Bendtsen et al., 1996, Ashina et al., 2005), there are few studies investigating the relationship between migraine and PPTs and the effect acupuncture has on them.

Hence, to date, the exact role of acupuncture in migraine treatment is not clear. It is important to review the effectiveness of acupuncture treatment for migraine in English and East Asian literature and to evaluate the effectiveness and safety of acupuncture for symptomatic relief of migraine and improvements in quality of life through a well-designed RCT.

This thesis includes the following chapters:

Chapter Two describes the epidemiological data of migraine; impacts on patients; current available knowledge on diagnosis, management approaches; clinical measurements and mechanisms of migraine and acupuncture.

Chapter Three provides the general methods of the systematic review, including background, search strategies, criteria for identifying studies, quality assessment and data analysis.
Chapter Four and Five present the results of systematic reviews (SRs) of literature included in English and East Asian databases, respectively. Chapter Four also compares the results of the two reviews and the current reviews on published data. Those SRs showed various shortcomings in current research, and identified that frequent migraine was an area requiring further study.

Chapter Six describes the general methods of the clinical trial, including recruitment, selection criteria, trial procedures, outcome measures, data collection and analysis.

Chapters Seven and Eight report the short- and long-term effects of acupuncture on migraine, respectively. The data was analyzed using intention-to-treat analysis. The limitations of the present clinical study are discussed.

Chapter Nine presents the data of PPTs measured in migraine patients before and after acupuncture, as well as discussing its relevance to the characteristics of migraine.

Chapter Ten, the final chapter, discusses the strengths and limitations of the whole project, outlines the overall evidence and provides recommendations for future research and clinical practice.
2.1 Migraine Headache

Migraine is a common, disabling, and typically unilateral headache disorder with symptoms such as nausea, vomiting, phonophobia or photophobia. It is ranked by the World Health Organization as the 19th disease world-wide to cause disability (IHS, 2004). Epidemiological studies have documented its high prevalence and high socioeconomic and personal impacts. Approximately 16% of Australians suffer from migraine in its chronic and acute forms (Heywood et al., 1998) while 0.32-0.48 million Australians (1.6-2.4%) suffer from chronic migraine (Castillo et al., 1999). A similar situation applies in other countries; 13% of the population in the United States of America (USA) (Lipton et al., 2000b) and 11% of the population in Germany (Göbel et al., 1994) suffer from migraine. A review of the recent epidemiologic studies of headache in Asia reported consistent findings, that the prevalence ranged from 8.4% to 12.7% (Wang, 2003).

The condition of migraine is associated with significant economic and social impacts, such as the loss of productivity, increased family burdens and economic costs to society. For example, 91% of migraineurs reported some level of functional impairment. Fifty-three percent of those who experienced severe headaches reported significant impairments on activities and as requiring bed rest (Lipton et al., 2001). Another group of investigators estimated that migraineurs in the USA spent more than three million days in bed each month due to pain (Stang and Osterhaus, 1993). Furthermore, the peak prevalence of migraine occurs in those aged between 25 and 55 years in the United State (Lipton et al., 2001), between 25 and 50 years in China (Guo et al., 1993) i.e., during the most productive years of one’s life. An Austrian survey reported 6.8 million working days per year were lost due to working people suffering from migraine (Lampl et al., 2003). Migraine affects not only migraineurs’ personal quality of life (QoL) but also that of the whole family. For example, it has been reported that
90% of migraineurs postponed their household work due to migraine, 30% had to cancel family and social activities during their last migraine attack, and two-thirds feared letting others down (Clarke et al., 1996). A survey conducted by the University of New South Wales estimated the major direct and indirect costs (including medical costs, social services, treatment time, work absence and productivity losses at work) of migraine as a whole in Australia from 1989 to 1990 was between 302 million to 721 million dollars (Parry, 1992).

2.2 Diagnosis of Migraine

According to the classifications of the International Headache Society (IHS), there are two major sub-types of migraine: migraine without aura (MO) and migraine with aura (MA). MO, or “common migraine”, is the most common subtype of migraine, affecting about 58% of migraineurs. It has a higher average attack frequency and is usually more disabling than MA (IHS, 2004). MA, or "classic migraine", is the form of migraine characterised by headache attacks being preceded by neurological manifestations called "aura"; MA affects around 28% of migraineurs (Russell et al., 1995b). The other types of migraine, such as retinal migraine and probable migraine occupy the remaining 14%. The 2nd edition of International Classification of Headache Disorders (2004) provides clear diagnostic criteria for all sub-types of migraine (Appendix 1). A new sub-type called chronic migraine (CM) is included. Chronic migraine (CM) refers to MO or MA with a frequency of more than 15 headache days each month for three months.

2.3 Mechanisms of Migraine

2.3.1 Migraine and Genetics

Generally, migraine is a neurovascular reaction in response to sudden changes in the internal or external environment, such as emotional stress or overload of afferent systems by excessive light, noise or other stimulation. The exact mechanism of migraine is not clear. However,
genetic disposition has been implicated. In recent years, scientists have found that genetic and environmental factors may contribute to migraine via population-based studies (Russell and Olesen, 1995, Ulrich et al., 1999).

A survey (Mulder et al., 2003) of six countries participating in the migraine GenomEUtwin project and involving a total number of 29,717 twin pairs found that genetic variance (heritability) plays a significant determining role in migraine in both sexes and in all countries. Estimates of heritability for migraine ranged from 34% to 57% with the lowest estimates in Australia and the highest estimates in Finland, the Netherlands, and Denmark. It is argued that genes could predispose the carriers to migraine recurrence by setting the brainstem pain pathways in a hypersensitive state thereby lowering the threshold for the manifestation of migraine. This could enhance a migraine sufferer’s sensitivity to environmental factors, resulting in an increased frequency of attacks. Indeed, stress, weather changes, menstrual cycle, and excessive sunlight are the leading trigger factors (Robbins, 1994); lack of sleep and alcohol use can also increase the number of attacks.

2.3.2 Biochemistry and Migraine

In terms of pathophysiology, each individual has a hereditary migraine threshold that depends on the susceptibility of the balance between excitation and inhibition in the nervous system. On a biochemical basis, such a balance may be influenced by magnesium deficiency, excitatory amino acids, monoamines, opioids and other factors (Donma and Donma, 2002). In the past few years, the fundamental role for magnesium in pathophysiologic mechanisms of migraine has become evident via a series of studies. A reduced magnesium level has been found in the serum of migraineurs with or without aura during the migraine-free period, and the magnesium level was further reduced in the attack (Gallai et al., 1992). A later study (Boska et al., 2002) confirmed that the magnesium deficiency may contribute to the brain
cortex hyperexcitability and the pathogenesis of migraine syndromes associated with neurologic symptoms, such as auras. On the other hand, Martinez and his colleagues (1992) found the plasma levels of amino acids in migraine patients during attacks were significantly lower than people suffering from stress, which plays a excitation role in migraine attacks.

The biochemical mechanisms of migraine is believed to be related to the following changes: increased extracellular potassium and intracellular sodium, calcium, and chloride; excessive release of excitatory amino acids; alterations in serotonin; abnormalities in catecholamines and endogenous opioids; decline in magnesium levels and increase in intracellular calcium; abnormalities in nitric oxide formation and function; and alterations in neuropeptides (Packard and Ham, 1997).

### 2.3.3 Mechanisms of Aura in Migraine

The typical aura is photophobia, which is a visual image of scintillating or shining crenellated-shapes, usually within one visual field lasting 5 to 20 minutes. Leao (1944) believed that genetic or environmental fluctuations in neurotransmitter composition can trigger a cortical spreading depression (CSD), which is a gradually spreading depolarization of cortical cellular elements followed by repolarization. The migraine aura is evoked by this series of aberrant spreads crossing the cerebral cortex. This theory was also supported by other scientists (Lauritzen, 1987). Drugs that can inhibit the development of CSD provide treatment for aura, such as the Amitriptyline (Elavil), a tricyclic anti-depressant (Silberstein, 2006).

During the CSD process, extracellular potassium (K⁺) increases up to 60-80mmol, which is enough to depolarize nerve endings around pial blood vessels, thereby releasing vasoactive peptides, such as calcitonin-gene related peptide (CGRP). Furthermore, vasoactive peptides...
induce neurogenic inflammation, which causes pain. The NSAID drugs can reduce inflammation, which, in turn, eliminates headache. Afferent pain impulses are modulated in the spinal cord and higher centres. If there is an active antinociceptive system, the migraine aura may occur alone without a headache phase (Olesen, 1993).

2.3.4 Hypothesis and Mechanisms of Migraine

Prior to an attack, some migraine sufferers experience an “aura”, consisting of visual disturbances such as partial vision loss, the appearance of “special effects” and distortion of objects. Other symptoms at this stage include vertigo (motion sickness or dizziness), imbalance, confusion, numbness, pallor face and cold hands. During a migraine attack, the patients often feel nausea and vomit and being hypersensitive to light and sound. The headache is often worsened by physical activities. Resting in a dark room often helps relieve the pain.

The early hypothesis of migraine is the vascular theory, introduced by Wolff (1963). This theory considers that the dilated blood vessels stimulate perivascular pain sensitive nerve endings thereby eliciting pain. Based on this hypothesis vasoconstrictor drugs like Ergotamine are used for migraine treatment. Nevertheless, the purely vascular theory apparently weakened when the blood flow changes in migraine could be produced by direct electrical stimulation of brainstem structures (Lance et al., 1983). The vascular theory alone might not be sufficient to explain migraine.

Current studies support that both neural and vascular elements contribute to migraine (Lance and Goadsby, 2005). The neurovascular hypothesis is the basis when considering the pathophysiology and therapeutics of migraine.
Figure 1 illustrates the mechanism of the migraine and the actions of anti-migraine agents and prophylaxis medications. Firstly, trigger factors, such as stress, hypoglycemia or tyramine can initiate the release of epinephrine and noradrenaline, which induces increasing platelet aggregation (Holmsen, 1986). Secondary to platelet aggregation, pain-sensitizing agents, such as serotonin, bradykinin and histamine are released from platelets, basophils and mast cells (Dalessio, 1979). Bradykinin stimulate the release of prostaglandins and e-leukotriene, resulting in the sensitization of high-threshold mechanoreceptors in the perivascular trigeminal nerve causing pain (Theisler, 1990, Moskowitz, 1984). This process is also called inflammation reaction. Consequently, some non-steroidal anti-inflammatory drugs (NSAIDs) can be used for acute pain at this stage.

Secondly, activated platelets also increases the release of serotonin (5-HT), causing cerebral vasoconstriction (Vinken et al., 1985), thereby leading to reduced infusion of internal carotid artery oligemia and cerebral ischemia (Anthony, 1986). At this stage, CSD is found in patients experiencing aura (Leao, 1944). After the ischemia stage, the serotonin levels automatically fall. Because serotonin is a potent vasoconstrictor, there is a reactive hyperemia with vasodilatation. Intracranial vasodilatation activates the “stretch receptors” in the wall of the blood vessels, stimulating the perivascular trigeminal nerves fibers. Nociceptive peptides such as substance P (SP), calcitonin gene-related peptide (CGRP), prostaglandins, vasoactive intestinal polypeptide (VIP), and neuropeptide Y were released as a part of axon reflex, leading to vasodilatation, increasing permeation of the vessels. (De Vries et al., 1999, Villalón et al., 2002). The process is called neurogenic inflammation (Edvinsson et al., 1987). Meanwhile, these peptides further reinforce vasodilation and perivascular nerve activity (Saxena, 1994), causing peripheral and central sensitization, resulting in enhanced pain (Goadsby et al., 2002, Silberstein, 2004). Meanwhile, the trigeminal cranial nerve conveys
nociceptive information to central trigeminal nuclei that, in turn, relay the pain signals to higher centres where headache is perceived (Edvinsson, 2004).

Thirdly, some studies indicate that the brainstem might have a “migraine generator”. Once the “generator” is switched on due to unknown reasons, the cerebral blood flow changes, followed by the CSD (Weiller et al., 1995).
Figure 1: Diagram of the mechanism of migraine

--- indicates the mechanisms of anti-migraine medications for the treatment of acute attack; --- indicates the mechanisms of preventive medications
2.4 Current Western Pharmacotherapy

At present there is no cure for migraine. Current treatment for migraine is symptomatic management, such as a reduction of the frequency, duration and severity of the attacks. Medications used for acute migraine includes non-specific drugs, such as acetaminophen, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), opiates for pain and antiemetic drugs to reduce vomiting; migraine-specific drugs include Ergots and serotonin (5-hydroxy-tryptamine, 5-HT) agonists known as the Triptans. For chronic migraine sufferers, preventative drug therapy can be used for prophylactic purposes to reduce the frequency, duration, and severity of future attacks. These drugs include β-adrenergic blockers, anti-depressants, anti-convulsants, calcium channel blockers, serotonin antagonists, and NSAIDs; their mechanisms are explained as follows.

2.4.1 Drugs for Acute Pain

Most mild migraine sufferers self-medicate using non-prescription analgesics. Two major classes of such medications exist on the market: acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs have two subgroups, aspirin and non-aspirin. The drugs in this class, which inhibit sterile inflammation, are used to reduce the intensity of the pain or eliminate the pain.

Acetaminophen (brand name: Tylenol): The exact mechanism of action regarding Acetaminophen is not well understood. However, it is believed that it relieves pain by inhibiting the prostaglandin synthesis, which causes inflammation and pain. However, the effectiveness of acetaminophen for migraine is controversial (Lipton et al., 2000a, Diamond, 1976). Consequently, the American Academy of Family Physicians does not recommend acetaminophen alone for migraine attacks (Snow et al., 2002).
**NSAIDs** are the first-line choice in treating migraine attacks. They work by blocking cyclooxygenase (COX) which is crucial for the production of prostaglandins, and peripherally blocking pain impulse generation. NSAIDs have two classes, namely “selective” and “nonselective”. “Selective” NSAIDs block COX-2 only and “nonselective” NSAIDs block COX-1 and COX-2. COX-2 is the enzyme responsible for inflammation and fever; COX-1 has other functions such as protecting the gastric mucosa from the acid that the stomach naturally produces. However, most popular NSAIDs for migraine, such as Aspirin, Ibuprofen, and Naproxen, are nonselective. An example of a selective NSAID is Celebrex. One of the problems with nonselective NSAIDs is that they block both types of the COX enzymes; while inflammation and pain is reduced, so are some of the beneficial effects of prostaglandins such as protection of the stomach lining. The selective NSAIDs are a newer type of analgesic and are always recommended to people with stomach problems. Clinical studies have demonstrated the effectiveness of various NSAIDs for migraine, such as aspirin (Hakkarainen et al., 1979, Boureau et al., 1994, Tfelt-Hansen and Olesen, 1984); ibuprofen (Havanka-Kanniainen, 1989, Kloster et al., 1992); naproxen sodium (Sargent et al., 1988, Landy et al., 2007), and tolfenamic acid (Myllylä et al., 1998, Larsen et al., 1990). However, NSAIDs produce good responses only in cases of mild migraine. For those migraines associated with moderate-to-severe headache, migraine-specific drugs should be used.

**Opioids** alone are not recommended for mild migraineurs because of the risk of dependence and aggravation of gastrointestinal symptoms. However, the combination of aspirin with codeine may be used for severe migraine (Lipton et al., 1998).
2.4.2 Migraine-Specific Drugs

**Ergotamine** is a vasoconstrictor and acts on 5-HT receptors, alpha-adrenergic receptors and dopaminergic receptors (Goodman and Gilman, 2001). It is generally believed to exert its anti-migraine effect via being a 5-HT receptor agonist. The vascular theory of migraine considers that dilated arteries can stimulate the perivascular nociceptors, thereby causing migraine. Ergotamine constricts the dilated arteries to reduce the stimulation to perivascular nociceptors. Although Ergotamine has been used for treating migraine for more than 50 years, evidence of efficiency is insufficient. Moreover, it was considered to be useful only in a small numbers of migraineurs. Further to this, a number of side effects have been reported in medical literature, including myocardial infarction, ischaemia of limb extremities, and fibrotic changes. Long-term use has led to reported cases of ergotamine-induced headache, vascular reactivity, and sub-clinical ergotism. Consequently, following a systematic review by an European expert group in 2000 (Dahlöf, 1993, Tfelt-Hansen et al., 2000) it is recommended that Ergotamine should not be used until further clinical data becomes available.

**Sumatriptan** is 5-HT$_1$ agonists. It relieves headache in 50-75% of migraineurs, and improves migraine symptoms such as vomiting, nausea, photophobia and phonophobia. Unlike Ergotamine, Sumatriptan can selectively act on one type of the 5HT$_1$ receptors located in the cranial vascular bed, thereby reducing inflammation and constricting the blood vessels. Furthermore, it has been demonstrated to produce high response rates in mild, moderate or even severe migraines and is superior to the effect of Ergotamine plus Caffeine or Aspirin plus Metoclopramide (Cady et al., 2000). There is good evidence for the efficacy of Sumatriptan (Russell et al., 1995a, Ryan et al., 1997), although it is associated with AEs, such as throat and chest pain.
2.4.3 Drugs for Migraine Symptoms

Antiemetic drugs, such as Metoclopramide and Domperidone, can be used orally to reduce vomiting and nausea when patients feel the first symptoms of migraine and are then taken every 6-8 hours. Metoclopramide can increase the gastric motility, thereby normalizing the absorption of other drugs. A controlled study demonstrated that the combination of Tolfenamic acid (NSAID) and Metoclopramide is significantly better than Tolfenamic acid alone in treating migraine attacks (Tokola et al., 1984). However, a neuroleptic type of antiemetic, such as Tiethylperazine and Chlorpromazine, cannot normalize the absorption of drugs. Therefore, for these two neuroleptic drugs, oral administration should be avoided. Clinically, the first treatment of an attack is antimetic drugs administered orally or via intramuscular injection depending on the severity of nausea or vomiting, then followed by the painkillers (Tfelt-hansen, 1993). The AEs of antiemetic drugs are acute dystonia and drowsiness.

2.4.4 Prophylactic Drugs for Migraine

Prophylactic medications are taken daily in order to reduce the frequency and duration of migraine attacks. They are given to patients who suffer from migraine for two or more times per month and have associated disability lasting three or more days per month (Snow et al., 2002). There are several classes of prophylactics such as beta-andrenoreceptor blockers (propranolol, timolol), antidepressants (amitriptyline), anticonvulsants (sodium valproate), calcium-channel blockers (nimodipine), 5-HT receptors antagonists (methysergide) and NSAIDs (naproxen), which can be used for different stages of migraine. Silbestein (2006) reviewed evidence of the effectiveness of migraine preventive drugs and found the beta-andrenoreceptor blockers decrease sympathetic activities and prevent vasoconstriction; calcium channel blockers can prevent migraine attacks by inhibiting CSD; both antidepressants and anticonvulsants inhibit CSD and enhance anti-nociception; NSAIDs block
the production of prostaglandin, therefore reducing central sensitization. Preventative drugs should be chosen with caution. Physicians should be aware of the co-morbidity of the migraineurs in order to avoid AEs brought by these agents such as beta-blockers for asthma sufferers or calcium channel blockers for patients with low blood pressure.

### 2.4.5 Pharmacotherapy: Strength and Weakness

Effective pharmacologic management of migraine is challenging due to the complexity of migraine and the difficulty of selecting proper treatments from a large variety of pharmaceutical products. A clinical guideline (Snow et al., 2002) for pharmacologic management of migraine has been produced by the American Society of Internal Medicine based on a comprehensive review of the scientific literature. Based upon that guideline, NSAIDs are considered as the first choice for mild-to-moderate migraine, or even severe attacks that have responded to NSAIDs. However, for patients whose migraines are always moderate-to-severe in intensity, migraine-specific drugs like Sumatriptan should be taken upon feeling the first symptoms of migraine. Opioids are strong analgesics, but should only be used when sedation effects are not a concern or the risk of abuse has been addressed. Moreover, concerning the disability issue, patients with two or more severe attacks per month are suggested to take preventative therapy.

There are a few limitations with current pharmacotherapy management. Firstly, many patients dislike taking medications for a long term, as such medications are not always optimal and associated with AEs such as low blood pressure, decreased libido, nausea, depression, sedation, dry mouth, and increased appetite and weight. Secondly, nearly half of all migraine sufferers treat themselves with over the counter medications (Lipton et al., 2002). Overuse of medicines is common in chronic migraine sufferers, and the overuse of medicines is likely to lower the pain threshold necessary to trigger further migraine attacks (Eric and Eross, 2006). Nearly 80% of chronic migraineurs overuse symptomatic medications (Mathew, 1993).
non-prescriptive drugs for acute pains are used as often as three times a week, patients may experience a gradual shift from episodic migraine to chronic migraine (Snow et al., 2002). A headache study conducted on 216 patients overusing medication found that 4% were overusing Ergots, 6% Narcotics, 20% Triptans, 29% simple Analgesics (pain relievers) and 42% combination of Analgesics (Eric and Eross, 2006).

As discussed above, current pharmacology management involves some side effects such as the changes in heart rate, vasodilation in cutaneous blood vessels, vasoconstriction in the external carotid bed and gastrointestinal effects, etc. (Saxena and Villalón, 1990b, Saxena and Villalón, 1990a). Future medications are aimed at identifying drugs that do not impact on 5-HT receptors as to reduce their cardiovascular side effects. CGRP receptor antagonists could be the ideal candidate (Maassenvandenbrink and Chan, 2008).

2.5 Non-pharmacological Treatment Approaches for Migraine

Due to the above risk and side effect of existing pharmacological approaches, many people seek “natural” treatment. Furthermore, some experts pointed out that the pharmacological therapy should only be applied if non-pharmacological management is ineffective (Olesen, 1993). Non-pharmacological treatments aim to avoid the trigger of migraine, like stress, weather, fasting, dietary factor and sleep and to reduce the frequency, duration and intensity. They include psychological management, physical management, acupuncture, and other complementary therapies.

2.5.1 Psychological Management

Psychological management includes relaxation training, biofeedback and cognitive behavioural therapy. Since the beginning of 1970s, a series of psychological approaches have been developed for headaches including migraine (Rains et al., 2005). There are two groups, namely, physiologically oriented techniques and cognitive behaviourally oriented methods.
The former includes the various types of biofeedback treatment. The latter encompasses a series of forms of relaxation training (progressive relaxation training, autogenic training, hypnosis), transcendental meditation and cognitive-behavioural therapy (Martin et al., 2007). In 2002, The Association for Applied Psychophysiology and Biofeedback classified psychological treatment into five levels of efficacy, level one being not supported by evidence and level five being efficacious and specific (LaVaque et al., 2002, Moss and Gunkelman, 2002). It is concluded that these psychological therapies including temperature, muscle tension and pulse biofeedback are efficacious for migraine, and are ranked at level 4 (Yucha and Gilbert, 2004).

2.5.1.1 Biofeedback (BFB)

Biofeedback theory is based on the idea that the autonomic nervous system can come under voluntary control through operant conditioning. Biofeedback therapy involves the recording and displaying small changes in the status of involuntary biological functions that are related to the recurrent disease, such as pulse, skin temperature and breathing patterns. Patients are instructed to use various techniques to change the levels of the parameter using the feedback from the display as a guide to avoid the onset of the disease. Migraineurs can monitor one of the three parameters and regulate then by warming their hands, reducing sweating, slowing down breathing and lowering muscle tension. The most commonly used methods of BFB for migraine are peripheral skin temperature feedback (TEMP-FB), blood-volume-pulse feedback (BVP-FB) and electromyography feedback (EMG-FB). The effectiveness of biofeedback for migraine had been demonstrated when compared with control conditions in frequency and perceived self-efficacy in a meta-analysis study (Nestoriuc and Martin, 2007). Nestoriuc and Martin also found that BVP feedback (weighted mean effect size = 0.68) was more effective than TEMP (0.52) and EMG feedback (0.5).
Biofeedback can be used by itself or in combination with relaxation training. Furthermore, the combination of biofeedback and home training has been shown to be more effective than biofeedback alone (Nestoriuc and Martin, 2007). Meta-analysis suggests that relaxation is as effective as biofeedback (Blanchard et al., 1980, Penzien et al., 1985).

2.5.1.2 Progressive Relaxation Training

Progressive relaxation, also named progressive muscle relaxation, was developed by an American Physician, Edmund Jacobson in 1929 (Sadock et al., 2007). It is based on a principle of muscle physiology. The process of progressive relaxation is simply that of isolating and contracting specific muscles or muscle groups, one at a time, creating tenseness for 8-10 seconds, and then letting the muscle relax and the tenseness go. Jacobson used the word “tenseness” rather than “tension” to emphasise the patient’s role in tensing the muscles (Sadock et al., 2007). This method can relax the deep level of muscles. There are many parallels with autogenic training, which was developed independently.

2.5.1.3 Autogenic Training and Hypnosis

Autogenic training emerged from German, developed by Dr. Johannes Schultz. This method was first published in 1932 (Schultz and Luthe, 1959). It is a method of self-suggestion, which directs patient’s attention to specific bodily areas that reflect a relaxed state. Such phrases include heaviness, warmth, cardiac regulation, breathing adjustment, solar plexus and forehead. For example, “my solar plexus is warm”.

Hypnosis, firstly described as a therapeutic modality in the 18th century by Anton Franz Anton Mesmer (Sadock et al., 2007). It is currently understood as a normal activity of a normal mind through which attention is more focused, critical judgment is partially suspended, and peripheral awareness is diminished. Hypnosis reduces distress as it does in pain disorders. A
meta-analysis of largely uncontrolled trials suggested that hypnosis combined with cognitive-behavioural therapy (CBT) can enhance the outcomes of migraine when compared with using CBT alone (Kirsch et al., 1995). To date, some clinicians use hypnosis to facilitate relaxation or use tape-recorded exercise to allow patients to practice relaxation on their own.

2.5.1.4  **Cognitive - Behavioural Therapy**

Cognitive therapy and behavioural therapy are two independent therapies. Cognitive therapy was developed by an American psychiatrist, Aaron Temkin Beck in the 1960s. It is based on the idea that our thought can create our mood, thereby influencing/affecting some diseases. Behavioural therapy involves changing the behaviours of patients to reduce dysfunction and to improve quality of life. These two therapies go hand in hand; behavioural techniques can test and change maladaptive and inaccurate cognitions. Consequently, they are combined to be adopted in clinic, and named cognitive-behavioural therapy (CBT). Generally, CBT can help patients identify and modify maladaptive responses that may trigger or aggravate a migraine headache (Pryse-Phillips et al., 1998).

CBT consists of self-monitoring, education, relaxation training and pain-management strategies, including rational emotive behavioural therapy, rational behavioural therapy, rational living therapy, cognitive therapy and dialectic behavioural therapy. In general, CBT teaches patients how to change their maladaptive thought, incorrect beliefs and fears to prevent patients form illnesses. In migraine, CBT aims to calm down patients’ emotion. Psychologists and patients can work together to plan when and what the migraineur should do to prevent or reduce pain, if the migraine is coming. They then develop alternative behaviours to try in the same situation in the hope that changing the behaviour will change the migraine. For example, they work together to make a migraineur’s daily plan for restricting salt, decreasing water retention and eliminating trigger diets.
The effectiveness of CBT for migraine has been supported by some studies (Knapp and Florin, 1981, Sorbi and Tellegen, 1986, Richardson and McGrath, 1989). CBT is ranked at the second level, B, by the Canadian Headache Society (Pryse-Phillips et al., 1998). According to this society, there are six levels of evidence ranging from A to F, with A being good evidence to recommend the clinical preventative action and F being insufficient evidence.

2.5.2 Physical Management

Physical management is a common part of pain management programs, which include transcutaneous electrical stimulation (TENS), Yoga, cervical manipulation, hyperbaric oxygen, and even occlusal adjustment.

TENS is a non-invasive, electronic device with few known side effects. A TENS unit consists of a pulse generator, transformer, frequency and intensity controls and a number of electrodes. It can produce electrical signals used to stimulate nerves through unbroken skin to decrease pain perception. TENS has been used for a series of pain conditions, including migraine (Solomon and Guglielmo, 1985, Carroll et al., 2001, Sheftell et al., 1989).

Yoga originated in India, associated with diversified postures, which couples physical exercise with breathing to produce relaxation. It is a popular form of mind-body therapy, and has been used to deal with the emotional aspects of chronic pain in term of reducing anxiety and depression (Kim et al., 2005, Kakigi et al., 2005). In a randomised controlled trial, Yoga has shown to reduce the frequency of migraine from 10.22 days per months to 4.56 days, much better than the self-care group from 9.82 to 10.18 days (John et al., 2007).

Cervical manipulation directs short or long-term high velocity thrusts at one or more joints of the upper seven spines, which can increase β-endorphin levels (Buchmann et al., 2005).
β-endorphin is believed to be 50 times more powerful than morphine and hence unmatched for their ability to control pain (Terrett and Vernon, 1984). Milne conducted a study in 150 migraineurs, and found that cervical manipulation is useful for terminating ongoing migraine attacks (Milne, 1989). Other studies have also demonstrated that this therapy can reduce the severity of pain in migraine attacks (Parker, 1978, Wight, 1972). Furthermore, Vernon (1982) has shown manipulation to be effective in ameliorating autonomic symptoms associated with migraine, such as nausea and vomiting.

Occlusal adjustment is a dental procedure used to adjust a patient's biting surfaces, thereby relieving muscle tension in the jaw. Based on the belief that migraine is related to the tension of that area, this therapy might reduce migraine pain. However, a study conducted in Finland, did not report any benefits of occlusal adjustment for migraineurs compared with mock occlusal adjustment (Forssell et al., 1985).

Hyperbaric oxygen therapy is a new form of physical approach. It has been theorized that the increased levels of oxygen in the blood act as a vasoconstrictor of cerebral vessels, thereby alleviating headache pain. Patients are placed a hyperbaric chamber (100% oxygen, delivered at greater than normal atmospheric conditions) to increase pressurization of the blood gases. However, the effectiveness for migraine is still conflicting in RCTs (Eftedal et al., 2004, Wilson et al., 1998, Myers and Myers, 1995).

### 2.5.3 Complementary Therapy

Complementary therapy includes massage, osteopathy, chiropractic, herbal medicine and acupuncture. The theory of massage is quite similar to physiotherapy, aiming to release the tension of muscle to prevent and reduce headache. Osteopathy and chiropractic are based on the misalignments of the vertebrae that can cause migraine, although there is no evidence for this hypothesis. They all apply some specific techniques to adjust the misalignments. To date,
the most popular medicinal herb in western country for migraine is feverfew, and its effect for migraine has been demonstrated by some RCTs (Pfaffenrath et al., 2002, Diener et al., 2005).

2.6 Chinese Medicine’s Understanding of Migraine and Its Treatment

2.6.1 Introduction

Traditional Chinese Medicine (TCM) utilizes a philosophic understanding of nature, such as Yin, Yang and the Five Element theory, to explain health and illness. Other key concepts include the Zang-Fu (Visceral organ), Qi, Blood, Body Fluid and meridian Theories (Liu and Dong, 1998). One of the most outstanding characteristics in TCM is its holistic view. Most of the traditional theories and principles of TCM are founded not upon anatomy but rather upon functional activities and interaction with other Zang-Fu organs. For instance, when TCM says Liver Qi stagnation, it does not refer to the Liver organ the same way as Western medicine does. Liver in Chinese medicine is like the “hinge” of a door, regulating the Qi flow in the whole body. Part of this function is manifested in its interaction with the stomach and spleen in digestion. It also stores blood and is therefore involved in menstruation. Liver Qi stagnation refers to a set of signs and symptoms including indigestion, nausea, pain in the hypochondriac area, nervousness, and possible premenstrual tension in females.

TCM also holds the view that health exists when Yin and Yang within the human body and between the human body and the external environment are kept in a normal, dynamic balance. Once the balance is impaired, a disease will result. The ultimate principles of treatment are to balance Yin and Yang, encourage the free flow of Qi and harmonize the relationship between the body and its environment.
2.6.2 Pathogenesis in Traditional Chinese Medicine

Migraine in TCM is called “Tou Feng” or “Lei Tou Feng” (Hu and Zhang, 1997) due to its severe pain and sudden onset feature. Based on the manifestation, there are 4-8 types of migraine sub-type. Four of them are most commonly seen as types suitable for acupuncture treatment.

2.6.2.1 Ascending Hyperactivity of Liver Yang and Liver Wind Up Surge

The head is the confluence of all Yang Qi. When the Liver becomes hyperactive it is unable to store blood and thus leads to symptoms of blood and Yin deficiency. The latter cannot root Yang due to a loss of the balance between the two, therefore Yang Qi rises to disturb the brain, causing a throbbing headache. Other diagnostic criteria of this type of migraine are irritability; dizziness; distending pain; lassitude in the lower back and legs; feeling heavy in the head; bitter taste in mouth; red tongue body and yellow dry coating; string-taut or rapid pulse.

2.6.2.2 Deficiency of Both Qi and Blood

Blood is considered as the base substance that nourishes the brain, which is provided by Qi. If insufficient Qi cannot take blood to the brain or the insufficient blood fails to nourish the brain, headache may occur. This type of headache usually has the following symptoms: pale or sallow complexion; shortness of breath after slight physical exertion; weak limbs; pale tongue with white and thin coating; deep, thready and feeble pulse.

2.6.2.3 Wind Phlegm Blocking the Meridians

The lung, spleen and kidney may cause retention of excessive fluids in the body. If the excessive fluid accumulates in a certain part of the body and congeals, phlegm is formed. Phlegm blocks the meridians located in the head, leading to headache. The features of this
type of migraine are chest distress; corpulent tongue body with tooth-prints; white and greasy
tongue coating; deep and taut or deep and slippery pulse.

### 2.6.2.4 Blood Stasis

As mentioned above, one of the functions of Qi is to allow the blood to flow freely. Stagnated
Qi causes blood stasis, which in turn becomes a pathogenic factor that causes various
disorders including headache. This type of migraine involves stabbing pain; cyanotic lips and
nails; purplish tongue with thin white coating; deep, thready or thready-sluggish pulse.

In general, during an attack there is always an involvement of Liver Yang and Liver wind. In
between attacks, the underlying pathology, such as phlegm, blood stasis, Liver Yin and Blood
deficiency or Qi and Blood deficiency manifest more clearly.

### 2.6.3 Treatment of Migraine in Chinese Medicine

The principle of treatment is based on the diagnosis, which determines the nature of a
condition as deficient or excessive. The aim of treatment is to restore the balance of Qi and
blood, the balance of Yin and Yang and the balance of the organs. In general, it is enhancing
and strengthening the deficient syndromes through the elimination and dispelling of the
excessive pathogens in order to bring the patient back to the state of equilibrium that is
postulated to exist prior to illness.

According to the four pathogenesis of TCM, the principle of treating migraine is pacifying the
liver to subdue Yang Qi; tonifying Qi and replenishing blood; extinguishing wind and
resolving phlegm and activating blood and resolving stasis.

The detailed information regarding the acupoint selection for the different four sub-groups is
described in Section 6.4.3.2.
2.7 Acupuncture for Migraine

2.7.1 History of Acupuncture

Acupuncture, a technique of traditional Chinese medicine, based on the meridian theory, has
been used in China for thousands of years for treating diseases. It originated in China, and has
been developed into different types, namely, Classical Chinese, Japanese and Korean
acupunctures. To date, acupuncture is widely practiced by traditionally trained acupuncturists,
medical doctors and physiotherapists in western countries. In the contrast to traditional
Chinese acupuncture method with inserting needles into the traditional acupoints, medical
acupuncturists always prefer to choose trigger points or choose points according to neural
anatomy for treatment.

In the early 19th century, acupuncture was introduced to the west, mainly Europe and America.
By the 1970s it began to capture the public interest and become to be widely practiced,
especially for pain relief (Mann et al., 1973). Since then western scientists began to publish
researches into acupuncture (Bache, 1826, Berliozs, 1816, Churchill, 1821, Cloquet, 1826).
The World Health Organization (WHO) has endorsed the effectiveness of acupuncture in
relieving postoperative pain, nausea during pregnancy, nausea and vomiting resulting from
chemotherapy, and dental pain, anxiety, panic disorders and insomnia (WHO, 2003).

Scientists are researching the mechanisms and assessing the efficacy of acupuncture.

2.7.2 Mechanisms of Acupuncture for Anti-migraine

There are several theories explaining the mechanisms of acupuncture analgesia (AA). One of
the earliest theories was that acupuncture meridians and acupoints were related to the nerves
and blood vessels (Chan, 1984). However, so far, no unifying and persuadable theory has
been proposed. The following theories have been supported by empirical data; they are
Melzack’s gate control theory (segmental inhibition), endorphin hypothesis, diffuse noxious inhibitory control (DNIC), regulation of the autonomic system and the anti-inflammation effect.

Acupuncture needling is an invasive procedure, stimulating the Aδ afferent nerves, and possibly Aβ fibres, resulting a cascade of reaction at the spinal and supraspinal levels. First, Aδ and Aβ afferent fibres end primarily in the most superficial zone and neck of the dorsal horn of the spinal grey matter (Kumazawa and Perl, 1978), in turn activate inhibitory interneurons and stimulate the release of γ-amino butyric acid (GABA). The latter produces pre-synaptic inhibition on spinal transmission interneurons (T). T neurons are also activated by inputs from unmyelinated afferent fibres (C), primarily activated by noxious stimulation, and transmit nociceptive information. Thus, at the segmental level, activation of large myelinated afferent fibres inhibits the input from C fibres directly and indirectly via the spinal grey matter of the dorsal horn. This is part of the gate control theory (Melzack and Wall, 1996), explaining the segmental effects of acupuncture. This hypothesis has been supported by a recent study in which electroacupuncture (EA) with low intensity increased the homotopic, but not heterotopic pain threshold (Xu et al., 2003). This study suggest that local acupuncture-induced analgesia is effective with activation of large afferent fibers, whereas heterotopic acupuncture-induced analgesia is only effective with intensities strong enough to excite small afferent fibers. Local analgesic effects of acupoint stimulation involve segmental inhibition, whereas systemic analgesic effects of acupoint stimulation are involved in contra-lateral effects. The latter may recruit the diffuse noxious inhibitory controls (DNIC) system. The specific function of an acupoint is determined by the anatomical relationship between the disease focus and the segmental location of the acupoint.
Second, the signals from the Aδ afferent fibres are relayed to the suprapsinal centres, leading to the release of endogenous opioid peptides. A few lines of evidence support this hypothesis. 1) AA is blocked or reversed by naloxone, an endogenous opioid antagonist. (Cheng and Pomeranz, 1980, Fine et al., 1988, Han et al., 1986); 2) Similar brain regions are involved in both morphine and acupuncture analgesia. AA was significantly attenuated by microinjection of naloxone into the nucleus accumbens, amygdala, habenula and periaqueductal gray matter (PAG) of the rabbit, areas that are involved in morphine analgesia; 3) The release of the types of opioid neuropeptides depends on the frequency of EA with high frequency EA (100 Hz) stimulating the release of dynorphin and lower frequency EA of enkephalin and β-endorphin (2 and 15 Hz) (Han, 2003a, Han, 2003b).

Two major descending inhibition pathways, serotonin (5-HT) and nonepinephrine, are also involved in AA. Upon acupuncture stimulation, 5-HT is released from nucleus raphe magnus, and descends in the dorsolateral funiculus to terminate directly on enkephalin-neurons which then produces post-synaptic inhibition on transmission neurons at the segment where the painful stimulation comes (White and Ernst, 1999). The nonepinephrine pathway descends from the hypothalamus and induces inhibition on transmission neurons at the dorsal horn via the dorsal lateral funiculus as the serotonin pathway does (Han, 2003a). Acupuncture activates the descending inhibition system so that reduces pain.

Third, diffuse noxious inhibition controls (DNICs) may explain the non-segmental effects of AA (Le Bars et al., 1991). The dorsal horn neurons are inhibited by nociceptive afferent signals applied to heterotopic part of the body. This action is likely due to the inhibition of acupuncture on wide dynamic range neurons (Hashimoto and Aikawa, 1993).
Four, acupuncture has a strong anti-inflammation effect. Numerous studies have shown that EA reduces acute and chronic inflammation and attenuates both heat and mechanical hyperalgesia in animals (Zhang et al., 2004a, Zhang et al., 2004b, Zhang et al., 2005a, Zhang et al., 2005b, Zhang et al., 2005c). In particular, EA of low frequency has a strong anti-inflammation effect whereas that of a high frequency reduces pain (Lao et al., 2004).

Finally, Acupuncture regulates the autonomic nervous system. Bakers and colleagues found that acupuncture reduced lower frequency band of heart rate variability of migraine patients, indicating an inhibition on the sympathetic nervous system (Bäcker et al., 2008). Furthermore, acupuncture-like stimulation has been shown to improve the cortical cerebral blood flow (CBF) of rats (Uchida et al., 2002). In migraine subjects, the CBF is reduced at the posterior pole of the brain and the area of low blood flow spreads gradually, resulting in the cerebral ischemia that causes the headache (Olesen, 1993). Increasing in the CBF can potentially relieve headache and prevent migraine attack.

Acupuncture operates on the multi systems of pain control. Based on the neural mechanism, acupuncture could abolish migraine via segmental and general pain inhibition systems. It might also prevent migraine via its effects on anti-inflammation, regulation of sympathetic nervous system and enhancing descending inhibition.

2.7.3 Current Clinical Research of Acupuncture for Headache

Clinical trials have shown that acupuncture is an effective alternative treatment for tension-type headache (Endres et al., 2007a, Xue et al., 2004, Melchart et al., 2005), and chronic headache (Vickers et al., 2004a). To date, there have been a number of systematic reviews on the use of acupuncture for chronic pain in general (ter Riet et al., 1990, Patel et al., 1989); headaches as a whole (Manias et al., 2000, Melchart et al., 1999); idiopathic headache
(Melchart et al., 2001) and migraine in particular (Scott and Deare, 2006, Griggs and Jensen, 2006b) as well as tension-type headache (Davis et al., 2008). However, there are a number of major issues associated with current migraine literature. Firstly, the results appear conflicting: Pintov (1997) supported the effectiveness of acupuncture in migraine patients when compared with sham acupuncture. However, Linde and her colleagues (2004) found no difference in effectiveness between real and sham acupuncture in treating migraines. Secondly, the quality of part of available trials is low, as most of these studies suffered from problems of either small sample size (usually less than 50), or inappropriate choice of instruments for outcome measure, or non-adherence to the IHS classification of migraine headaches in the inclusion criteria. Thirdly, according to Scott and Deare’s SR (2006), less than half of the included studies selected the acupoints according to Chinese medicine individual syndrome differentiation; this is against the principles of Chinese medicine. Therefore, to date, use of acupuncture for migraine, though promising, still suffers from insufficient quality in design which undermines the validity of the clinical trials. Further research is warranted to strengthen or refute the available evidence.

2.8 Assessments of Migraine

Assessment of treatment outcomes is very important for both practitioners and researchers. In measuring any pain complaints, the patient as a whole should be considered, not just the pain itself, because pain impacts on the physical, psychological and social aspects of patients’ life (Seres, 2003). Theisler (1990) pointed out that successful treatment should reduce patients’ headache activity as measured by the frequency, intensity and duration, eliminate or reduce reliance on medications and on headache’s interference with the activities of daily living, improve patients’ ability to cope with the headache problem, and reduce over-utilization of the health care system. All in all, the above aspects can be summed up into four domains, namely pain dimensions, pain quality, medication consumption and functional impact.
2.8.1 Pain Dimensions

Migraine, like other pain conditions, is subjective, without reliable objective markers. So far, subjective ratings of self-reported head pain using various scales are regarded as the “gold standard”. Because changes in headache can occur on various dimensions, data from the changes can be summarised in the following ways: frequency, intensity, duration and headache index.

2.8.1.1 Frequency

Researchers always record either the number of the days with migraine or the migraine-free days in a 4-week period to assess the frequency of migraine. These are recorded with a diary.

2.8.1.2 Intensity

There are many measurements of pain intensity, and can be grouped into three broad types: verbal rating scales (VRSs; e.g., “none”, “mild”, “moderate”, “severe”); numerical rating scales (NRSs; e.g. four-grade scale, from 0 to 4 corresponds to no headache, mild pain, moderate pain and severe pain); and visual analogue scales (VASs; e.g. a 10-cm line anchored by “no pain” and “pain as bad as it could be”). Each type has been used in clinical trials to investigate the effects of a treatment on pain. Among these methods, VAS and VRS are the most frequently used measurements. Their variability and reliability have been evaluated (Corran et al., 1991). VAS is recognized to be more sensitive than VRS, reflecting changes in the intensity of pain more precisely (Deschamps et al., 1988, Ohnhaus and Adler, 1975). However, it can be difficult for old individuals to use (Carlsson, 1983).
2.8.1.3  Duration

Duration means the length of time in hours between migraine onset and offset. The original measurement was a grid card (Figure 2), and x-axis and y-axis reflect the duration and intensity, respectively. This original form does not measure the two dments separately.

![Intensity Grid Diagram](image)

Figure 2: A sample of grid diary

In 1977, Epstein and Abel (1977) noted that most patients did not record headache continuously via directly observing patients; rather, they would like to periodically fill in later by recalling the headaches. Hence, Epstein and Abel modified the procedure to record patients’ situation four times per day: wakeup, lunch, dinner and bedtime. Later, Collins and Martin (1980) compared this modified format with a bihourly schedule and found they yielded fairly equivalent results. Although the Epstein’s new format is convenient for patients and provides reliable and valid data, it does have some demerits. For instance, clinicians and researchers, who chose either frequency or duration as the primary interest, found this format did not provide the exact data of frequency and duration. Since then, several modification to the Epstein’s format have been proposed in order to improve adherence and accuracy, until researchers decided to separate these two dimensions. To date, the widely used measurement
of duration is a 24-hour scale (Figure 3). Patients are required to draw a line representing a period of time within 24 hours that they experienced pain.

![24-hour scale of duration](image)

**Figure 3: 24-hour scale of duration**

### 2.8.1.4 Headache Index

Headache index is a composite measure that incorporates all dimensions, calculated by summing headache frequency, intensity and duration together (frequency × intensity × duration). Headache index can reflect the total suffering of patients, however, it weighs these three dimensions in an arbitrary manner, which renders it of little value when comparisons are being made across patients. Furthermore, the clinical meaning of changes is not clear based on the headache index. In fact, it has been argued that there is no need for headache index, because in most cases where there is a decrease in the index value, it is usually due to a decrease in frequency of attacks (Tfelt-Hansen et al., 1984). Consequently, IHS community recommended this composite measure no longer be used (International Headache Society Clinical Trials Subcommittee, 2000).

### 2.8.2 Pain Quality

In clinical practice, assessing pain quality is as important as pain intensity, because treatment intervention may alter certain qualities of pain while not impacting on pain intensity. The items contained in the McGill Pain Questionnaire (MPQ) are designed to access various components of pain, such as sensory, affective and evaluative, using 78 adjectives in 20 categories. MPQ was developed by Melzack and colleagues (Melzack, 1975a). Its validity and reliability have been tested extensively in acute and chronic pain (Melzack and Perry, 1975, Reading, 1982, Wilkie et al., 1990).
2.8.3 Medication Consumption

Medication consumption has been frequently monitored by clinicians and researchers, even in the non-drug trial. It is not only related to the social burden, it is also another way to assess behaviours motivated by pain. The direct way of measurement is to request the patients to record and count the number of pills consumed. In fact, the simple pill count cannot be suitable for some conditions, such as participants take more than one medication in non-drug trials; patients switch medication during treatment. In 1976, some medical experts rate the potent weight of analgesics for migraine control (Coyne et al., 1976). Later on Blanchard and Andrasik (1985) modified that potent weight into a “1 to 7” list and summarised a medication index, which multiplies the number of pill count by the respective potency value. Based on that, scientists developed the medication quantification scale (MQS) of pain for both clinical and research purposes in 1992, and has been updated to version III in 2003. The MQS covers simple analgesics, opioids, anti-depressants to steroids (Harden et al., 2005). The reliability, validity and sensitivity of the MQS have been demonstrated (Guck et al., 1999a, Stormo et al., 1998). Furthermore, it has been used as a standard measurement to validate other measurements (Guck et al., 1999b). IHS guidelines committees recommend that the medication consumption should be recorded and as a secondary effect parameter.

2.8.4 Functional Impact

Until last decade, researchers have begun to note that the effectiveness of a treatment for pain disorders, is not only determined by the degree of pain reduction, but also in the improvement of impacted functioning (Portenoy, 1991, Turk et al., 1993). Especially for migraineurs, the impact can be more serious than some other diseases, such as hypertension, diabetes, gastrointestinal disorders (Andrasik, 2001), and other types of headache (Kryst and Scherl, 1994). So far, a number of scales are available for assessing the functional impact, without
reliability and validity issues, such as the SF-36 (Ware, 2000), the Beck Depression Inventory (BDI) (Flor et al., 1992) and the Migraine Disability Assessment Questionnaire (Stewart et al., 1999b, Stewart et al., 1999a).

Most recently, researchers began to focus on scales specific to migraine or headache in general. Migraine Specific Quality of Life Questionnaire (MSQOL) was developed by Glaxo Wellcome Inc. to assess the effect of migraine treatment. Although MSQOL takes the SF-36 as the basis, the dimensions of MSQOL had been demonstrated to have low-to-modest correlations with the two component scores of the SF-36 and were modestly to moderately correlated with migraine symptoms (Martin et al., 2000). Moreover, the validity and reliability of the MSQOL have been confirmed by a few studies (Cole et al., 2007, Martin et al., 2000).

MSQOL contains three aspects, namely role function-restrictive (question 1-7), role function-preventive (questionnaire 8-11) and emotional function (questionnaire 12-14). Each dimension is scored from 0-100 and a higher score indicates better health. The use of tools assessing headache impact or disability is increasingly being recommended by generalized headache management guidelines (Dowson, 2001, Dowson et al., 2002).

2.9 Pressure Pain Threshold (PPT)

2.9.1 Introduction

The term pain threshold refers to the minimum intensity or duration of a sensory stimulus at which it becomes painful as interpreted by the subject (Cook, 2006). For instance, the temperature, the pressure, or the duration of muscle being ischaemia, at which a change from ordinary sensation to pain occurs, is the pain threshold. It is clearly different to the term “pain tolerance”, which refers to the degree of pain that a subject can tolerate. Pressure pain
threshold is most commonly tested. It has been used as the outcome measure for testing the efficacy of analgesics or other specific therapies mainly for clinical purposes (Tunks et al., 1988, Meyer et al., 2008), such as manual oscillation for rheumatoid arthritis (Dhondt et al., 1999) and evaluating activity of 3alpha-hydroxysteroid oxido-reductase in sciatic nerve injury (Meyer et al., 2008).

2.9.2 Thermal Pain Threshold (TPT)

Noxious thermal pain threshold includes heat and cold TPTs. Females (Riley et al., 1998, Edwards et al., 2004), non-white races (Edwards and Fillingim, 1999, Campbell et al., 2005) and younger people (Bravenboer et al., 1992) have lower TPT. Moreover, TPT has been reported to vary among different areas of the body (Chery-Croze and Duclaux, 1980, Melzack and Wall, 1962); and increases with decreased stimulation area (Defrin and Urca, 1996, Defrin et al., 2002). Apart from the above factors, TPT is also affected by some external factors. Kundermann and his colleagues (2004) found sleep deprivation produces a significant decrease in heat pain threshold in healthy volunteers. In addition, a study involving 13 healthy subjects revealed that electroacupuncture can increase heat pain threshold (HPT) (Leung et al., 2005).

TPT as a laboratory-based assessment has been researched in headache patients. Patients with cluster headache reported a reduced cold pain threshold (CPT) and increased HPT on the affected side compared with the contralateral asymptomatic side (Ellrich et al., 2006). Patients with tension-type headache experienced a significant decrease in HPT measured in the temporal region, but reported normal HPT in the hand during the headache attacks (Jensen, 1996).
The reliability and reproducibility of TPT measurements has been demonstrated by studies in young adults (Cathcart and Pritchard, 2006, Bravenboer et al., 1992) as well as other age groups (Bravenboer et al., 1992).
2.9.3 Pressure Pain Threshold (PPT)

Pressure pain thresholds in the general population vary by age and gender (Jensen et al., 1992). Women have lower PPT values than men (Takala, 1990, Chesterton et al., 2003, Garcia et al., 2007). Moreover, PPT has been detected to be significantly lower in healthy females during the premenstrual phases (Isselée et al., 2001). Furthermore, Fischer (1987) has noted that the PPT of healthy people varies among different muscles and individuals, and with a wide range of values (Davenport, 1969, McMillan, 1995). In 1990, Takala (1990) tested PPT on the upper trapezius and levator scapulae muscles finding that even in the same tissue the values of PPT in the non-symptomatic population displayed wide variation. A study involving 27 sites including the nape, shoulder, arm and lumbar back areas revealed that PPTs were lower in the nape region, The PPT values of nape region were 55% of those tested in the lumbosacral region, the least sensitive area to pressure (Kosek et al., 1993). Such results are consistent with other publications (Fischer, 1987, Hogeweg et al., 1992).

PPT has been used in determining the beneficial effect of physical therapies in the deeper tissues (Vernon et al., 1990, Fischer, 1998) such as spinal manipulation for chronic neck pain (Vernon et al., 1990) or low back pain (Cote and Mior, 1994); neck muscle training for neck pain (Ylinen et al., 2005).

The relationship between PPT and headaches including migraines is not well understood. Bovim (1992) compared PPT in cervicogenic headache, migraine, tension-type headache and healthy people measured with algometer, and found that there was no significant difference between migraine or tension-type headache and healthy controls. However, lower PPTs have been observed in cephalic and extra-cephalic muscles in tension-type headache sufferers (Schoenen et al., 1991, Bendtsen et al., 1996, Ashina et al., 2005); in the head and at the deltoid muscle in cluster headache patients (Bono et al., 1996), when compared with healthy
volunteers. In addition, some headache studies reported that compared with the PPT in a pain-free state, the PPT during pain was decreased (Drummond, 1986), or unchanged (Jensen et al., 1988, Bove and Nilsson, 1999). Furthermore, another study involved cervicogenic headache, migraine and tension-type headache as a whole revealed that a lower PPT was recorded when the headache was more intense (Sand et al., 1997). Jensen and his colleagues (1988) also demonstrated that PPT did not change during the attacks of common migraine as well as during headache-free intervals, which is in conflict with another study (Sandrini et al., 1994) which reported a lower PPT in migraine attacks compared to healthy people. Moreover, a recent study revealed significant differences in PPTs of the neck muscles between the patients with unilateral migraine and healthy volunteers, and in PPTs of the neck region between symptomatic and non-symptomatic sides, however without a significant side difference in the cephalic points of these unilateral migraine sufferers (Fernández-de-Las-Peñas et al., 2008). In contrast, other studies reported the lower PPTs on the symptomatic side than on the non-symptomatic side in the craniofacial area (Bono et al., 1996) and temporalis muscle (Bono et al., 1996, Ellrich et al., 2006) of cluster headache sufferers and in the cranial area of migraine patients (Smith et al., 2006).

In addition, TPT is significantly and strongly correlated with PPT in healthy volunteers (McManusa et al., 2006, Bhalang et al., 2005).

2.9.4 Reliability of PPT

An algometer is a device that measures sensitivity to pain and determines a patient's PPT. It was developed in 1988 by the companies 3M and Racia, based on the work of Claude Willer, and has been introduced as semi-objective method (Takala, 1990).
The high intrarater and interrater reliability of PPT has been demonstrated on cranial and neck muscles by studies with healthy individuals (Chung et al., 1992, Antonaci et al., 1998, Delaney and McKee, 1993) and on cephalic points of headache patients (Sand et al., 1997).

Some technical issues have been identified as affecting the reliability of PPT assessed with an algometer, including sites, reaction time of the rater and the speed in which pressure is increased. Jensen and his colleagues (1986) found that measurements of PPT were most reliable when the measurement site was flat, wide, and bony as opposed to a soft tissue site where the hard rubber tip might slide off the target. However, Kosek (1993) reported no consistent differences between PPT values of muscle bellies and bony sites when compared within the same body region. The reaction time of the rater and the rate of pressure increase were other factors that affected reliability (Jensen et al., 1986). The reliability is enhanced when all measurements are taken by one examiner (Nussbaum and Downes, 1998). An increasing rate at 1 kg/cm\(^2\) is more reliable than 2 kg/cm\(^2\) (List et al., 1989), which may be due to a certain time being necessary for the patient and rater to react to applied pressure. Such rates have been widely used by a series PPT studies (Zaslawski et al., 2003, Fischer, 1987).

A study testing the reproducibility of PPT in patients with different types of headaches revealed that the variability was reported as higher among tension-type headache patients than migraine and cervicogenic headache patients (Sand et al., 1997).

Repeatability varies between measurement sites. The most reliable measurements are the temporal muscles among the 11 points located in the temporal, sternocleidomastoid insertion and frontal region (Sand et al., 1997). A study to determine the number of measurements that provided the most precise estimate of PPT was carried out by Ohrbach and Gale (1989), and
revealed that PPT increased and decreased unsystematically from measurement to measurement. The mean of two readings provided a more reliable estimate of PPT than using one reading.

In summary, PPT measured with an algometer has a high intrarater reliability when it is measured on the bony sites of head and neck, at 1 kg/cm$^2$ increasing rate and by one rater.

### 2.10 Research Questions

Both clinical evidence and neural mechanisms support that acupuncture may benefit migraine by abolishing and preventing attacks. There are some weaknesses and gaps in the current body of literature. Existing systematic reviews on acupuncture for migraine failed to adequately represent non-English studies such as those were conducted in China, Japan and Korea. In addition, acupuncture effects on other types of migraine, those with frequent headache or menstrual migraine have not been properly examined.

The objectives of this study were to:

1) systematically review the current state of evidence from English and East Asian literature of acupuncture for migraine; and,

2) design and conduct a RCT that addresses the key identified methodological problems from the systematic review (SR), to determine the short- and long-term effect and safety of acupuncture for patients with migraine.
CHAPTER THREE: METHODOLOGY OF SYSTEMATIC REVIEW

Clinicians, researchers, healthcare providers and relevant policy makers are inundated by the amounts of available research and clinical data. Such information should therefore be managed and assessed systematically so that appropriate decisions based on the research / data can be made. Taking an intervention for migraine as an example, before any healthcare provider decides to provide an intervention to a migraine sufferer, the effectiveness of the intervention should be evaluated systematically; this is referred to as an ‘evidence-based decision’.

Investigating the efficacy of an intervention is not the only aim of a systematic review; sometimes due to the limitations of literature, we cannot make a decision at that time. Systematic reviews can also assist researchers in finding flaws in the available literature, which is useful for the purposes of further research.

Systematic reviews can synthesize the results of multiple primary investigations by using appropriate strategies which can limit biases and reduce chance effects so that every single right conclusion and decision is based on reliable results (Antman EM, 1992). The usual methods of a systematic review include a comprehensive search of all potentially relevant studies; the use of explicit, reproducible criteria in the selection of studies for review; identifying the evidence; appraising the quality of evidence; synthesizing the data and reporting the findings (Cook et al., 1997). A meta-analysis is the statistical method used to synthesize, combine and summarise the results of several primary studies in the systematic review.

In the past 20 years, guides have been created to help with the critical appraisal (Oxman et al., 1994) and application (Guyatt et al., 1995) of literatures. Furthermore, an international
initiative, called the Cochrane Collaboration, has evolved to help prepare, maintain, and disseminate the results of systematic reviews of health care interventions since 1992. Presently, the Cochrane reviews are widely accepted as reviews of the highest quality. The methods of current systematic reviews followed those recommended by the “Cochrane Handbook for Systematic Reviews of Interventions” (Higgins and Green, 2006).

In this project, two systematic reviews were conducted; a systematic review of studies included in English databases and a systematic review of studies in East Asian databases. Two systematic reviews were conducted as acupuncture is widely accepted as the mainstream medicine in most Asian countries, especially in China and Korea, therefore literature from these countries is important to the overall understanding of the clinical applications of acupuncture. Unfortunately, most studies conducted in these countries are not published in English and are often not included in commonly used databases in Western countries, such as PubMed.

The aims of the two systematic reviews were:

1) To assess the efficacy and safety of acupuncture in the treatment of migraine in the following comparisons
   Real acupuncture vs sham or placebo acupuncture
   Real acupuncture vs non-acupuncture treatment
   Real acupuncture vs standard therapies

2) To compare the study design and quality of literature published in these two groups of databases, i.e., English and East Asian databases.
3.1 Search Strategy for Identification of Studies

“Acupuncture”, “electro-acupuncture”, “Chinese medicine”, “point-stimulation”, “headache” and “migraine” were used as search terms and searched for in selected Chinese, English, Japanese and Korean electronic databases from the inception of the databases to August 2006, January 2008, January 2008, and May 2007 respectively. The Chinese data was searched and assessed by two researchers. The Japanese and Korean data was searched and translated with the help of three acupuncture researchers from Korea and Japan who are specialized in systematic reviews. The work contributed by Dr. Yamashita Hitoshi, Dr. Junchul Seo and Dr. Jae Cheol Kong was acknowledged. The search strategies were explained to the three experts. The included databases were chosen by the individuals according to their prior knowledge of relevant medical journals and are listed below in Table 1.
Table 1: The databases used in different systematic reviews

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese Database</td>
<td><em>Vi Pu</em>, <a href="http://www.cqvip.com">www.cqvip.com</a></td>
</tr>
<tr>
<td></td>
<td><em>Wan Fang</em>, <a href="http://www.wanfangdata.com.cn">www.wanfangdata.com.cn</a></td>
</tr>
<tr>
<td>English Database</td>
<td><em>EMBASE</em>, <a href="http://www.embase.com">www.embase.com</a></td>
</tr>
<tr>
<td></td>
<td><em>Cochrane library</em>, <a href="http://www.thecochranelibrary.com">www.thecochranelibrary.com</a></td>
</tr>
<tr>
<td>Japanese Database</td>
<td><em>Ichushi Web</em>, <a href="http://www.jamas.or.jp">www.jamas.or.jp</a></td>
</tr>
<tr>
<td>Korean Database</td>
<td><em>National Assembly Library</em>, <a href="http://www.nanet.go.kr">www.nanet.go.kr</a></td>
</tr>
<tr>
<td></td>
<td><em>KoreaMed</em>, <a href="http://www.koreamed.org">www.koreamed.org</a></td>
</tr>
<tr>
<td></td>
<td><em>Journal of Korean Oriental Medicine</em>, <a href="http://www.koms.or.kr">www.koms.or.kr</a></td>
</tr>
<tr>
<td></td>
<td><em>The Journal of Korean Acupuncture &amp; Moxibustion Society</em>, <a href="http://www.acumoxa.or.kr">www.acumoxa.or.kr</a></td>
</tr>
<tr>
<td></td>
<td><em>Oriental Medicine Information System</em>, <a href="http://www.omis.dhu.ac.kr">www.omis.dhu.ac.kr</a></td>
</tr>
</tbody>
</table>

3.2 Criteria for Considering Studies for Reviews

3.2.1 Language of Studies

The full-text of included studies must have been published in Chinese, English, Japanese or Korean databases.

3.2.2 Types of Studies

Studies with a randomized and controlled design were included. Quasi-randomized studies (e.g. by the order of admission or date of birth) were also included. Ongoing or unpublished studies were excluded.
3.2.3 Types of Participants

Participants were migraine patients diagnosed according to the standard criteria, such as those recommended by the Ad Hoc committee of the National Institute of Neurological Diseases and Blindness (Ad Hoc Committee on Classification of Headache of the National Institute of Neurological Diseases and Blindness, 1962) or the International Headache Society (IHS) (Headache Classification Subcommittee of the International Headache Society, 2004), for participants recruitment. Studies that did not separate migraine patients from those with other types of headache, such as tension-type headache, were excluded.

3.2.4 Types of Intervention

Studies involving needle insertion at acupuncture points, tender points, or trigger points and other invasive methods of stimulating these points (e.g. electro-acupuncture) were included. Studies examining non-invasive acupuncture, such as laser acupuncture or acupressure were excluded as were studies utilizing point-injection. Studies comparing a combined therapy of acupuncture and Chinese herbal medicine or Tuina with a control group were included because acupuncture was often used together with other therapies in clinical practice.

Control interventions considered were:

- No treatment,
- Sham or placebo acupuncture, or
- Other active treatments.

Studies comparing different modalities of acupuncture were excluded, for instance comparing manual acupuncture with electroacupuncture. Studies without a valid control group which did not allow the effects of acupuncture alone to be assessed (for instance, comparing acupuncture with acupuncture plus Qigong) were also excluded.
3.2.5 Types of Outcome Measures

Included studies should report at least one clinically related outcome for migraine, such as the frequency or intensity of migraine. Studies using respondent rates to present improvements in frequency, intensity or duration were also included. Trials reporting only physiological or laboratory parameters as outcome measures, such as electroencephalogram, were excluded.

3.3 Data Extraction

Information on participants, randomization, blinding, interventions, outcome measures as well as results were extracted using the standard form adopted by Melchart and colleagues (Melchart et al., 2001). One reviewer extracted the data. Another reviewer checked the extraction according to the pre-defined form (Appendix 2). Differences between the reviewers were solved through discussion. Extracted data were presented using separate tables.

3.4 Assessment of Quality

The quality of included studies was assessed independently by two reviewers using a Jadad Scale (Jadad et al., 1996), Internal Validity Scale (IVS) (Linde et al., 1997), and the Oxford Pain Validity Scale (OPVS) (Smith et al., 2000). Jadad scales and IVS have been used in several SRs on acupuncture (Melchart et al., 2001, Melchart et al., 1999). The OPVS was designed specifically to examine the internal validity of trials in the field of pain research (Smith et al., 2000). In addition, Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) were used to assess the reporting quality of acupuncture interventions (MacPherson et al., 2002). In the two systematic reviews conducted (see chapters four and five), points awarded for each item of Jadad Scale, IVS and OPVS were listed in order for each trial in tables.
3.4.1 Jadad Scale

The Jadad Scale (Jaded et al., 1996) (Table 2) consists of five questions assessing the following five aspects: random allocation, description of randomization, double blinding, description of double blinding and reporting of drop-outs. The maximum score of the Jadad Scale is 5. Studies scoring 3 or more points are considered high quality with 3 points being 60% of the maximum score. In each category, if “yes” is answered, one point is awarded. If “no” is answered, then no points are awarded. The Jadad Scale utilised in this research was the latest version. The former version of the Jadad Scale contained three items; it combined items 1 and 2 of the current version, and also combined items 3 and 4 of the current version.

Table 2: Scoring of Jadad Scale

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Yes=1; No=0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study described as randomized?</td>
<td></td>
</tr>
<tr>
<td>Was the randomization described and appropriate?</td>
<td></td>
</tr>
<tr>
<td>Was the study described as double blind?</td>
<td></td>
</tr>
<tr>
<td>Was the method of double blinding appropriate?</td>
<td></td>
</tr>
<tr>
<td>Was there a description of drop-outs and withdrawals?</td>
<td></td>
</tr>
</tbody>
</table>

3.4.2 Internal Validity Scale (IVS)

The IVS consists of six items (Table 3) which assess the method of allocation, concealment of allocation, baseline comparability, blinding patients and evaluators and likelihood of selection bias respectively. Each item is scored as 0 (criterion not met or insufficient information provided), 0.5 (criterion partially met), or 1 (criterion met).

Item 1 “Method of allocation to groups”: If the study was titled “randomized study” or “randomized trial” or the authors mentioned that “patients were randomized”, 0.5 was given
to Item 1. Furthermore, if the study used appreciate allocation approaches another 0.5 was given to Item 1.

**Item 2** “Concealment of allocation”: If the paper mentioned “the person who executed the allocation sequence was different from the person who recruited participants,” 0.5 was given. If the authors described the method of concealment, such as “sealed envelope”, another 0.5 was given to Item 2.

**Item 3** “Baseline comparability”: If the demographic data was comparable, 0.5 was given. If the baseline data of main outcomes was comparable, another 0.5 was given.

**Item 4** “Blinding of patients”: If the paper only mentioned that “participants were blinded”, 0.5 was given. If the paper described the process of blinding participants or investigated the creditability of blinding that was success, another 0.5 was given.

**Item 5** “Blinding of evaluators”: If the paper mentioned blinding the evaluator, 0.5 was given. If the paper described the process of blinding the evaluator, another 0.5 was given.

**Item 6** “Likelihood of selection bias”: If the paper mentioned the number of drop-outs or the number of participants between baselines and after treatment was presented (thereby enabling the calculation of the number of drop-outs) 0.5 was given. If the paper provided detailed information (reason, allocation of drop-out, etc) about the drop-out, another 0.5 was given.

---

**Table 3: Scoring of IVS**

<table>
<thead>
<tr>
<th>ITEM</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of allocation to groups</td>
<td></td>
</tr>
<tr>
<td>Concealment of allocation</td>
<td></td>
</tr>
<tr>
<td>Baseline comparability</td>
<td></td>
</tr>
<tr>
<td>Blinding of patients</td>
<td></td>
</tr>
<tr>
<td>Blinding of evaluators</td>
<td></td>
</tr>
<tr>
<td>Likelihood of selection bias after allocation to groups by drop-outs, etc.</td>
<td></td>
</tr>
</tbody>
</table>
3.4.3 Oxford Pain Validity Scale (OPVS)

The Oxford Pain Validity Scale (OPVS) (Smith et al., 2000), was developed by a pain research group and specifically examines five aspects (Table 4) of trial methodology that are the sources of biases in the field of pain research: blinding, sample size, outcome measure, demonstration of internal sensitivity and data analysis. Generally, OPVS is more comprehensive in assessing the quality of clinical trials, as it not only focuses on randomization and blinding, but also assesses the outcome measure and data analysis. So far, there is no standard cutoff score to determine what constitutes a high quality study. Following the Jadad Scale, a study with 60% of the maximum score was considered as high quality.

Table 4: Description of OPVS

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Score (circle one number per item)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blinding</td>
<td></td>
</tr>
<tr>
<td>Was the trial convincingly double-blind?</td>
<td>6</td>
</tr>
<tr>
<td>Was the trial convincingly single-blind or unconvincingly double-blind?</td>
<td>3</td>
</tr>
<tr>
<td>Was the trial either not blind or the blinding is unclear?</td>
<td>0</td>
</tr>
<tr>
<td>2. Size of trial groups</td>
<td></td>
</tr>
<tr>
<td>Was the start group start size $\geq$ 40?</td>
<td>3</td>
</tr>
<tr>
<td>Was the start group start size 30 to 39?</td>
<td>2</td>
</tr>
<tr>
<td>Was the start group start size 20 to 29?</td>
<td>1</td>
</tr>
<tr>
<td>Was the start group start size 10 to 19?</td>
<td>0</td>
</tr>
<tr>
<td>3. Outcome</td>
<td></td>
</tr>
<tr>
<td>Look at pre hoc list of most desirable outcomes relevant to the review question:</td>
<td></td>
</tr>
<tr>
<td>Did the paper include results for at least one pre hoc desirable outcome, and use the outcome appropriately?</td>
<td>2</td>
</tr>
<tr>
<td>There were no results for any of the pre hoc desirable outcomes, or, a pre hoc desirable outcome was used inappropriately.</td>
<td>0</td>
</tr>
</tbody>
</table>
Continued Table 4: Description of OPVS

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Description</th>
<th>Score (circle one number per item)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4. Demonstration of internal sensitivity</strong></td>
<td>Look at the baseline levels for the outcomes relevant to the review question:</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>For all treatment groups, baseline levels were sufficient for the trialist to be able to measure a change following the intervention (e.g. Enough baseline pain to detect a difference between baseline and post-treatment levels). Alternatively, did the trial demonstrate internal sensitivity?</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>For all treatment groups, baseline levels were insufficient to be able to measure a change following the intervention, or, baseline levels could not be assessed, or internal sensitivity was not demonstrated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i. Definition of outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Did the paper define the relevant outcomes clearly, including where relevant, exactly what ‘improved’, ‘successful treatment’, etc represented?</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>The paper failed to define the outcomes clearly</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ii. Data presentation: Location and dispersion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Did the paper present either mean data with standard deviations, or dichotomous outcomes, or median with range, or sufficient data to enable extraction of any of these?</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>The paper presented none of the above</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>iii. Statistical Testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Did the trialist choose an appropriate statistical test, with correction for multiple tests where relevant?</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Inappropriate statistical tests were chosen and/or multiple testing was carried out, but with no correction, or, no statistics were carried out.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>iv. Handling of Drop-out</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The drop-out rate was either $\leq 10%$, or was $&gt; 10%$ and includes an intention-to-treat analysis in which drop-outs were included appropriately.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>The drop-out rate was $&gt; 10%$ and drop-out were not included in the analysis, or, it is not possible to calculate a drop-out rate from data presented in the paper.</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL SCORE</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

53
3.4.4 Allocation Concealment

In addition, concealment of allocation was assessed using the method recommended by the Cochrane Collaboration if the method was adequate, uncertain, inadequate or not mentioned, and scored A, B, C and D, appropriately (Higgins and Green, 2006). This method has been used by other systematic reviews (Ezzo et al., 2006, Smith et al., 2007). Concealment of allocation is the process of concealing assignments of the interventions. “A” refers to studies adopting correct concealment methods, such as using centralized randomization or sequentially numbered sealed, opaque envelopes. If studies do not report any concealment approach, “B” should be coded, and this code should also be used for studies that merely state that a list, table or sealed envelopes were used. “C” includes the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation, such as an open list of random numbers. “D” refers to studies that clearly state that allocation concealment is not used (Higgins and Green, 2006).

3.4.5 Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA)

The STRICTA recommendations (Table 5) were proposed by an international group of researchers in acupuncture in an attempt to improve the quality of reporting interventions of acupuncture (MacPherson et al., 2002). It is suitable for both western trigger point treatment and traditional Chinese acupuncture treatment using manual acupuncture, electro-acupuncture or auricular acupuncture. Implementing the STRICTA recommendations amends inadequate acupuncture reporting, facilitates the improvement of critical appraisal, and helps researchers developing criteria for assessing acupuncture treatment in earlier studies (White and Ernst, 1998). STRICTA is a qualitative assessment tool and does not have a scoring mechanism. It contains the following six items.
<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>ITEM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture rationale</td>
<td>1</td>
<td>Style of acupuncture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rationale for treatment (e.g. syndrome patterns, segmental levels, trigger points) and individualization if used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Literature sources to justify rationale</td>
</tr>
<tr>
<td>Needling details</td>
<td>2</td>
<td>Points used (uni/bilateral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Numbers of needles inserted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depths of insertion (e.g. tissue level, mm or cun)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Responses elicited (e.g. de qi or twitch response)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needle stimulation (e.g. manual or electrical)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needle retention time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needle type (gauge, length, and manufacturer or material)</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>3</td>
<td>Number of treatment sessions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequency of treatment</td>
</tr>
<tr>
<td>Co-interventions</td>
<td>4</td>
<td>Other interventions (e.g. moxibustion, cupping, herbs, exercises, life-style advice)</td>
</tr>
<tr>
<td>Practitioner background</td>
<td>5</td>
<td>Duration of relevant training</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Length of clinical experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expertise in specific condition</td>
</tr>
<tr>
<td>Control intervention(s)</td>
<td>6</td>
<td>Intended effect of control intervention and its appropriateness to research question and, if appropriate, blinding of participants (e.g. active comparison, minimally active penetrating or non-penetrating sham, inert)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Explanations given to patients of treatment and control interventions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Details of control intervention (precise description, as for Item 2 above, and other items if different)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sources that justify choice of control</td>
</tr>
</tbody>
</table>
3.5 Data Analysis

Qualitative assessment was used to analyze methodological data. RevMan 4.2 was used for meta-analysis. If significant heterogeneity among the trials was detected with $I^2$ statistic ($I^2 \geq 50\%$), a random-effects model was used. Otherwise, a fix-effects model was used. For continuous data, weighted mean difference (WMD) was calculated. For dichotomous data, relative risks were calculated. If different numerical scales were used to assess one outcome measure, a standardised mean difference (SMD) was calculated.

We also adopted the method described by van Tulder and colleagues in 2003 for the qualitative assessment of the overall evidence. This method classifies the evidence into the categories of “strong”, “moderate”, “limited”, “conflicting” or “no evidence” depending on the quality, number and results of the studies (van Tulder et al., 2003).

**Strong evidence:** Refers to consistent findings in multiple high quality RCTs.

**Moderate evidence:** Refers to findings in a single, high quality RCT or consistent findings in multiple low-quality trials.

**Limited evidence:** Refers to findings in a single low-quality RCT.

**Conflicting evidence:** Refers to inconsistent results in multiple RCTs.

**No evidence:** Meant no studies were identified.
CHAPTER FOUR: SYSTEMIC REVIEW OF ENGLISH LITERATURES ON ACUPUNCTURE FOR MIGRAINE

4.1 Introduction

A systematic review on idiopathic headache, published in 2001, stated the overall effectiveness of acupuncture in the treatment of headache was conflicting (Melchart et al., 2001) as most of the included studies suffered from problems of either small sample size (usually less than 50), the inappropriate choice of instruments for measuring outcomes, or, non-adherence to the IHS classifications for migraine headaches in the inclusion criteria. The latest systematic review (Scott and Deare, 2006) to evaluate the effectiveness of acupuncture for migraine alone included studies published before March 2006. The 2006 review also found that acupuncture studies for migraine still suffered from the same flaws as the earlier systematic review published in 2001. However, according to the 2006 systematic review, the methodological quality of acupuncture studies has improved recently. Since the 2006 systematic review, some high quality clinical trials have been published thus there is a need to re-conduct a systematic review to evaluate the efficacy of acupuncture for migraine alone. Furthermore, such a review can be compared with the SR in East Asian literatures to explore whether any differences exist in RCTs of acupuncture between Western and East Asian countries.

4.2 Objective

Through systematically reviewing English literature, the objectives of this review were to determine whether acupuncture was:

1. More effective than no treatment;
2. More effective than “sham/placebo” acupuncture; and
3. As effective as other active interventions for migraine.
4.3 **Methodology**

The following strategies were conducted.

“Acupuncture”, “electroacupuncture”, “point stimulation”, “headache”, “migraine” and “chronic migraine” and their combinations were used as text words to search the EMBASE, PUBMED and Cochrane Library from their inception to January 2008.

The following list contains the terms used to search PubMed:

#1 search acupuncture [tw]
#2 search electroacupuncture [tw]
#3 search point stimulation [tw]
#4 search migraine [tw]
#5 search chronic migraine [tw]
#6 search headache [tw]
#7 search #1 or #2 or #3 [tw]
#8 search #4 or #5 or #6 [tw]
#9 search #7 and #8 and Human (MeSH) and clinical trial [pt]

The methodology utilised in this study is described in chapter three.

4.4 **Result**

4.4.1 **Identification of Studies**

One hundred and five papers were found through the search. Fifty-four studies were excluded because they reported either other disease, other kinds of headaches or idiopathic headache as a whole. Seven papers did not report clinical relevant outcome measures or were protocols, and they were therefore excluded. Nine of the remaining 34 studies were excluded as TENS, laser-therapy treatment or other therapies were the active intervention. A further eleven studies were excluded for not having a valid control intervention, such as comparing
acupuncture plus Western medication with acupuncture plus placebo tablet (Lenhard and Waite, 1983), or not being RCTs. Another study was excluded as it was not a clinical trial. Two papers did not report original data and used previously published data to conduct further analyses (Linde et al., 2007c, Linde et al., 2007a); these two papers were excluded. Furthermore, three studies were excluded as they did not use standard diagnostic criteria in recruiting participants. Three studies published in German were excluded as we could not have them translated. Finally, 15 studies were identified. Figure 4 illustrates the process of study identification.
Figure 4: Flowchart illustrating the process of study identification.
4.4.2 Description of the Studies

Data from the 15 included studies was extracted and is summarised in Table 6. One study (Pintov et al., 1997) implemented Prensky’s classification to identify participants (Prensky and Sommer, 1979); twelve studies adopted the IHS criteria for the diagnosis of migraine, and the remaining two trials (Liguori et al., 2000, Dowson et al., 1985) used the Ad Hoc Committee’s criteria. In total, 2468 participants (median 81; range 22 - 960) were included in this review.

Fourteen of the 15 studies used acupuncture in the treatment group and the remaining one study used dry needling (Hesse et al., 1994). Four studies compared acupuncture with Western medication and one study compared acupuncture with usual care (avoid acupuncture) (Vickers et al., 2004a). Four studies had a three-arm design, comparing acupuncture with sham acupuncture or Western medication (Diener et al., 2006); acupuncture with TENS or laser therapy (Allais et al., 2003); acupuncture with placebo Western medication or Western medication (Melchart et al., 2003a); acupuncture with sham acupuncture or waiting list (Linde et al., 2005a), respectively. Four of the remaining six studies compared acupuncture with Western medication. The final two studies used a combination of massage and relaxation (Wylie et al., 1997), and mock TENS (Dowson et al., 1985) as the control intervention, respectively.
<table>
<thead>
<tr>
<th>Author and Date</th>
<th>Definition of Participants</th>
<th>Intervention</th>
<th>Sample Population</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Drop-out</th>
<th>Quality</th>
<th>AC*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute attacks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Melchart et al., 2003b)</td>
<td>IHS</td>
<td>Acupuncture</td>
<td>Acu: n = 60</td>
<td>Number of participants in whom a attack was prevented</td>
<td>2 days</td>
<td>Not report</td>
<td>Jadad: 1-1-0-0-1</td>
<td>IVS: 1-1-1-0.5-0-1</td>
</tr>
<tr>
<td></td>
<td>vs Placebo WM vs WM</td>
<td>vs Placebo</td>
<td>PWM: n =61</td>
<td></td>
<td></td>
<td></td>
<td>OPVS: 0-3-2-1-1-1-1</td>
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<tr>
<td></td>
<td></td>
<td>WM vs WM</td>
<td>WM: n = 58</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(Streng et al., 2006)</td>
<td>IHS</td>
<td>Acupuncture</td>
<td>Acu: n = 59</td>
<td>Frequency: headache days; number of attacks; days with medication Intensity</td>
<td>3 months</td>
<td></td>
<td>Acu: n = 2</td>
<td>Jadad: 1-1-0-0-1</td>
</tr>
<tr>
<td></td>
<td>vs Western Medication (WM)</td>
<td>vs Western</td>
<td>WM: n = 55</td>
<td>Quality of life (SF-36) Disability (PDI) Emotional of pain (SES) Depression)</td>
<td></td>
<td></td>
<td>WM: n = 17</td>
<td>IVS: 1-1-0-0-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medication</td>
<td>WM: n = 55</td>
<td>Working days lost Proportion of treatment respondents: percentage of</td>
<td></td>
<td></td>
<td>OPVS: 3-3-2-0-1-1-1-1</td>
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<td></td>
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<td>patients with a reduction of &gt;= 50% in migraine attacks Number of</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>patients with adverse side effects Number of drop-out due to side effects</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(Alecrim-Andrade et al., 2006)</td>
<td>IHS</td>
<td>Acupuncture</td>
<td>Acu: n = 16</td>
<td>Frequency: headache days, number of attacks Proportion of treatment</td>
<td>6 months</td>
<td></td>
<td>Acu: n = 2</td>
<td>Jadad: 1-1-1-1-1</td>
</tr>
<tr>
<td></td>
<td>vs Sham Acupuncture</td>
<td>vs Sham</td>
<td>SA: n = 15</td>
<td>respondents: percentage of patients with a reduction of &gt;=40% and 50%</td>
<td></td>
<td></td>
<td>WM: n = 1</td>
<td>IVS: 1-1-1-1-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acupuncture</td>
<td>WM: n = 15</td>
<td>in migraine attacks Duration: average duration of a migraine attack,</td>
<td></td>
<td></td>
<td>OPVS: 6-2-2-0-1-1-1-1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>total duration of pain per diary Intensity: average severity (0-3 scale)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Diener et al., 2006)</td>
<td>IHS</td>
<td>Acupuncture</td>
<td>Acu: n = 313</td>
<td>Frequency: the difference in migraine days Proportion of treatment</td>
<td>5 months</td>
<td></td>
<td>Acu: n = 23</td>
<td>Jadad: 1-1-0-0-1</td>
</tr>
<tr>
<td></td>
<td>vs SA vs WM</td>
<td>vs SA vs</td>
<td>SA: n = 339</td>
<td>respondents: percentage of patients with a reduction of &gt;= 50% in</td>
<td></td>
<td></td>
<td>WM: n = 22</td>
<td>IVS: 1-1-0.5-0.5-1-0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WM vs WM</td>
<td>WM: n = 308</td>
<td>migraine days</td>
<td></td>
<td></td>
<td>OPVS: 3-3-2-1-1-1-1-0</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Acupuncture vs</td>
<td>Acup: n</td>
<td>SA: n</td>
<td>WL: n</td>
<td>Outcome Measures</td>
<td></td>
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</tr>
<tr>
<td>(Linde et al., 2005a)</td>
<td>IHS</td>
<td>Acupuncture vs SA vs Waiting list</td>
<td>Acu: 145</td>
<td>SA: 81</td>
<td>WL: 76</td>
<td>Frequency: headache days; number of attacks; days with medication; difference in numbers of days with moderate or severe headache. Intensity (0-10 scale). Quality of life (SF-36). Disability (PDI). Emotional pain (SES). Depression (ADS). Working days lost. Proportion of patients with a reduction of &gt;= 50% in migraine attacks.</td>
<td>4 months</td>
<td>Acu: 29</td>
</tr>
<tr>
<td>(Linde et al., 2004)</td>
<td>IHS</td>
<td>Acupuncture vs SA</td>
<td>Acu: 17</td>
<td>SA: 14</td>
<td></td>
<td>Frequency: headache days; number of attacks; Intensity (0-10 VAS). Medication consumption (total sum).</td>
<td>6 months</td>
<td>Acu: 2</td>
</tr>
<tr>
<td>(Allais et al., 2003)</td>
<td>IHS</td>
<td>Acupuncture vs TENS vs Lasertherapy</td>
<td>Acu: 20</td>
<td>Tens: 20</td>
<td>Laser: 20</td>
<td>Frequency: headache days. Proportion of patients with a reduction of &gt;= 50% in migraine days.</td>
<td>2 months</td>
<td>Acu: 2</td>
</tr>
<tr>
<td>(Liguori et al., 2000)</td>
<td>Ad Hoc</td>
<td>Acupuncture vs WM</td>
<td>Acu: 60</td>
<td>WM: 80</td>
<td></td>
<td>Headache index: duration, intensity, quality of life.</td>
<td>45 weeks</td>
<td>Acu: 3</td>
</tr>
<tr>
<td>Study Authors and Year</td>
<td>Design</td>
<td>Acupuncture vs</td>
<td>n Acupuncture</td>
<td>n Sham Acupuncture</td>
<td>Outcome Measures</td>
<td>Duration</td>
<td>Jadad</td>
<td>IVS</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Pintov et al., 1997</td>
<td>Prensky</td>
<td>Acupuncture vs SA</td>
<td>Acu: n = 12</td>
<td>SA: n = 10</td>
<td>Frequency: number of attacks Duration Intensity (0-10 VAS)</td>
<td>10 weeks</td>
<td>No</td>
<td>1-0-1-1-1</td>
</tr>
<tr>
<td>Wylie et al., 1997</td>
<td>IHS</td>
<td>Acupuncture vs massage plus relaxation</td>
<td>Acu: n = 13</td>
<td>Control: n = 14</td>
<td>Frequency: pain total index, headache index Duration: totally hours Intensity (1-3 scale)</td>
<td>Not report</td>
<td>Not report</td>
<td>1-0-0-0-0</td>
</tr>
<tr>
<td>Hesse et al., 1994</td>
<td>IHS</td>
<td>Acupuncture plus placebo WM vs WM</td>
<td>Acu + Placebo: n = 40</td>
<td>WM: n = 41</td>
<td>Frequency: number of attacks Intensity (3-point scale) Duration Global rating of migraine (intensity, duration and symptoms) Medication consumption</td>
<td>No</td>
<td>Acu + Placebo: n = 2</td>
<td>WM: n = 2</td>
</tr>
<tr>
<td>Vincent, 1989a</td>
<td>IHS</td>
<td>Acupuncture vs SA</td>
<td>Acu: n = 16</td>
<td>SA: n = 16</td>
<td>Frequency: headache days Intensity (0-5 scale): peak pain, total pain score per week Medication consumption Anxiety scales Pain behaviour scale</td>
<td>1 year</td>
<td>Acu: n = 1</td>
<td>SA: n = 1</td>
</tr>
<tr>
<td>Dowson et al., 1985</td>
<td>Ad Hoc</td>
<td>Acupuncture vs Mock TENS</td>
<td>Acu: n = 25</td>
<td>SA: n = 23</td>
<td>Frequency: self-defined respondent rate Intensity (0-6 scale) Duration Medication consumption</td>
<td>24 weeks</td>
<td>Acu: n = 4</td>
<td>SA: n = 4</td>
</tr>
</tbody>
</table>

WM = Western Medication; PWM = Placebo Western Medication; PDI = Pain Disability Index; SES = Schemerzempfindungs-Skala (assessing emotional scale)

ADS = Depression Scale; AC = Allocation Concealment; SA = Sham Acupuncture; WL = Waiting List; UC = Usual Care

TENS = Transcutaneous Electrical Nerve Stimulation
Allocation concealment:

A: Indicates adequate concealment of the allocation (e.g. by telephone randomisation, or use of consecutively numbered, sealed, opaque envelopes)

B: Indicates uncertainty about whether the allocation was adequately concealed (e.g. where the method of concealment is not known)

C: Indicates that the allocation was definitely not adequately concealed (e.g. open random number lists or quasi-randomisation such alternate days, odd/even date of birth, or hospital number)

D: Indicates the score was not assigned, i.e. not used.
4.4.3 Quality Assessment

Jadad, IVS, OPVS and STRICTA were used to assess the quality of the included studies (see chapter three for a detailed description of the methods). The results are provided in Table 1. Studies scoring 3 or more in Jadad, 3.5 in IVS and 10 in OPVS were considered as high quality, which is 60% of the maximum possible score.

The median Jadad score was 3 (range 1-5) out of a possible score of 5; the median IVS was 4 (range 1.5 - 6) out of 6; and the median OPVS was 12 (range 7 - 16) out of 16. Ten of the 15 studies were of good quality in Jadad. However, two of the five studies with poor quality achieved 1 point only in randomization (Wylie et al., 1997, Liguori et al., 2000). Based on the IVS, eleven of the included 15 studies were of high quality. There was one study having 1.5 in IVS (Wylie et al., 1997). In OPVS, 13 papers had 10 or more points and were considered as high quality.

All 15 trials were described as randomised studies; consequently, a score of 1 or 0.5 was given to item one in Jadad and IVS. In seven studies the method of randomisation was briefly mentioned; these were considered as an “unclear” concealment allocation hence “B” was coded. Eight trials reported the allocation approaches clearly and the methods were appropriate therefore “A: adequate” was coded. No studies were coded as “C: Inadequate” or “D: not used”.

Furthermore, in nine of the 15 studies the participants were blinded and details regarding the process of blinding was reported. Two of the nine studies tested the credibility of sham control (Alecrim-Andrade et al., 2006, Vincent, 1989a); consequently, 1 or 0.5 points were granted to the fourth item of Jadad or IVS. The involvement of blinding the assessor was reported in nine of 15 studies, thereby scoring 1 in the fifth item of IVS.
Two of 15 studies did not report participant drop-outs (Melchart et al., 2003a, Liguori et al., 2000, Wylie et al., 1997), the other 13 studies gained one point in Jadad for reporting drop-outs. In five studies, a drop-out rate over 10% was reported, and three of these studies (Diener et al., 2006, Allais et al., 2003, Dowson et al., 1985) did not use the intention-to-treat analysis, therefore 0 was given in the last item of OPVS. Two other studies (Liguori et al., 2000, Wylie et al., 1997) did not report drop-out rates, and therefore did not score any points on this item.

In six studies, either the comparability of demographic data or the comparability in baseline characteristics of headache data between treatment and control groups was not reported. Therefore these six studies scored 0.5 on the 3rd item of IVS on the basis that some did not report the comparability of demographic data and some did not report the comparability of the headache data (Streng et al., 2006, Diener et al., 2006, Linde et al., 2005a, Pintov et al., 1997, Hesse et al., 1994, Vincent, 1989a).

Eight of the 15 included studies stated that both the demographic data and the outcome measures of the baseline were comparable. The remaining three papers (Wylie et al., 1997, Liguori et al., 2000, Dowson et al., 1985) did not mention comparability or the data was not comparable, therefore 0 was given on the 3rd item of IVS. All of the studies presented mean and standard deviations of demographic data or the outcome measures of baseline or post-treatment and were awarded one point each for data presentation, and for choosing an appropriate statistical test in OPVS.

All in all, the included studies had a moderate quality.
4.4.4 STRICTA

Consistent with the moderate reporting quality, most of the studies also achieved satisfactory results in STRICTA, reporting quality of intervention. Only four trials did not provide exact acupoints. One study did not provide treatment regimes and merely stated that dry needling treatment was conducted on the individual tender trigger points (Hesse et al., 1994). All 15 trials gave detailed information for co-interventions and the control interventions. The item that had the poorest reporting was information on the background or the qualifications of acupuncturists. Seven studies did not include this information. Detailed data about STRICTA is given in Table 7.
Table 7 Details of acupuncture and control interventions of the 15 included studies

<table>
<thead>
<tr>
<th>Author and date</th>
<th>Study Intervention</th>
<th>Type of Acupuncture Treatment</th>
<th>Acupuncture points &amp; Needling</th>
<th>Other treatment</th>
<th>Treatment Regime</th>
<th>Practitioner Background</th>
<th>Control Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author and date</td>
<td>Study Intervention</td>
<td>Type of Acupuncture Treatment</td>
<td>Acupuncture points &amp; Needling</td>
<td>Other treatment</td>
<td>Treatment Regime</td>
<td>Practitioner Background</td>
<td>Control Intervention</td>
</tr>
<tr>
<td>(Melchart et al., 2003b)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture plus complementary points based on associated symptoms of migraine</td>
<td>Ex-HN5, GB8, GB10, GB14, GB15, GB20, GB41, GV20, LI4, LR3, SJ5 Complementary points: not mentioned De Qi mentioned</td>
<td>No</td>
<td>Once only, 1.5h (range, 0.5-2.1)</td>
<td>Experienced Chinese acupuncturists</td>
<td>Sumatriptan: 6 mg in 1 ml NaCl solution Placebo: 1 ml NaCl solution</td>
</tr>
<tr>
<td>(Streng et al., 2006)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture plus complementary points based on TCM syndrome differentiation and location of pain</td>
<td>Ex-HN5, GB20, GB40/41/42, GV20, LR3, SJ3/5 Ashi points De Qi mentioned</td>
<td>No</td>
<td>8-15 sessions during 12 weeks</td>
<td>At least 140 hours of acupuncture training</td>
<td>Metoprolol 100-200 mg o.d. daily</td>
</tr>
<tr>
<td>(Alecrim-Andrade et al., 2006)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture plus complementary points based on location of pain</td>
<td>BL10, GB12, GB20, GB21 Complementary points: BL60, SI3 or BL2, GV23, LI4, ST36 or GB8, GB34, SJ5 or DU20, LR3, SI3 or SP6 or LR3 De Qi mentioned</td>
<td>No</td>
<td>2/w for 4 weeks 1/w for 8 weeks 16 sessions during 12 weeks</td>
<td>N/A</td>
<td>Sham acupuncture: minimal acupuncture Ex-B1, LU5, SP7, ST37, SJ17, SJ20 16 sessions during 12 weeks</td>
</tr>
<tr>
<td>Study</td>
<td>Acupuncture Strategy</td>
<td>Acupoints/Points Details</td>
<td>Training Requirements</td>
<td>Sessions Details</td>
<td>Prophylactic Treatment</td>
<td>Sham Acupuncture Details</td>
<td></td>
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</tr>
<tr>
<td>(Diener et al., 2006)</td>
<td>Acupuncture alone</td>
<td>Acupoints were not mentioned; Ashi points; De Qi mentioned</td>
<td>No</td>
<td>2/w or 10 sessions during 6 weeks</td>
<td>At least 140 hours of acupuncture training and 2 years’ acupuncturist experience</td>
<td>Sham acupuncture: minimal acupuncture on unacupoints; Standard migraine prophylactic treatment</td>
<td></td>
</tr>
<tr>
<td>(Linde et al., 2005a)</td>
<td>Acupuncture alone</td>
<td>Ex-HN5, GB20, GB40/41/42, GV20, LR3, SJ3/5; Complementary points: not mentioned; De Qi mentioned</td>
<td>No</td>
<td>2/w for 4 weeks 1/w for 4 weeks 12 sessions during 8 weeks</td>
<td>At least 140 hours of acupuncture training and experienced in acupuncture</td>
<td>Sham acupuncture: minimal acupuncture on unacupoints; Waiting list: without prophylactic treatment</td>
<td></td>
</tr>
<tr>
<td>(Linde et al., 2004)</td>
<td>Acupuncture alone</td>
<td>GB8, GB20, LI4, LR3, SP6; Complementary points: BL10 or Ex-HN5 or GB14; De Qi mentioned</td>
<td>No</td>
<td>3/M for 3 months 9 sessions during 3 months</td>
<td>Experienced physiotherapist</td>
<td>Sham acupuncture: blunt placebo needles</td>
<td></td>
</tr>
<tr>
<td>(Vickers et al., 2004a)</td>
<td>Acupuncture alone</td>
<td>Not mentioned</td>
<td>No</td>
<td>12 sessions during 12 weeks</td>
<td>A minimum of 250 hours of postgraduate training</td>
<td>Usual care: avoid acupuncture</td>
<td></td>
</tr>
<tr>
<td>(Allais et al., 2003)</td>
<td>Acupuncture alone</td>
<td>Ex-HN5, GB20, GV20, LI4, LR3, SP6; Complementary points: BL10 or GB14 or GB21 or CV12, ST36 or HT7; De Qi mentioned</td>
<td>No</td>
<td>2/w for 2 weeks 1/w for 6 weeks 10 sessions during 8 weeks</td>
<td>Experienced and qualified acupuncturists</td>
<td>TENS: BL2, Ex-HN5, GB20, GB21, LI4, SI3; Laser therapy: Ex-HN5, GB14, GB20, GV20,</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Formula acupuncture</td>
<td>De Qi</td>
<td>Frequency</td>
<td>Duration</td>
<td>Therapists/Adjuvants</td>
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<tr>
<td>(Allais et al., 2002)</td>
<td>Acupuncture alone</td>
<td>CV12, Ex-HN5, GB14, GB20, GV20, LI4, LR3, PC6, SP6, ST36</td>
<td>N0</td>
<td>1/w for 8 weeks 1/4 w for 16 weeks 12 sessions during 24 weeks</td>
<td>Experienced and qualified acupuncturists</td>
<td>Flunarizine 10 mg daily for 2 months then, 20 days per month for 4 months</td>
<td></td>
</tr>
<tr>
<td>(Liguori et al., 2000)</td>
<td>Acupuncture alone</td>
<td>GB5, GB20, GV14, LU7, ST8, De Qi mentioned</td>
<td>No</td>
<td>2/w 10 sessions during 7 weeks</td>
<td>Not report</td>
<td>Flunarizine 90 mg/d Nimodipine 90 mg/d Dihydroergotamine 10 mg/d Some participants also accept TENS as well</td>
<td></td>
</tr>
<tr>
<td>(Pintov et al., 1997)</td>
<td>Acupuncture alone</td>
<td>Not report</td>
<td>No</td>
<td>1/w for 10 weeks 10 sessions during 10 weeks</td>
<td>Not report</td>
<td>Sham acupuncture: minimal acupuncture</td>
<td></td>
</tr>
<tr>
<td>(Wylie et al., 1997)</td>
<td>Acupuncture alone</td>
<td>Pick up points from the following: BL2, GV20, Ex-HN5, Ex-HN3, GB14, GB20, GB41, KI3, LI4, PC6, SJ5, SP6, ST36, ST40 Complementary points: Ashi points</td>
<td>No</td>
<td>1/ day for 6 days 6 sessions during 6 days</td>
<td>Not report</td>
<td>Massage plus relaxation</td>
<td></td>
</tr>
<tr>
<td>(Hesse et al., 1994)</td>
<td>Dry needling</td>
<td>Individual tender trigger points</td>
<td>Placebo tablets</td>
<td>Not specified</td>
<td>Not report</td>
<td>Metoprolol 100 mg daily for 17 weeks</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Type</td>
<td>Acupuncture Points</td>
<td>Complementary Points</td>
<td>Comparator</td>
<td>Duration</td>
<td>Comparator Details</td>
<td>Sham Comparator</td>
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<td>----------------------------------------------------------------------</td>
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<td>-------------------------------------------</td>
<td>-----------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>(Vincent, 1989a)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture plus complementary points based on associated symptoms of migraine</td>
<td>Ex-HN5, LR3 Complementary points: GB20/BL10 or BL11/GB21/SJ15/SI14/SI15</td>
<td>No</td>
<td>1/w for 6 weeks 6 sessions during 6 weeks</td>
<td>Not report</td>
<td>Sham acupuncture: minimal acupuncture on unacupoints</td>
</tr>
<tr>
<td>(Dowson et al., 1985)</td>
<td>Acupuncture alone</td>
<td>Acupoints based on associated the location of pain</td>
<td>Not report</td>
<td>No</td>
<td>1/w for 6 weeks 6 sessions during 6 weeks</td>
<td>Not report</td>
<td>Mock TENS</td>
</tr>
</tbody>
</table>
4.4.4.1 Acupuncture Intervention

Among the 14 studies that used acupuncture as the treatment, 11 trials implemented formula acupuncture; one paper did not provide detailed information (Pintov et al., 1997); one study allowed the treating acupuncturists to choose acupoints based on individual discretion (Vickers et al., 2004a); the remaining study chose acupoints based on the location of pain without description of these points (Dowson et al., 1985). Furthermore, nine of 11 formula acupuncture trials also included complementary points selected according to the traditional Chinese medicine (TCM) syndrome differentiation. The remaining two trials used formula points only (Liguori et al., 2000, Allais et al., 2002).

De qi, a sensation of numbness, heaviness, distension or irradiation, was considered as essential for clinical efficacy according to traditional Chinese medicine (Shanghai College of TCM, 1980) and was reported in nine studies.

The treatment regimen is an essential part of treatment, and includes treatment frequency and duration in the STRICTA. The objective of one study was to test the effectiveness of acupuncture for acute migraine, therefore the acupuncture treatment was conducted once only and was observed for 48 hours (Melchart et al., 2003a). Another study did not report the treatment regimen, which used dry needling (Hesse et al., 1994). In the remaining 13 studies, the median treatment period was 8 weeks (range 1 – 24 weeks), with an average of 10 treatment sessions (range 6 - 16). In addition, the frequency of treatment was different among the studies. The most frequent treatment, once per day, occurred in Wylie’s study (Wylie et al., 1997). The study with the least frequent treatment used three treatment sessions per month (Linde et al., 1997). There were two (Diener et al., 2006, Liguori et al., 2000) and three (Pintov et al., 1997, Vincent, 1989a, Dowson et al., 1985) trials which implemented twice a week and weekly treatment, respectively. In four trials, the frequency of treatment reduced
during the trial. Three of these four trials used twice a week treatment for two to four weeks, followed by weekly treatment for four to eight weeks (Alecrim-Andrade et al., 2006, Linde et al., 2005a, Allais et al., 2003); the remaining one study used weekly treatment for eight weeks followed by once per four-week treatment for 16 weeks (Allais et al., 2002). The remaining three papers did not report the relevant information (Streng et al., 2006, Vickers et al., 2004a, Hesse et al., 1994).

The most common acupoints used in trials were: Yintang EX-HN5, Baihui DU 20, Fengchi GB20, Hegu LI4, and Taichong LR3.

### 4.4.4.2 Control Intervention

In all 15 trials, eight included placebo control, including three three-arm studies (Diener et al., 2006, Linde et al., 2005a, Melchart et al., 2003a), in which at least one control intervention is a placebo. Among these eight trials, one applied mock TENS (Dowson et al., 1985); one used intravenous injection with 1 ml NaCl solution as placebo medication (Melchart et al., 2003a); the rest six used sham acupuncture, including one study that used minimal acupuncture on acupoints (Alecrim-Andrade et al., 2006); three studies used minimal acupuncture on non-acupoints; one paper used minimal acupuncture without clear description (Pintov et al., 1997); and one implemented blunt placebo needles(Linde et al., 2004).

Nine trials included one to two active control interventions. Six of the trials used Western medication as the control intervention. Two trials used usual care (avoid acupuncture) (Vickers et al., 2004a) and massage plus relaxation as control (Wylie et al., 1997). The remaining study compared acupuncture with TENS and laser therapy separately (Allais et al., 2003).
Prophylactic medications were used by five out of six trials, in which Western medication was the control intervention. The remaining study used Sumatriptan for acute attack (Melchart et al., 2003a).

4.4.4.3 Follow-up

One paper did not provide the follow-up information (Wylie et al., 1997). Melchart and his colleagues (2003a) wanted to test the efficiency of acupuncture in preventing acute attacks, hence no follow-up period was involved. Furthermore, another two trials did not monitor the data after treatment was terminated (Allais et al., 2002, Hesse et al., 1994). The median of follow-up period in the other 11 studies was six months (ranging from 2.5-12 months).

Due to the length of the follow-up period varying considerably between the remaining studies, we could not evaluate the long-term effects of acupuncture. The length of the follow-up period ranged between two to twelve months depending on the study, hence the results from the follow-up periods did not provide comparable data. The data extracted from last phase of treatment was used in the analysis for evaluating the effectiveness of acupuncture.

4.4.5 Outcome Measures

The outcomes used in these trials were frequency, intensity and duration of migraine, medication consumption, quality of life, emotional pain, disability and depression. Fourteen of 15 trials monitored the frequency of migraine, using headache days, the numbers of attacks, pain-free days or a headache index. The remaining one study tested the immediate effect of acupuncture for acute attacks, hence no frequency data was available. All of the 14 studies observed the intensity of pain, via a series of measurements, such as 0-10 VAS, 0-100 VAS or pain index. Seven trials adopted medication consumption as one of the outcome measures.
Pill accounts were used by five studies but only two studies provided this data. A Medication Quantification Scale (MQS) was used by two studies. The next common outcomes were respondent rate and duration of attacks, which was adopted by six and five studies respectively. Quality of life was assessed by five studies, including three of them using SF-36 and the remaining two employing SF-12.

Due to the inconsistent types of outcome measurements used in the 15 studies, the effectiveness of acupuncture in the following aspects were evaluated: the number of days with migraine; the number of migraine attacks per month; the intensity of pain as well as patient respondent rate. The dates of medication consumption were provided by four studies with different control interventions. Consequently, no meta-analysis could be conducted. A similar situation also applied to information regarding quality of life.

4.5 Analysis

Trials were divided into two groups to investigate the acute analgesic and prophylactic effect of acupuncture for migraine respectively. Moreover, these two groups contained three sub-groups according to the control interventions for analysis. These three sub-groups were categorised into i) no treatment ii) “sham/placebo” acupuncture and iii) other interventions.

One study, conducted by Vickers and his colleagues (2004a), used usual care (avoid acupuncture) as the control intervention, is not appropriate to be divided into any sub-groups. This study found that acupuncture can prevent migraine attack in frequency, intensity as well as can reduce the medication consumption. Furthermore, the effectiveness of acupuncture was found to be best in patients who have more than five days with migraine per month.
4.5.1 The Effectiveness of Acupuncture in Acute Attacks

4.5.1.1 Acupuncture VS. No Treatment

There was no study under this comparison.

4.5.1.2 Acupuncture VS. Sham/Placebo Acupuncture

No study was available in this comparison.

4.5.1.3 Acupuncture VS. Western Medication

One trial only was conducted by Melchart and his colleagues (2003a) to assess the effectiveness of acupuncture for acute attacks. Participants were recruited into the study when they felt the first symptom of migraine and were randomised into acupuncture, Western medication (Sumatriptan) and placebo (1 ml NaCl solution) groups. The migraine of participants was monitored for 48 hours. The researchers found that 1st injection of sumatripan injection prevented migraine attacks in 36% of the participants, similar to the acupuncture group with a 35% success rate (Figure 5).

4.5.1.4 Acupuncture VS. Other Sham Interventions

In the study mentioned above, researchers found acupuncture was more effective, and prevented the migraine attacks in 35% of the participants in comparison to 18% prevented by the placebo injection. The difference between acupuncture and placebo was statistically significant (p = 0.04) (RR = 1.94; 95% CI, 1.06-3.07) (Figure 6).
### Figure 5: Acupuncture vs. Western medication in acute attack

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>acupuncture n/N</th>
<th>Western medication n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melchart et al. 2003</td>
<td>21/60</td>
<td>21/58</td>
<td>1.00 (0.89, 1.07)</td>
<td>100.00</td>
<td>0.97 (0.89, 1.07)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>60</td>
<td>58</td>
<td></td>
<td>100.00</td>
<td>0.97 (0.89, 1.07)</td>
</tr>
</tbody>
</table>

Total events: 21 (acupuncture), 21 (Western medication)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
Figure 6: Acupuncture vs. placebo injection in acute attack
4.5.2 The Effectiveness of Acupuncture as a Prophylactic Treatment

4.5.2.1 Acupuncture VS. No Treatment

There was only one paper in this comparison (Linde et al., 2005a). A total of 221 participants were randomly divided into acupuncture (n = 145) and waiting list (n = 76). Baseline data was comparable. Participants in the waiting list group did not receive any prophylactic treatment during the 12-week treatment period. After 12-weeks of treatment, acupuncture achieved significant improvements in the number of migraine attacks (Figure 7), intensity of migraine (Figure 8), medication usage and accompanying symptoms and activities impairment when compared with the waiting list ($p < 0.001$ in all above outcomes).
**Review:** The Prophylactic Effectiveness of Acupuncture on Migraine in English Literature
**Comparison:** 07 acupuncture vs. no treatment
**Outcome:** 02 acupuncture vs. waiting list in number of migraine attacks

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>acupuncture Mean (SD)</th>
<th>waiting list Mean (SD)</th>
<th>VMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>VMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linde et al. 2005</td>
<td>145</td>
<td>1.50 (1.20)</td>
<td>76 2.80 (1.10)</td>
<td>100.00 -0.80 [-1.12, -0.48]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 4.98 (P < 0.00001)

Figure 7: Acupuncture vs. no treatment in the number of migraine attacks
**Review:** The Prophylactic Effectiveness of Acupuncture on Migraine in English Literature

**Comparison:** Acupuncture vs. no treatment

**Outcome:** Acupuncture vs. waiting list in intensity of migraine

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>acupuncture</th>
<th>waiting list</th>
<th>VMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>VMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linde et al. 2005</td>
<td>145 3.70 (2.00)</td>
<td>76 5.60 (2.10)</td>
<td>[ ] 100.00</td>
<td>-1.90 [(-2.47, -1.33)]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>145</td>
<td>76</td>
<td>[ ] 100.00</td>
<td>-1.90 [(-2.47, -1.33)]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable

Test for overall effect: Z = 8.49 (P < 0.00001)

![Figure 8: Acupuncture vs. no treatment in the intensity of migraine](image)

Figure 8: Acupuncture vs. no treatment in the intensity of migraine
4.5.2.2  Acupuncture VS. Sham/Placebo Acupuncture

Sham or placebo acupuncture was compared with real acupuncture in seven trials. Two of the seven papers did not present any detailed data of pre-planned outcome measurements (Alecrim-Andrade et al., 2006, Dowson et al., 1985, Vincent, 1989a), though they stated they assessed the frequency and intensity etc. No data can be exacted from the above two papers. The remaining five studies presented at least one of the pre-planned outcomes in mean (SD). The intensity of migraine was presented in four studies (Linde et al., 2004, Linde et al., 2005a, Diener et al., 2006, Pintov et al., 1997). Furthermore, numbers of migraine attacks and global responses were reported by three trials. Detailed information is listed in Table 8.

Table 8: Outcome measures included in trials comparing real acupuncture with sham/placebo acupuncture

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intensity</th>
<th>Migraine days</th>
<th>Number of Attacks</th>
<th>Global responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Alecrim-Andrade et al., 2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Diener et al., 2006)</td>
<td>√</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>(Linde et al., 2005a)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>(Linde et al., 2004)</td>
<td>√</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>(Pintov et al., 1997)</td>
<td>√</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>(Vincent, 1989a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Dowson et al., 1985)</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>
Three comparisons were conducted to evaluate the effectiveness of acupuncture in relation to the intensity of migraine, number of migraine attacks and overall improvement (respondent rate). Significant heterogeneity was indicated by $I^2$ statistic (88.4%, 93.5%), and a random-effects model was applied to the first two comparisons. Moreover, as different measurements were conducted for assessing the intensity of migraine, such as 0-100 VAS or 0-10 VAS, the standardised mean difference (SMD) was applied in the meta-analysis. As indicated in Figure 9, Figure 10 and Figure 11, acupuncture was not statically significantly better than sham/placebo acupuncture with regard to the intensity of migraine ($p = 0.4$, SMD -0.25; 95% CI -0.83 to 0.33), number of migraine attacks ($p = 0.17$, WMD -2.41; 95% CI -5.87 to 1.06), and global response ($p = 0.35$, RR 1.07; 95% CI 0.93 to 1.25).
**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean (SD)</th>
<th>N</th>
<th>Mean (SD)</th>
<th>SMD (random)</th>
<th>Weight</th>
<th>SMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prtov et al. 1997</td>
<td>12</td>
<td>3.30 (1.00)</td>
<td>10</td>
<td>6.20 (0.40)</td>
<td>-3.38 [-4.96, -2.11]</td>
<td>11.29</td>
<td></td>
</tr>
<tr>
<td>Linde et al. 2004</td>
<td>15</td>
<td>4.10 (1.20)</td>
<td>13</td>
<td>3.40 (1.30)</td>
<td>0.48 [-0.21, 1.00]</td>
<td>21.98</td>
<td></td>
</tr>
<tr>
<td>Linde et al. 2005</td>
<td>145</td>
<td>3.70 (2.00)</td>
<td>81</td>
<td>3.60 (2.10)</td>
<td>0.05 [-0.22, 0.32]</td>
<td>32.37</td>
<td></td>
</tr>
<tr>
<td>Diener et al. 2006</td>
<td>290</td>
<td>53.50 (19.10)</td>
<td>317</td>
<td>62.60 (18.90)</td>
<td>0.05 [-0.11, 0.21]</td>
<td>34.16</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>462</td>
<td></td>
<td>421</td>
<td></td>
<td>-0.25 [-0.83, 0.33]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi = 25.86, df = 3 (P < 0.0001), I² = 88.4%
Test for overall effect: Z = 0.83 (P = 0.40)

**Figure 9:** Acupuncture vs. sham/placebo acupuncture in the reduction of intensity of migraine
**Review:** The Prophylactic Effectiveness of Acupuncture on Migraine in English Literature

**Comparison:** Acupuncture VS. sham/placebo acupuncture

**Outcome:** Acupuncture VS. sham/placebo acupuncture in the numbers of migraine attacks

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>acupuncture N</th>
<th>Mean (SD)</th>
<th>sham/placebo acupuncture N</th>
<th>Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>V/MMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirlov et al. 1997</td>
<td>12</td>
<td>4.40 (1.60)</td>
<td>10</td>
<td>9.30 (1.40)</td>
<td></td>
<td>32.57</td>
<td>-7.90</td>
<td>[-9.15, -6.65]</td>
</tr>
<tr>
<td>Linde et al. 2004</td>
<td>13</td>
<td>2.80 (1.00)</td>
<td>13</td>
<td>1.90 (0.35)</td>
<td></td>
<td>33.52</td>
<td>0.60</td>
<td>[-0.12, 1.32]</td>
</tr>
<tr>
<td>Linde et al. 2005</td>
<td>14</td>
<td>1.50 (1.20)</td>
<td>81</td>
<td>1.60 (1.30)</td>
<td></td>
<td>33.91</td>
<td>-0.10</td>
<td>[-0.44, 0.24]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>172</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>-2.41</td>
<td>[-5.87, 1.06]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 147.65, df = 2 (P < 0.00001), I² = 98.6%

Test for overall effect: Z = 1.36 (P = 0.17)

Figure 10: Acupuncture vs. sham/placebo acupuncture in the numbers of migraine attacks
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Acupuncture n/N</th>
<th>sham/placebo acupuncture n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dowson et al. 1985</td>
<td>9/25</td>
<td>5/23</td>
<td>8.40 1.23 [0.50, 3.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linde et al. 2005</td>
<td>79/145</td>
<td>43/81</td>
<td>30.03 1.01 [0.79, 1.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diener et al. 2006</td>
<td>129/290</td>
<td>128/317</td>
<td>66.57 1.09 [0.91, 1.32]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>460</td>
<td>421</td>
<td>100.00 1.07 [0.93, 1.25]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 214 (Acupuncture), 177 (sham/placebo acupuncture)
Test for heterogeneity: Chi² = 0.32, df = 2 (P = 0.85), I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

Figure 11: Acupuncture vs. sham/placebo acupuncture in global responses
Acupuncture VS. Western Medication

Five studies compared acupuncture with Western medication. However, mean data was only presented in three studies. In the remaining two studies, data was presented using a headache index (Liguori et al., 2000) and mean data without standard deviation (Hesse et al., 1994). Consequently, meta-analysis was applied to data from three trials (Streng et al., 2006, Diener et al., 2006, Allais et al., 2002). The types of outcome measures used in the three studies are listed below in Table 9. The drugs used as control intervention in these five studies are standard preventive medication, and included four categories: Ca++ channel blocker (Nimodipine), antihistamines (Flunarizine), beta receptor blocker (Metoprolol) and 5-HT agonist (Sumatriptan).

Table 9: The outcome measures used by studies comparing real acupuncture with Western medication

<table>
<thead>
<tr>
<th></th>
<th>Intensity</th>
<th>Migraine days</th>
<th>Number of Attacks</th>
<th>Global responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Streng et al., 2006)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>(Diener et al., 2006)</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>(Allais et al., 2002)</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>(Liguori et al., 2000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Hesse et al., 1994)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Three comparisons were conducted to evaluate the effectiveness of acupuncture in terms of the intensity of migraine, number of migraine attacks and overall improvement (respondent rate). The random-effects model was used in comparisons to evaluate the action of acupuncture in intensity of migraine, because the $I^2$ statistic was 73.1%. Furthermore, inconsistent measurements in assessing the intensity of migraine led to the use of standardised mean difference.

Acupuncture was superior to Western medication in preventing migraine attacks ($p < 0.01$, WMD -0.63; 95% CI -0.7 to -0.56) (Figure 12), and at least as effective as Western medication in reducing the intensity of migraine ($p = 0.06$, SMD -0.39; 95% CI -0.79 to 0.01) (Figure 13) and global responses ($p = 0.08$, RR 1.19; 95% CI 0.98 to 1.46) (Figure 14). However, there was a trend for a statistically significant difference in these two aspects.
### Figure 12: Acupuncture vs. Western medication in the numbers of migraine attacks

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Acupuncture</th>
<th>Western medication</th>
<th>WMD (fixed)</th>
<th>Weight</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Allais et al. 2002</td>
<td>77</td>
<td>2.36 (0.20)</td>
<td>73</td>
<td>2.93 (0.24)</td>
<td>99.75</td>
</tr>
<tr>
<td>Strong et al. 2006</td>
<td>56</td>
<td>4.50 (3.60)</td>
<td>33</td>
<td>4.60 (3.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>133</td>
<td>4.93 (2.00)</td>
<td>106</td>
<td>5.00 (2.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chii = 0.54, df = 1 (P = 0.46), I² = 0%
Test for overall effect: Z = 17.40 (P < 0.00001)
Figure 13: Acupuncture vs. Western medication in the intensity of migraine
Review: The Prophylactic Effectiveness of Acupuncture on Migraine in English Literature
Comparison: 05 Acupuncture VS. western medication
Outcome: 03 Acupuncture vs. western medication in global responses

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>acupuncture ( n/N )</th>
<th>Western medication ( n/N )</th>
<th>RR (fixed) ( 95% ) CI</th>
<th>Weight %</th>
<th>RR (fixed) ( 95% ) CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dierer et al. 2006</td>
<td>128/290</td>
<td>79/187</td>
<td>0.67 (0.48, 0.88)</td>
<td>80.87</td>
<td>1.18 (0.94, 1.48)</td>
</tr>
<tr>
<td>Streng et al. 2006</td>
<td>34/56</td>
<td>15/33</td>
<td>1.38 (1.17, 1.62)</td>
<td>15.13</td>
<td>1.25 (0.83, 1.89)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>346/556</td>
<td>220</td>
<td></td>
<td>100.00</td>
<td>1.19 (0.98, 1.46)</td>
</tr>
</tbody>
</table>

Total events: 152 (acupuncture), 86 (Western medication)
Test for heterogeneity: \( \chi^2 = 0.06, df = 1 (P = 0.80), I^2 = 0\%
Test for overall effect: \( Z = 1.74 (P = 0.08) \)

Figure 14: Acupuncture vs. Western medication in global responses
4.6 Discussion

4.6.1 Summary of the Findings

To date, only one published study is available on acute attack. This study revealed that acupuncture was as effective as Western medicine, and superior to placebo injection, in stopping acute attacks.

As to the prophylaxis effect of acupuncture on migraine, three subgroups were identified according to different control interventions, namely i) no treatment ii) sham/placebo acupuncture iii) Western medication. However, only one corresponding study (Linde et al., 2005a) was identified regarding the use of acupuncture compared with no treatment; this study illustrates the greater effects of acupuncture on different aspects of migraine such as intensity, frequency of attack and medication consumption. Furthermore, there is moderate evidence from English literature supporting that acupuncture is as effective as Western medication for both abolishing and preventing migraine attacks. However, evidence supporting the value of acupuncture for the treatment and prevention of migraine when compared with sham/placebo acupuncture is conflicting due to the inconsistent results in multiple RCTs with moderate quality.

4.6.2 Strengths of This Review

As stated in the Guidelines for RCT on migraine by IHS (2000), evaluating the effectiveness of interventions for migraine should involve measuring different aspects, such as the frequency of attack, the number of days with migraine, intensity or respondent rate. This systematic review is the first study evaluating the effectiveness of acupuncture on different
features of migraine separately, such as intensity and the numbers of migraine attacks. Based on the comparisons between acupuncture and Western medication, the numbers of migraine attacks \( (p < 0.01) \) was more likely to be affected by acupuncture than the intensity of migraine \( (p = 0.06) \). Similar findings were detected by other studies (Tfelt-Hansen et al., 1984), indicating that in most cases where there is a decrease in headache index, this is due to a decrease in frequency of attacks.

### 4.6.3 Weaknesses of This Review

The major limitation of this SR is that we were not able to search databases in other languages, such as French, Italian and German. Moreover, though some non-English studies were indexed in the PubMed, we could not access them due to a lack of language assistance. However, it is unlikely the missing data would influence our findings. Three papers published in German (Heydenreich and Thiessen, 1989) (Schnorrenberger and Baust, 1979, Baust and Stürtzbecher, 1978), were published in 1980’s. It is likely they were of poor quality similar to other studies produced at that time.

Thirteen studies in Scott and Deare’s review (2006) were not included in the current review. The language barrier was not the only contributing factor. The different selection criteria might also have contributed to the difference of included studies. For instance, the following seven studies of Scott and Deare’s review were not included into our current review as they had conducted real acupuncture treatment in both groups and injected naloxone and saline respectively to test the effect of naloxone (Lenhard and Waite, 1983); did not report the migraine data separately (Loh et al., 1984); used various TCM therapies not limited to
acupuncture as treatment (Melchart et al., 2004a); even tested the changes of cerebrovascular response to visual stimulation in migraineurs after acupuncture compared with healthy volunteers (Bäcker et al., 2004); did not use either IHS or Ad Hoc’s classification to recruit participants (Gao et al., 1999, Ceccherelli, 1987, Agrò et al., 2005). Furthermore, we also included four studies, which were not mentioned in Scott and Deare’s SR (Allais et al., 2003, Streng et al., 2006, Liguori et al., 2000, Pintov et al., 1997).

4.6.4 Reporting of Outcome Measures

Fourteen of the 15 included studies aimed to test the prophylactic effect of acupuncture and used frequency as the primary outcome. However, two of them combined the frequency with intensity of migraine presenting a headache index. Furthermore, the measurements for the frequency of migraine varied from study to study. Five studies (Pintov et al., 1997, Allais et al., 2002, Streng et al., 2006, Linde et al., 2005a, Linde et al., 2004) adopted the number of migraine attacks as the outcome measure. Four studies (Allais et al., 2003, Vickers et al., 2004a, Linde et al., 2007c, Streng et al., 2006) used the number of days with migraine. Other studies used the percentage of participants with a reduction of 50% or more in migraine attacks or migraine days; the difference in migraine days between baseline and after treatment (Diener et al., 2006); or headache index and pain total index (Liguori et al., 2000, Wylie et al., 1997). In addition, two studies did not present data in mean (SD) (Alecrim-Andrade et al., 2006, Hesse et al., 1994), and one used self-defined respondent rates (Dowson, 2001). Hence the inconsistent measurements and data presentation make it difficult to extract information to evaluate the prophylactic effect of acupuncture. The same situation also occurred in the outcome assessments of quality of life and medication consumption.
Medication consumption is a tool for assessing the effect of acupuncture. Seven trials monitored the dosage of medication including analgesic drugs for acute pain and prophylaxis anti-migraine medication. These papers however used different methods to calculate and present data. Taking Allais’ trial (2002) as an example, the number of analgesic tablets was used. In fact, participants in that study not only took analgesics for acute attack, but also took anti-migraine medications, such as Sumatriptan, when they felt the first symptoms of migraine. Counting one type of medication, but not all medications used by patients, has certainly biased the results of Allais’ study. Furthermore, analgesics vary in strength. For instance, Panadeine and Panadeine Forte all belong to compound analgesics, and contain Paracetamol 500 mg plus codeine phosphate 8 mg, and Paracetamol 500 mg plus codeine phosphate 30 mg respectively. Obviously, the latter is stronger than the former. Four tablets of Panadeine Forte are nearly four times stronger than four pills of Panadine and therefore pill counting is not an accurate method for assessing medication consumption. To accurately measure medication consumption, the Medication Quantification Scale (MQS) published in 1998 is recommended. However, only one acupuncture study for headache used the MQS method (Vickers et al., 2004a). Another study (Vincent, 1989a) used the potency scale, which is the basis of the MQS.

Due to the use of a range of outcome measures, each meta-analysis only included one to four studies.
4.6.5  Heterogeneity of the Studies

There was a high heterogeneity among eight comparisons. Two comparisons contained one study each, consequently no heterogeneity existed. Three of the remaining six comparisons were highly heterogeneous ($I^2 > 50\%$). This is consistent with our findings that studies were of various sample sizes, using different treatment regimes, adopting different sham designs, and having various outcome measurements without detailed data presentation. Moreover, some included trials presented intention-to-treat data whereas others used per protocol data.

The design of sham/placebo acupuncture studies, a disputed issue (Lewith and Machin, 1983), varied from one study to another, including invasive or no-invasive needling, and choosing acupoints or non-acupoints. This problem is evident that the American Headache Society (AHS) emphasises the need for developing a reliable sham/placebo control for acupuncture studies in headache (Mauskop, 2001).

4.6.6  A Comparison with Other SRs

A comparison of findings from our review with those in the two previous SRs in general headache (Melchart et al., 2001) and migraine (Scott and Deare, 2006) is presented in Table 10. The Melchart review focused on general headache and included both English and European literature. Melchart also assessed the effectiveness of acupuncture for migraine separately. Unfortunately, most of the trials either did not present the detailed data or lacked consistent measurements. Scott and Deare’s review focussed on migraines only and used studies mainly published in English or European languages. The current systematic review identified papers published in English which focussed on migraine only.
Table 10: A comparison of our review and two other SRs of acupuncture for migraine.

<table>
<thead>
<tr>
<th></th>
<th>Current English review</th>
<th>Melchart et al</th>
<th>Scott and Deare</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size (median)</strong></td>
<td>81</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td><strong>Frequency of treatment</strong></td>
<td>mostly 1 - 2</td>
<td>1-2</td>
<td>mostly 1 - 2</td>
</tr>
<tr>
<td><strong>De qi sensation</strong></td>
<td>9 / 15 trials reported</td>
<td>9 / 26 trials reported</td>
<td>10 / 25 trials reported</td>
</tr>
<tr>
<td><strong>Jadad, Median (range)</strong></td>
<td>3 (1 - 5)</td>
<td>1.5 (1 - 4)</td>
<td>2.3 (1 - 5)</td>
</tr>
<tr>
<td><strong>IVS</strong></td>
<td>4 (1.5 - 6)</td>
<td>2.5 (1 - 4)</td>
<td>3 (0.5 - 6)</td>
</tr>
<tr>
<td><strong>Acupoint selection</strong></td>
<td>67% of the studies chose acupoints according to Chinese medicine individual syndrome differentiation or location of pain</td>
<td>N/A</td>
<td>44% of the studies chose acupoints according to Chinese medicine individual syndrome differentiation</td>
</tr>
<tr>
<td><strong>Control intervention</strong></td>
<td>Waiting list</td>
<td>Sham/placebo acupuncture</td>
<td>Physiotherapy (massage and relaxation)</td>
</tr>
<tr>
<td></td>
<td>Sham/placebo acupuncture</td>
<td>Waiting list</td>
<td>Waiting list</td>
</tr>
<tr>
<td></td>
<td>Western medications</td>
<td>Western medications</td>
<td>Standard GP care</td>
</tr>
<tr>
<td><strong>Respondent rate</strong></td>
<td>N/A</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Relative risk</strong> (acupuncture vs western medications)</td>
<td>1.19 (0.98 to 1.46)</td>
<td>N/A</td>
<td>1.38 (1.08 - 1.76) Favour acupuncture</td>
</tr>
<tr>
<td><strong>Relative risk</strong> (acupuncture vs sham/placebo acupuncture)</td>
<td>1.07 (0.93 to 1.25)</td>
<td>N/A</td>
<td>1.14 (0.98 - 1.34)</td>
</tr>
<tr>
<td><strong>Relative risk</strong> (acupuncture vs waiting list)</td>
<td>Intensity: WMD -0.8, 95% CI (-1.12, -0.48), P &lt; 0.01</td>
<td>N/A</td>
<td>3.17 (2.00 – 5.00) Favour acupuncture</td>
</tr>
<tr>
<td></td>
<td>Frequency: WMD -1.90, 95% CI (-2.47, -1.33), P &lt; 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In general, studies published in the current review had larger sample sizes, were of better quality, had a similar frequency of acupuncture treatment and used similar standard control interventions. Nine out of 15 studies in our review emphasised the achievement of Deqi sensation; this was more frequently than in the Melchart et al review (2001) where only 9 out of 26 trials emphasised achievement of Deqi sensation, and in Scott and Deare’s review (2006), where only 10 out of 25 studies emphasised achievement of Deqi sensation.

Sixty-seven percent of the English trials (10 out of 15 studies) used semi-standardised acupuncture treatment based on Chinese medicine syndrome differentiation or location of pain. In comparison, 44% of the trials reported in Scott’s review adopted this method.

We used the outcome measures presented in the studies for the meta-analysis. This is different from Scott and Deare’s or Melchart’s SRs in which the percentage of respondents was calculated from mean data presented by the authors. Their approach introduces another level of complexity to the already heterogeneous data. For instance, respondents could be defined as a 50% improvement (Melchart et al 2001) or a 33% improvement (Scott and Deare 2006). Furthermore, converting mean and SD to percentage of improvement could be a problem of its own. While our approach of using the original data reduced the available studies for analysis, it provides a more detailed understanding of how acupuncture could help migraine, such as reducing migraine frequency or intensity.
4.6. 7 Impacts on the Conclusion

Differences between the current and Scott and Deare’s reviews could lead to variations in conclusion. Both reviews concluded that acupuncture is significantly better than no treatment, however acupuncture was not superior to sham/placebo acupuncture. In this review we found that acupuncture was similar to Western medication in preventing migraine when respondent rates were used, however acupuncture was slighter better than Western medication in reducing the frequency of attacks. Scott and Deare’s review, using the respondent rate, concluded that acupuncture was superior to Western medication. This discrepancy might be due to the sample size as we only had two studies under this comparison whereas the other review has four studies. The conclusions of the two reviews highlight the importance of adopting a set of uniform, standard outcome measures in future trials.

4.7 Conclusion

4.7.1 Implications for Research

Over all, acupuncture is as effective as Western medication in managing migraine. However, due to the lack of consistent measurements in the monitoring of specific aspects of migraine (including frequency, intensity, medication consumption or quality of life), the overall effectiveness of acupuncture on migraine is still unknown. In the future, researchers are encouraged to use standard outcome measurements, adopt appropriate statistical methods, and present detailed data. More clinical studies of good quality are urgently needed. Furthermore, the cost-effectiveness of acupuncture also needs to be taken into account in future studies.
4.7.2 Implication for Clinical Practice

Acupuncture is an effective alternative to prophylaxis of migraine. It has few side effects, and can be used by patients who do not want, or cannot tolerate, anti-migraine medications. Due to the high heterogeneity existing among trials, we cannot recommend an ideal acupuncture treatment regime.
CHAPTER FIVE: SYSTEMIC REVIEW OF EAST ASIAN LITERATURE ON ACUPUNCTURE FOR MIGRAINE

5.1 Introduction

Currently available systematic reviews (SRs) on the topic of acupuncture and migraine focus primarily on published studies undertaken in Western countries; few studies published in Asian languages are incorporated into these SRs (Melchart et al., 2001, Griggs and Jensen, 2006a, Scott and Deare, 2006). The majority of Asian studies are neglected possibly due to language difficulties and a lack of access to the relevant databases (Melchart et al., 2001). In parts of Asia, such as China, Japan and Korea, acupuncture is widely used and therefore data from this region needs to be taken into consideration when determining the effectiveness and safety of acupuncture for migraine treatment.

5.2 Objectives

Through systematically reviewing Chinese, Japanese and Korean literature, the objectives of this review were to:

1) Determine whether acupuncture was
   - More effective than no treatment;
   - More effective than “sham/placebo” acupuncture; and
   - As effective as other interventions for migraine.

2) Compare East Asian and English literature on acupuncture and migraine.
5.3 Methodology

“Acupuncture (针灸),” “electro-acupuncture（电针）,” “Chinese medicine（中医药疗法）,”
“point-stimulation（穴位刺激）,” “headache（头痛）” and “migraine（偏头痛）” were used
as search parameters. These search terms were used to search the two largest Chinese
electronic databases Vi Pu (重庆维普, www.cqvip.com, inception 1989) and Wan Fang (万方
data, www.wanfangdata.com.cn, inception 1982) for papers published from the inception of
the databases to August 2006. The same search terms were searched for in Ichushi Web
(Japana Centra Revuo Medicina, www.jamas.or.jp, inception 1983) for papers published from
its inception to March 2008. The search terms were also searched for in the Korean databases
The National Assembly Library (www.nanet.go.kr), KoreaMed (www.koreamed.org), Journal
of Korean Oriental Medicine (www.koms.or.kr), the Journal of Korean Acupuncture &
Moxibustion Society (www.acumoxa.or.kr), the Korean Journal of Meridian & Acupoint
(www.acupoint.org) and Oriental Medicine Information System (www.omis.dhu.ac.kr) from
their inception to May 2007.

Identified papers were selected according to the criteria described in chapter three.

5.4 Results

5.4.1 Identifying Studies

In Chinese literature, of 266 papers found, 177 were either not RCTs, used Chinese herbs as
the active intervention, or did not have a valid control intervention. A further 55 papers were
excluded because they reported other types of headache. Two researchers assessed the
remaining 34 papers. Two were excluded because non-invasive acupuncture was used and
seven papers were excluded due to the use of point-injection alone as the treatment. A further eight papers were eliminated for not providing any clinically relevant outcome measures. Finally, a total of 17 studies were included and analyzed. The following flowchart (Figure 15) illustrates the process of identifying studies.

![Flowchart](image)

**Figure 15:** A flowchart illustrating the process of identifying Chinese studies

The Japanese data was searched through with the help of a Japanese expert. In total 290 articles were found, however, 289 of these articles were excluded as they were not RCTs. The remaining one study used acupuncture to treat neck stiffness, where headache was just an accessory symptom, and was therefore also excluded. Thus none of the Japanese studies were included in the current systematic review.
The search of Korean literature was conducted by a visiting Korean post-doctorate fellow in the Division of Chinese Medicine at RMIT University. The data was translated into English by a Korean student studying Chinese medicine in Australia. The data search selection was also verified by an Korean expert. Of the fifty-six publications found, 40 were excluded for not being a RCTs or because headache was just a symptom of the recruited participants. Another 15 publications reported other types of headache conditions or did not report data of migraine separately from other types of headache. The remaining one migraine study used blood flow of the brain as the measurement, which was not related to the pre-defined clinical outcome. This study was excluded. None of the Korean studies were therefore included into the current systematic review. The process of the identification of Korean studies is illustrated in the following flowchart (Figure 16).

![Flowchart](image)

Figure 16: A flowchart illustrating the process of Korean study identification
5.4.2 Description of the Studies

Table 11 summarises the characteristics of the 17 included Chinese studies. Sixteen trials adopted the IHS criteria for the diagnosis of migraine, and one trial used the Ad Hoc Committee’s criteria (Li et al., 1998). A total of 2097 participants (median 91; range 62 - 414) were included in our review.

All studies compared acupuncture with Western medication treatments. Ten studies used acupuncture alone. Six studies used a combined therapy of acupuncture with acupoint injection (Liu et al., 2002b), with intravenous injection of a purified Chinese herb (Wang and Gao, 2004), with Chinese Tuina (Shao et al., 2005, Lu and Yan, 2004), or with hyperbaric oxygen (Wang and Chen, 2004, Liu et al., 2002a). The remaining study compared acupuncture plus Western medication with Western medication alone (Wang and Gao, 2004, Zhang, 2005). None of the studies compared acupuncture with no-treatment control or sham/placebo acupuncture.
Table 11: Characteristics of included studies

<table>
<thead>
<tr>
<th>Author and Date</th>
<th>Intervention</th>
<th>Sample Population</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Drop-out</th>
<th>No. and percentage of respondent</th>
<th>Quality</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou, J.H. (2005)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 35 WM: n = 35</td>
<td>▲</td>
<td>6 months</td>
<td>No</td>
<td>Treatment: 21 / 35, 60% Control: 9 / 35, 25.7%</td>
<td>Jadad: 1-0-0-0-1 IVS: 0.5-0-0.5-0-0.1 OPVS: 0-3-2-0-1-1-0-1</td>
<td>C</td>
</tr>
<tr>
<td>Cui, R., et al (2004)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 48 WM: n = 38</td>
<td>▲</td>
<td>3 months</td>
<td>No</td>
<td>Treatment: 28 / 48, 58.3% Control: 17 / 38, 44.7%</td>
<td>Jadad: 1-0-0-0-1 IVS: 0.5-0-1-0-0-1 OPVS: 0-3-2-0-1-0-1</td>
<td>C</td>
</tr>
<tr>
<td>Wang, B. (2004)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 125 WM: n = 61</td>
<td>▲</td>
<td>N/A</td>
<td>No</td>
<td>Treatment: 100 / 125, 80% Control: 36 / 61, 59%</td>
<td>Jadad: 1-0-0-0-1 IVS: 0.5-0-1-0-0-1 OPVS: 0-3-2-0-1-0-1</td>
<td>B</td>
</tr>
<tr>
<td>Lao, J.X. (2003)</td>
<td>Electronic acupuncture vs Western medication</td>
<td>Acu: n = 87 WM: n = 61</td>
<td>▲</td>
<td>2 months</td>
<td>No</td>
<td>Treatment: 41 / 87, 47.1% Control: 14 / 61, 23%</td>
<td>Jadad: 1-0-0-0-1 IVS: 0.5-0-0.5-0-0-1 OPVS: 0-3-2-0-1-1-0-1</td>
<td>B</td>
</tr>
<tr>
<td>Zhou, L.S. (2003)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 43 WM: n = 20</td>
<td>▲</td>
<td>3 months</td>
<td>No</td>
<td>Treatment: 40 / 43, 93% Control: 15 / 20, 75%</td>
<td>Jadad: 1-0-0-0-1 IVS: 0.5-0-0.5-0-0-1 OPVS: 0-3-2-0-1-0-1</td>
<td>B</td>
</tr>
<tr>
<td>Liu, K.Y., et al (2001)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 43 WM: n = 43</td>
<td>▲ and frequency and duration</td>
<td>1 months</td>
<td>No</td>
<td>Treatment: 33 / 43, 76.7% Control: 25 / 43, 58.1% Frequency: 0.3 ± 1.4 vs 2.6 ± 1.6 Duration: 2.54 ± 1.37 vs 14.7 ± 15.6</td>
<td>Jadad: 1-0-0-0-1 IVS: 0.5-0-1-0-0-1 OPVS: 0-3-2-0-1-1-1-1</td>
<td>B</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Comparator 1</td>
<td>Comparator 2</td>
<td>Sample Size</td>
<td>Follow-up</td>
<td>Treatment Effect</td>
<td>Jadad Score</td>
<td>IVS Score</td>
<td>OPVS Score</td>
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<tr>
<td>Li, W. et al (1998)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 70 WM: n = 32</td>
<td>▲</td>
<td>N/A</td>
<td>Yes</td>
<td>Treatment: 37 / 70, 52.9% Control: 15 / 32, 46.9%</td>
<td>1-0-0-0-0</td>
<td>0.5-0-0-0-0-0.5</td>
</tr>
<tr>
<td>Chen, X.S. (1997)</td>
<td>Acupuncture vs Western medication</td>
<td>Acu: n = 45 WM: n = 30</td>
<td>■</td>
<td>6 months</td>
<td>No</td>
<td>Treatment: 30 / 45, 66.7% Control: 16 / 30, 53.3%</td>
<td>1-0-0-0-1</td>
<td>0.5-0-1-0-0-1</td>
</tr>
<tr>
<td>Shao, Y., et al (2005)</td>
<td>Electronic acupuncture plus massage VS Western medication</td>
<td>Acu: n = 35 WM: n = 33</td>
<td>▲</td>
<td>6 months</td>
<td>No</td>
<td>Short-term: Treatment: 26 / 35, 74.3% Control: 25 / 33, 75.8% After 6 months Treatment: 26 / 35, 74.3% Control: 17/33, 51.5%</td>
<td>1-0-0-0-1</td>
<td>0.5-0-0.5-0-0-1</td>
</tr>
<tr>
<td>Lu, Z.Q. (2004)</td>
<td>Acupuncture plus massage vs Western medication</td>
<td>Acu: n = 54 WM: n = 30</td>
<td>■</td>
<td>6 months</td>
<td>Yes (16)</td>
<td>Treatment: 35 / 46, 76.1% Control: 12 / 26, 46.2%</td>
<td>1-0-0-0-0</td>
<td>0.5-0-0.5-0-0-0.5</td>
</tr>
<tr>
<td>Wang J.L., et al (2004)</td>
<td>Acupuncture plus Chinese medicine injection vs Western medication</td>
<td>Acu: n = 60 WM: n = 60</td>
<td>■</td>
<td>6 months</td>
<td>No</td>
<td>Treatment: 37 / 60, 61.7% Control: 19 / 60, 31.7%</td>
<td>1-0-0-0-1</td>
<td>0.5-0-0.5-0-0-1</td>
</tr>
<tr>
<td>Liu Y., et al (2002)</td>
<td>Acupuncture plus acupoint injection vs Western medication</td>
<td>Acu: n = 54 WM: n = 52</td>
<td>■</td>
<td>8 weeks</td>
<td>No</td>
<td>Treatment: 41 / 54, 75.9% Control: 32 / 52, 61.5%</td>
<td>1-0-0-0-1</td>
<td>0.5-0-0.5-0-0-1</td>
</tr>
<tr>
<td>Wang, L.Q., et al (2004)</td>
<td>Acupuncture plus hyperbaric oxygen vs Western medication</td>
<td>Acu: n = 63 WM: n = 28</td>
<td>●</td>
<td>1 year</td>
<td>No</td>
<td>Treatment: 53 / 63, 84.1% Control: 33 / 56, 58.9%</td>
<td>1-0-0-0-1</td>
<td>0.5-0-0.5-0-0-1</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Acu: n = 256 WM: n = 158</td>
<td>Jadad: 1-0-0-0-1</td>
<td>IVS: 0.5-0-1-0-0-1</td>
<td>OPVS: 0-3-2-0-1-1-0-1</td>
<td>Treatment: 103 / 256, 40.2% Control: 50 / 158, 31.6%</td>
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<tr>
<td>Liu X.L., et al</td>
<td>Acupuncture plus hyperbaric oxygen vs Western medication</td>
<td>■</td>
<td>N/A</td>
<td>No</td>
<td>A: indicates adequate concealment of the allocation (e.g. by telephone randomisation, or use of consecutively numbered, sealed, opaque envelopes). B: indicates uncertainty about whether the allocation was adequately concealed (e.g. where the method of concealment is not known). C: indicates that the allocation was definitely not adequately concealed (e.g. open random number lists or quasi-randomisation such alternate days, odd/even date of birth, or hospital number). D: indicates the score was not assigned, i.e. not used.</td>
<td></td>
<td></td>
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<td>(2002)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zhang, Y.K.</td>
<td>Acupuncture plus medication vs Western medication</td>
<td>Headache index</td>
<td>No</td>
<td>No</td>
<td>B: indicates uncertainty about whether the allocation was adequately concealed (e.g. where the method of concealment is not known). C: indicates that the allocation was definitely not adequately concealed (e.g. open random number lists or quasi-randomisation such alternate days, odd/even date of birth, or hospital number). D: indicates the score was not assigned, i.e. not used.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No: No difference

A: indicates adequate concealment of the allocation (e.g. by telephone randomisation, or use of consecutively numbered, sealed, opaque envelopes). B: indicates uncertainty about whether the allocation was adequately concealed (e.g. where the method of concealment is not known). C: indicates that the allocation was definitely not adequately concealed (e.g. open random number lists or quasi-randomisation such alternate days, odd/even date of birth, or hospital number). D: indicates the score was not assigned, i.e. not used.
5.4.3 Quality Assessment

The median Jadad score was 2 (range 1-2) out of a possible score of 5; the median IVS was 2.0 (range 1.5 - 2.5) out of 6; and the median OPVS was 8 (range 7 - 9) out of 16. None of the 17 studies had more than 60% of a maximum score of Jadad, IVS or OPVS.

All 17 trials were described as randomised studies. Six studies in which the method of randomisation was briefly mentioned used the order of admission or date of birth to allocate participants. These six studies can be considered as quasi-randomised, hence “C Inadequate” was coded for the six studies. The remaining twelve studies were in Category B because it is unclear if and how the allocation concealment was conducted. Detailed information about allocation concealment was absent in eleven studies, one trial merely stated the sortition method was used (Lao and Lai, 2002).

Furthermore, no study reported details regarding the process of blinding. The participants were not blinded to the treatment allocation because Western medications were the control intervention. The blinding of assessors was not reported in any of the studies. All studies gained one point for reporting drop-outs. In two studies, a drop-out rate of less than 10% was reported (Lu and Yan, 2004, Li et al., 1998). The remaining studies did not have any drop-outs.

Only two trials (Liu et al., 2001, Zhang, 2005) presented mean and standard deviations of the outcome measures and were awarded one point for data presentation in OPVS.

In contrast to the poor reporting quality of study designs, most of the studies achieved satisfactory results in STRICTA, reporting quality of intervention, which is not assessed by any other measurements. All 17 trials gave detailed information for acupuncture rationale,
needling techniques, treatment regimes, co-interventions and the control interventions; however, none of the studies gave details of practitioner backgrounds (Table 12).
### Table 12: Study and control interventions of included studies.

<table>
<thead>
<tr>
<th>Author and date</th>
<th>Study Intervention</th>
<th>Type of Acupuncture Treatment</th>
<th>Acupuncture points &amp; Needling</th>
<th>Other treatment</th>
<th>Treatment Regime</th>
<th>Practitioner Background</th>
<th>Control Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou, J.H. (2005)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (dredging meridian and activating Qi and blood)</td>
<td>GB8, GB19, TE20 De Qi mentioned</td>
<td>No</td>
<td>1 / day for 30 days</td>
<td>N/A</td>
<td>Nimodipine (Ca channel blocker) 40 mg, tid</td>
</tr>
<tr>
<td>Cui, R., et al (2004)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (regulating the liver)</td>
<td>GB8, GB20, GB39, GB41, LI4, LR3, RN12 De Qi mentioned</td>
<td>No</td>
<td>6 / week for 3 weeks</td>
<td>N/A</td>
<td>Nimodipine 40 mg, tid and oryzanol 20 mg, tid</td>
</tr>
</tbody>
</table>
| Wang, B. (2004) | Acupuncture alone | Formula acupuncture (dredging meridian and activating Qi and blood) | DU15, DU16, DU17 Split the distance from DU16 to GB12 into 6 spaces, needling on the cut-points. De Qi mentioned | No | 1 / 3 days for 30 days | N/A | 1. Cafergot 2 tabs for acute migraine attacks; if not effective within 30 mins, take another 1 - 2 tablets. Maximal dose 6 tab/day.  
2. Nimodipine 30 mg bid for 30 days |
<p>| Feng S.L., et al (2003) | Acupuncture alone | Formula acupuncture plus complementary point based on TCM syndrome differentiation | Empirical points: 1st point: 0.5 cun above GB8; 2nd/3rd points: 1 cun left or right to the 1sr point. Complementary points: BL23, KI3 ,LR3 or SP9 , ST8, ST40 or GB20, GB34, LR3, De Qi mentioned | No | 5 / week for 8 weeks | N/A | Nimodipine 40 mg, tid |
| Lao, J.X. (2003) | Electronic acupuncture alone | Formula acupuncture (regulating the liver) plus complementary point based on TCM syndrome differentiation | GB4, TE23 Complementary points: Ex-HN5, GB20, LU7, or KI3, LR3 or LI4, LR2 or GB8, ST40 De Qi mentioned | No | 1 / day for 10 days, then rest 5 days. Totally repeat 3 times | N/A | Rotudin 30 mg tid for 10 days, then rest 5 days. Totally 3 repeat 3 times |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Acupuncture Type</th>
<th>Formula Description</th>
<th>Points(s)</th>
<th>De Qi</th>
<th>Frequency</th>
<th>Duration</th>
<th>Dose/Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou, L.S.</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (regulating the liver)</td>
<td>GB8, GB41, GB44, TE3, TE5, TE19 De Qi mentioned</td>
<td>No</td>
<td>1 / day</td>
<td>40 days</td>
<td>N/A Ergotamine 1mg for acute migraine attacks. If not effective, take another 2 mg after 30 mins. Maximal dose 6 mg/day</td>
</tr>
<tr>
<td>Zhang, Y.C., et al (2002)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (dredging meridian and activating Qi and blood)</td>
<td>TE21 De Qi mentioned</td>
<td>No</td>
<td>1 / day</td>
<td>5 days</td>
<td>N/A Flunarizine (Antihistamines) 10 mg, qd for 5 days.</td>
</tr>
<tr>
<td>Liu, K.Y., et al (2001)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (regulating the liver)</td>
<td>Ex-HN5, GB8, GB20, GB34, GB 41, LR3, ST36, TE5, start and end points of lower sensory area in Head acupuncture De Qi mentioned</td>
<td>No</td>
<td>1 / day</td>
<td>30 days</td>
<td>N/A Nimodipine 30 mg, tid for 30 days</td>
</tr>
<tr>
<td>Li, W. et al (1998)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (regulating the liver) plus complementary point based on painful points</td>
<td>DU20, GB20, GB39, LR2 Complementary points: Ashi points De Qi mentioned</td>
<td>No</td>
<td>6 / week</td>
<td>3 weeks</td>
<td>N/A Carbamazepine (Anticonvulsants) 100 mg, tid for 21 days</td>
</tr>
<tr>
<td>Chen, X.S. (1997)</td>
<td>Acupuncture alone</td>
<td>Formula acupuncture (regulating the liver)</td>
<td>Ex-HN5, GB20, LR3, ST8, TE5, De Qi mentioned</td>
<td>No</td>
<td>1 / day</td>
<td>20 days</td>
<td>N/A Nimodipine 30 mg, tid for 20 days</td>
</tr>
<tr>
<td>Shao, Y., et al (2005)</td>
<td>Electronic acupuncture plus massage</td>
<td>Formula acupuncture (regulating the liver)</td>
<td>Ex-HN5, GB4, GB20, GB38, GB41, LR3, PC6, TE23, De Qi mentioned</td>
<td>Tuina along the gallbladder Meridian on the head for 15 min 1 / day for 10 days, then rest 3 days, totally 3 phases.</td>
<td>N/A Flunarizine 5 mg, q.d. Acute migraine attack, take ibuprofen 1-2 tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Formula</td>
<td>Acupuncture Points</td>
<td>Complementary Points</td>
<td>Acupuncture Frequency</td>
<td>Other Meds</td>
<td>Notes</td>
</tr>
<tr>
<td>-------</td>
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<td>---------</td>
<td>--------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>Lu, Z.Q. (2004)</td>
<td>Acupuncture plus massage</td>
<td>Formula acupuncture (dispelling wind) plus complementary point based on TCM syndrome differentiation</td>
<td>Ex-HN5, DU14 DU20, GB20 Complementary points: LI4, ST40 or KI3, LR3 or LI4, SP6 or LU9, ST36 De Qi mentioned</td>
<td>Tui na (pressuring DU2, EX-NH5, ST35, ST39 for 36 times and DU16 or 16 times) after acupuncture</td>
<td>1 / day for 30 days</td>
<td>1. Ergotamine 1 - 2 mg for acute migraine attacks, If not effective, take another 2 mg after 30 mins. Max 6 mg/day. 2. Indomethacin (NSAID) 25 mg bid for 30 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang J.L., et al (2004)</td>
<td>Acupuncture plus intravenous injection of a purified Chinese herb</td>
<td>Formula acupuncture (dispelling wind)</td>
<td>Ex-HN5, GB8, GB20, LI4, LR3, TE3 De Qi mentioned</td>
<td>Ligustrazine Hydrochloride (川芎嗪) 100ml i.v.drip q.d for 15 days</td>
<td>1/day for 15 days</td>
<td>Flunarizine 5 mg, qd</td>
<td>N/A</td>
</tr>
<tr>
<td>Liu Y., et al (2002)</td>
<td>Acupuncture plus acupoint injection</td>
<td>Formula acupuncture (dispelling wind)</td>
<td>DU20, Ex-HN5, GB8, GB20, LI4, LU7, ST8, TE23, De Qi mentioned</td>
<td>Acupoint injection using stauntoniae (野木瓜皂甙) on Ex-HN5 or GB16 2 ml for 8 weeks</td>
<td>1 / day for 10 days, then rest 2 day, lasting 8 weeks</td>
<td>Flunarizine 5 mg, qd for 8 weeks. Cafergot for acute migraine attacks</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang, L.Q., et al (2004)</td>
<td>Acupuncture plus hyperbaric oxygen</td>
<td>Formula acupuncture (regulating the liver) plus complementary point based on TCM syndrome differentiation</td>
<td>GB4, GB20, SJ19, SJ23 Complementary points: BL17, SP10 or BL12, BL60, or SP6, ST40, or BL23, KI3 De Qi mentioned</td>
<td>Hyperbaric oxygen</td>
<td>1 / day for 10 days</td>
<td>1. Cafergot (1-2 tabs for first symptoms) 2. Nimodipine 40 mg tid and Flunarizine (Antihistamines) 5 mg, tid for 10 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Liu X.L., et al (2002)</td>
<td>Acupuncture plus hyperbaric oxygen</td>
<td>Formula acupuncture (dredging meridian and activating Qi and blood)</td>
<td>Ex-HN5, LI4, LI11, LU4, De Qi mentioned</td>
<td>Hyperbaric oxygen</td>
<td>1 / day for 10 days</td>
<td>Somiton (a combination of analgesics and unnamed nature herbs) 500 mg, tid, oryzanol 10 mg, tid, and VB1 10 mg, t.i.d. for 7 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Zhang, Y.K. (2005)</td>
<td>Formula acupuncture plus medication</td>
<td>Formula acupuncture (dredging meridian and activating Qi and blood)</td>
<td>GB8, GB20, LI4, LR3 De Qi mentioned</td>
<td>Brufen 400 mg, tid for 30 days</td>
<td>1 / day for 30 days</td>
<td>N/A</td>
<td>Brufen 400 mg, tid for 30 days</td>
</tr>
</tbody>
</table>

- bid.: twice per day
- tid.: three times per day
- qd.: four times per day
5.4.4 Acupuncture Intervention


The median treatment period was 30 days (range 5 - 56 days) with an average of 30 treatment sessions (range 5 - 40). In 13 studies, participants were treated with acupuncture daily. Three studies gave five or six treatment sessions weekly (Feng and He, 2003, Li et al., 1998, Cui et al., 2004) and in the remaining one study, treatment was given once every three days (Wang, 2004).

The top five acupoints used in the 17 trials were GB8 Shuigu, GB20 Fengchi, LI4 Hegu, LR3 Taichong, and Ex-HN5 Yintang.

5.4.5 Control Intervention

All 17 trials used Western medications as the control intervention. Participants took prophylactics daily. These drugs were categorized as Ca++ channel blocker (Nimodipine), antihistamines (Flunarizine), anticonvulsant (Carbamazepine) and analgesics (Rotudin, a
combination of analgesics and unnamed natural herbs). In two studies, participants were instructed to use NSAIDs (Indomethacin and Brufen) daily (Lu and Yan, 2004, Zhang, 2005), which is not a standard Western pharmacotherapy for prophylactic treatment of migraine. These latter two studies were excluded from the meta-analysis.


5.4.6 Outcome Measures

All studies reported the use of at least one of the clinical-related outcome measures, such as frequency, intensity, and duration of migraine. However apart from two studies which presented the means and standard deviations of clinical data (Liu et al., 2001, Zhang, 2005), the remaining fifteen studies reported the number of participants in the “cured”, “marked improvement”, “improvement” and “no effect” categories. None of the studies mentioned the use of a diary to record patients’ migraine.

As a result, we extracted data of the “global response” to treatment. Response was defined as at least a 50% improvement in our review. We estimated whether a 50% improvement was met from the description provided by the authors. For instance, Lao (2002) recorded the reduction of migraine index (MI) during the third month after the end of the treatment. The MI reduction between 90% and 100% was considered as “cured”, between 55% and 89% as “marked improvement”, between 20% and 54% as “improvement” and less than 20% as “no effect”. The participants in the first two groups were considered to be respondents in our review. Most studies did not report the immediate and the long-term effects separately. For instance, Zhou (2003) defined “improvement” as a more than 50% reduction of MI in the
three months after the end of the treatment. Consequently, the 50% improvement in our review refers to the global response to acupuncture at 0 - 12 months after the treatment, and is not specific to either the immediate effect or the long-term effect. Relative risks and their 95% confidence intervals were calculated.

### 5.4.7 Follow-up

Follow-up was not clearly mentioned in three studies, and one trial did not include a follow-up period. Fourteen studies had a follow-up period ranging from one month to one year after treatment with a median of 4.5 months. Performance of the participants during the follow-up period was not reported separately from that immediately after acupuncture.

Side effects of acupuncture and Western medications were not reported.

### 5.5 Analysis

#### 5.5.1 Acupuncture VS. No Treatment

There was no study available offering this comparison.

#### 5.5.2 Acupuncture VS. Sham/Placebo Acupuncture

No study was available in this comparison.

#### 5.5.3 Acupuncture VS. Western Medications

In total, ten studies with 1094 participants were included in this analysis. All 10 studies reported positive results (Figure 17), however, the $I^2$ statistic (61.4%) indicated significant heterogeneity. Thus, a random-effects model was applied in the data analyses. The results significantly favored acupuncture as an intervention (RR 1.55; 95% CI 1.27 to 1.88). Only one study (Liu et al., 2001) presented the details of frequency and duration of migraine in
mean and SD (frequency per month: 0.3 ± 1.4 vs 2.6 ± 1.6; duration in hours: 2.54 ± 1.37 vs 14.7 ± 1.56). This study also provided the number of participants in the sub-groups of “cured”, “marked improvement”, “improvement” and “no effect”. The number of respondents in the study was chosen for the meta-analysis.
**Figure 17: Global responses to the treatments - acupuncture alone versus Western medications**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Acupuncture n/N</th>
<th>Western medicine n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen XS, 1997</td>
<td>30/45</td>
<td>16/30</td>
<td>1.25 [0.84, 1.86]</td>
<td>10.32</td>
<td></td>
</tr>
<tr>
<td>Li W, 1998</td>
<td>37/70</td>
<td>18/32</td>
<td>1.32 [0.93, 1.85]</td>
<td>9.55</td>
<td></td>
</tr>
<tr>
<td>Liu KY, 2001</td>
<td>33/43</td>
<td>25/43</td>
<td>1.44 [0.98, 1.97]</td>
<td>12.44</td>
<td></td>
</tr>
<tr>
<td>Lao JX, 2002</td>
<td>41/87</td>
<td>14/61</td>
<td>1.23 [1.23, 3.42]</td>
<td>8.03</td>
<td></td>
</tr>
<tr>
<td>Zhang YC, 2002</td>
<td>63/105</td>
<td>24/110</td>
<td>1.85 [4.01]</td>
<td>10.46</td>
<td>2.72</td>
</tr>
<tr>
<td>Feng SL, 2003</td>
<td>23/35</td>
<td>7/27</td>
<td>1.63 [5.01]</td>
<td>5.64</td>
<td>2.53</td>
</tr>
<tr>
<td>Wang B, 2004</td>
<td>100/125</td>
<td>36/61</td>
<td>1.29 [1.70]</td>
<td>14.29</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Total (95% CI) 537, 457

Total events: 416 (Acupuncture), 178 (Western medicine)

Test for heterogeneity: Ch = 23.34, df = 9 (P = 0.005), I² = 61.4%

Test for overall effect: Z = 4.35 (P < 0.0001)
5.5.4 Acupuncture plus Western Medication VS. Western Medication

There was only one study in this category. Zhang (2005) compared acupuncture plus Western medication with the same Western medication alone. In total, 120 participants were randomised into two groups with 1:1 ratio. After 30 treatment days, the acupuncture group (9.1 ± 2.07) was found statistically significantly better than the Western medication alone group (11.7 ± 3.04) in headache index, a combined measure of frequency and intensity of headache.

5.5.5 Acupuncture plus other TCM Therapies VS. Western Medications

Four studies compared a combined therapy of acupuncture and other Chinese medicine (CM) therapies, including acupoint injection (Liu et al., 2002b), intravenous injection of a purified Chinese herb (Wang and Gao, 2004) and Tuina (Lu and Yan, 2004, Shao et al., 2005) respectively with Western medications. Lu (2004) combined acupuncture with Chinese Tuina to compare with treatment by Indomethacin (NSAID) (25 mg twice a day for 30 days), an invalid pharmacology treatment for migraine. In fact, frequent use of NSAIDs could lead to migraine from medicine overuse (Bigal et al., 2004). Consequently, this study was not included in the meta-analysis.

Shao (2005) is the only study that presented both short-term data and the six-month follow-up data. The results indicated that acupuncture with massage produced a long-term effect, although the short-term effect was not better than Western medications. To be consistent with the data extracted from other studies, the follow-up data was included in the meta-analysis.

The fixed-effects model was used because the $I^2$ statistic was 43.1%. Figure 18 shows that acupuncture plus other CM therapies were significantly better than Western medications control (RR1.48, 95% CI 1.22 - 1.81).
### Figure 18: Global responses to the treatments - acupuncture with other traditional Chinese medicine versus Western medication

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Acup+TCM therapies n/N</th>
<th>Western medicine n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu Y, et al, 2002</td>
<td>41/54</td>
<td>32/52</td>
<td>1.23 [0.95, 1.60]</td>
<td>47.18</td>
<td></td>
</tr>
<tr>
<td>Yiang JL, 2004</td>
<td>37/60</td>
<td>19/60</td>
<td>1.95 [1.28, 2.97]</td>
<td>27.49</td>
<td></td>
</tr>
<tr>
<td>Shao Y, 2005</td>
<td>26/35</td>
<td>17/33</td>
<td>1.44 [0.98, 2.12]</td>
<td>25.32</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>149</strong></td>
<td><strong>145</strong></td>
<td><strong>1.48 [1.22, 1.81]</strong></td>
<td><strong>100.00</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi = 3.51, df = 2 (P = 0.17), I² = 43.1%

Test for overall effect: Z = 3.68 (P = 0.0001)
5.5.6 Acupuncture plus Other Therapy VS. Western Medication

Two studies of 503 participants combined acupuncture with hyperbaric oxygen to compare with Western medication (Liu et al., 2002a, Wang and Chen, 2004). Significant heterogeneity was indicated by $I^2$ statistic (84.7%), and a random-effects model was applied. Figure 19 indicates that the combined therapy was not statistically significantly better than the Western medication controls (RR 1.22; 95% CI 0.87 to 1.7).
Figure 19: Global responses to the treatments - Acupuncture and other therapy vs. Western medications
5.6 A Comparison of Our Reviews of Literatures Identified in English Databases and That in Chinese Databases

A comparison of findings from our reviews based on the English databases and Chinese databases is presented in Table 13. In general, studies published in China were of poorer quality, had acupuncture treatment more frequently and had pharmacotherapy controls only. All studies included in the Chinese review emphasised that Deqi sensation was achieved during treatment. Only nine out of 15 trials reported Deqi in the English review.

Twenty three percent of the Chinese trials (four out of 17 studies) used semi-standardised acupuncture treatment based on Chinese medicine syndrome differentiation. In comparison, 67% of the trials reported in the English literature adopted this method.

Trials published in English languages used sham / placebo acupuncture, waiting list, Western medicine or physiotherapy as the control interventions; blinding of participants was common in the sham-acupuncture controlled trials. All of the 17 Chinese studies used Western medications as a control. Except for two studies (Lu and Yan, 2004, Zhang, 2005), all drugs used in these 17 trials were recommended migraine medications (Lance and Goadsby, 2005), and were similar to those in trials included in the other SR.

As mentioned above, 15 of the total 17 Chinese studies self-defined the outcomes and reported the number of participants in the “cured”, “marked improvement”, “improvement” and “no effect” categories, without presenting the data in mean and standard division. Hence, only dichotomic meta-analysis could be conducted using the respondent rate. ‘Respondent’ was defined as a 50% or more improvement from the baseline data in frequency, intensity or duration of migraine. In contrast, all English literatures summarised the data into mean (SD),
although a few studies prior to 1990’s did not report the detailed data. Furthermore, in some studies, authors defined the respondent rate as a 40% or 50% improvement.
Table 13: A comparison of our review (overall data) and two other SRs of acupuncture for migraine.

<table>
<thead>
<tr>
<th>Sample size (median)</th>
<th>Current Chinese Review</th>
<th>Our English Review (Chapter Four)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (median)</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>Frequency of treatment (session per week)</td>
<td>5 - 7</td>
<td>Once per month to once per week mostly 1 - 2</td>
</tr>
<tr>
<td>De qi sensation</td>
<td>17 / 17 trials reported</td>
<td>9 / 15 trials reported</td>
</tr>
<tr>
<td>Jadad, Median (range)</td>
<td>2 (1 - 2)</td>
<td>3 (1 - 5)</td>
</tr>
<tr>
<td>IVS</td>
<td>2 (1.5 - 2.5)</td>
<td>4 (1.5 - 6)</td>
</tr>
<tr>
<td>Acupoint selection</td>
<td>23% of the studies chose acupoints according to Chinese medicine individual syndrome differentiation</td>
<td>67% of the studies chose acupoints according to Chinese medicine individual syndrome differentiation or location of pain</td>
</tr>
<tr>
<td>Control intervention</td>
<td>Western medications</td>
<td>Waiting list</td>
</tr>
<tr>
<td>Respondent rate</td>
<td>50%</td>
<td>N/A</td>
</tr>
<tr>
<td>Relative risk (acupuncture vs Western medications)</td>
<td>1.55 (1.27 - 1.88)</td>
<td>Favour acupuncture</td>
</tr>
<tr>
<td>Relative risk (acupuncture vs sham/placebo acupuncture)</td>
<td>N/A</td>
<td>1.07 (0.93 to 1.25)</td>
</tr>
<tr>
<td>Relative risk (acupuncture vs waiting list)</td>
<td>N/A</td>
<td>$P &lt; 0.01$ in frequency and intensity of migraine Favour acupuncture</td>
</tr>
</tbody>
</table>
5.7 Discussion

This review of East Asian literature was conducted to determine the effect of acupuncture on migraine when compared with sham acupuncture, no treatment and other therapies. No Japanese or Korean studies met the inclusion criteria. No relevant studies were identified for the first two comparisons. There is moderate evidence from Chinese literature supporting the value of acupuncture for preventing migraine when compared with Western medications. Furthermore, combining acupuncture with other modalities of Chinese medicine is superior to Western medications.

The major limitation of our SR was that we were not able to identify papers published prior to the 1980’s because the date of inception for the two databases used, Vi Pu (重庆维普) and Wan Fang (万方数据), were 1989 and 1982 respectively. These two databases are the most comprehensive Chinese e-databases and include all academically credible journals and theses published in China in the area of science and technology. Although studies published before the 1980’s are not included in these databases, it is unlikely we have missed many published papers in this area. Apart from two of the 17 papers being published in 1997 and 1998, the remaining fifteen studies were published after 2001.

The second limitation of our SR was that due to language barriers, we had to rely on other researchers to search Japanese and Korean data. It is possible that individual variations in data searches and selection existed. However we provided a standard protocol for conducting searches and the researchers involved were all experts in the area of systematic reviews. Therefore such variations are not likely to have contributed to a lack of literature being identified from these two countries.
None of the 17 studies in our review were included in the two other published SRs (Melchart et al., 2001, Scott and Deare, 2006) or our SR based on English databases (Chapter four), indicating a large body of research was not considered when the conclusion of the previous SRs was drawn. Given that the Chinese studies have larger sample sizes than those conducted in Western countries, potentially yielding a higher weighting in a meta-analysis, it is of significant importance to include such studies.

A search indicated that only one journal (Zhongguo Zhenjiu) included in our review was indexed in Pubmed (from 2005). Three studies (Liu et al., 2001, Zhang and Song, 2002, Cui et al., 2004) in our review were published in this journal before 2005 and so were not included in Pubmed. This confirms the view expressed by the authors of the other two SRs that there is a lack of access to Asian medical literature in Western reviews (Melchart et al., 2001, Scott and Deare, 2006).

In this review, we encountered the same difficulty that faced the authors of the other two SRs. Ideally, researchers should use the number of days with migraine per month or changed intensity or duration of migraine at the end of the treatment as the main outcome measure for quantitative analyses as recommended by the IHS (Dowson et al., 2002). Only two papers presented means and standard deviations of these outcome measures (Liu et al., 2001, Zhang, 2005). Due to detailed clinical data being unavailable, the number of respondents was used for meta-analyses. There are differences in the definition of respondents; 50% was used in our and Melchart et al’s reviews, and 33% in Scott and Deare’s review. Such a reduction of data limits our understanding of the exact effects of acupuncture on the frequency, intensity and duration of migraine.
Similar pharmacological treatments were used as the control interventions in our reviews and in Scott and Deare’s (2006). The effect size identified in our review (1.55) is comparable with the value reported by Scott and Deare (1.38) and by English literature in Chapter four (1.19). Considering the different definitions for the respondents, Chinese trials have a higher success rate. It is unknown whether the higher success rate is due to publication bias reported by Vickers and colleagues (1998), lower quality, or the differences in acupuncture treatment protocol.

The reporting quality and internal validity of the Asian literature was generally poor, as confirmed with three different scales. All 17 studies compared acupuncture with Western medications, and participants could not be blinded to treatment allocation. Furthermore, no trial described whether the acupuncturists were blinded to outcome assessment or whether an independent assessor/evaluator was employed. No trials reported the detailed process of randomisation or the reasons for drop-outs.

Another major shortcoming of the Chinese literature is the assessment of the outcomes. First, the effect of acupuncture on acute attacks was not investigated. Second, the Chinese trials neither presented detailed clinical data nor separated the immediate effect from the long-term effect. As a result, we cannot determine the duration of the effect of acupuncture on migraine. Third, although many included studies claimed that they assessed the time-profile and intensity of migraine, none of the studies described either the use of a diary, a method recommended by the IHS (2000), or how the data was recorded. The poor reporting quality and lower internal validity might have contributed to the over-estimation of the effect size.

Most Chinese trials implemented nearly daily treatment, which is much more frequent than the treatments provided in studies included in the other two previous SRs (Melchart et al.,
2001, Scott and Deare, 2006) and our English SR. It is unknown whether frequent treatment is associated with better results. Except for one study using empirical points alone, the remaining 16 trials selected traditional acupoints and provided the basis for point selection. All of them are in accordance with the classic literatures of TCM. From the available data, we cannot conclude how frequent the treatment should be and which formula is the best. The ideal acupuncture treatment, in terms of frequency of treatment and acupoint selection, should be investigated in future.

5.8 Conclusion

5.8.1 Implications for Research

Acupuncture shows promising effects on migraine. There is moderate evidence that acupuncture alone or combined with Western medications is more effective than Western medication alone for the prevention and treatment of migraine. However, the poor quality of the available studies and a lack of detailed data greatly reduced the level of overall evidence. Future studies should improve the reporting quality and trial design and present detailed data of the outcome measures. Profiles detailing the side effects of acupuncture should also be recorded. Furthermore, it is important to include trials published in Asian languages in meta-analyses. There is an urgent need to conduct acupuncture clinical trials in Japan and Korea, two of the three countries where acupuncture is commonly used.

5.8.2 Implication for Clinical Practice

Acupuncture might be an effective prophylactic treatment for migraine. It can be used either alone or in conjunction with Western medications.
5.9 Additional Notes

Before submitting the thesis, the databases were searched again. Six new studies were found.

These studies should be assessed for future SRs. The studies are listed below (Table 14):

Table 14: New published studies which was not included into current systematic SR

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Intervention</th>
<th>Control Intervention</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Zhou et al., 2007)</td>
<td>Electroacupuncture</td>
<td>Ergotamine</td>
<td>Acupuncture is as effective as Western medication in stopping acute attack, but can last longer than Western medication.</td>
</tr>
<tr>
<td>(Li, 2008)</td>
<td>Acupuncture and herbal formula</td>
<td>Nimodipine</td>
<td>The combination of acupuncture and herbal formula is more effective than Western medicine measured via headache index.</td>
</tr>
<tr>
<td>(Gao et al., 2008)</td>
<td>Acupuncture and Tuina</td>
<td>Flunarizine</td>
<td>The combination of acupuncture and tuina can achieve more long-term effects in preventing migraine, when compared with Western medication.</td>
</tr>
<tr>
<td>(Shen, 2006)</td>
<td>Acupuncture and blood-letting puncture</td>
<td>Flunarizine</td>
<td>This combination therapy is more effective than Western medication.</td>
</tr>
<tr>
<td>(Zhang, 2007)</td>
<td>Acupuncture plus intravenous injection of a purified Chinese herb (Ligustrazine Hydrochloride)</td>
<td>Flunarizine</td>
<td>This combination therapy is more effective than Western medication.</td>
</tr>
<tr>
<td>(Li et al., 2007)</td>
<td>Acupuncture</td>
<td>NSAID</td>
<td>Acupuncture is more effective than Western medication in reducing frequency, intensity and duration of migraine</td>
</tr>
</tbody>
</table>
CHAPTER SIX: METHOD OF CLINICAL TRIAL

This is a prospective, randomised, patient/assessor blind, sham-acupuncture controlled clinical trial. The project was conducted with the approval of the Human Research Ethics Committee of the RMIT University (Project No. 16/05). It was filed with the Australian Government’s Therapeutic Goods Administration under Clinical Trial Notification Scheme (CTN No. 08/07/2005), as well as the Australian New Zealand Clinical Trials Registry with the reference No. ACTRN12605000314628.

6.1 Participants

All participants were volunteers suffering from migraine and were recruited from the local community around Melbourne.

6.1.1 Diagnostic Criteria for migraine

All participants were screened based on the classification of migraine according to the International Headache Society (IHS) (2004), see (Appendix 1).

6.1.2 Inclusion Criteria

Participants must meet all of the criteria as follows.

A. Aged between 18 and 80 years and with a current history of migraine for at least 12 months;
B. Have a minimum of five days with migraine per four weeks;
C. Agree to avail themselves for the period of the study; and
D. Provide a written consent for participation.
6.1.3 Exclusion Criteria

Volunteers having any of the following conditions were excluded from the study:

A. Current pregnancy or malignancy;
B. Had experience of acupuncture treatment in the face, the hands, the legs and the front of the body in the previous six months. Volunteers who had received needling at sites that could not be seen by the volunteers, such as the back of the trunk, were included;
C. History of head injury or whiplash;
D. Severe arrhythmia or heart failure, brain tumor or epilepsy;
E. Hemophiliac;
F. Had participated in another clinical trial in the past six months;
G. Had tension-type headache more than six days a month;
H. Unable to distinguish between migraine attacks and additional tension-type headache; or
I. Did not comprehend English.

6.2 Procedure of Recruitment

Participants were recruited from the local community using a series of media releases including a story on MX (a free pick up newspaper in the CBD of Melbourne), The Age, Herald Sun and Leaders (a community local newspaper). Advertisement for the study was also distributed to all RMIT University students and staff via RMIT email and to all the members of the Australia Acupuncture & Chinese Medicine Association (AACMA) via emails and the AACMA newsletter. Television and radio interviews of the main researchers by Channel Nine (a TV station) and ABC radio of Melbourne were also conducted. Some examples of media advertisement are listed in the Appendix 3.

Volunteers who were interested in the study phoned the investigator (YYW) for further information. During the telephone enquiries, the investigator conducted the initial screening for the symptoms of migraine (Appendix 4). Volunteers with tension-type headache only or other types of headache were excluded. Potential participants were sent a plain language
statement (PLS) (Appendix 5) and the Expression of Interest Form (Appendix 6) together with a pre-paid envelope. Based on the returned information, those who met the selection criteria were invited to attend an interview, during which further eligibility assessment was conducted according to the inclusion and exclusion criteria. Eligible participants were then given the opportunity to reconsider their participation and sign the informed consent form (Appendix 7).

6.3 Trial Design

6.3.1 Randomisation

Block randomisation was used to ensure a similar number of participants were allocated to the real acupuncture (RA) treatment and the sham acupuncture (SA) control groups, respectively. Eight participants were in each block. Random numbers were generated using a computer-generated sequence of numbers by an independent researcher. Each number was printed on a piece of paper, which was then concealed in a sealed envelope. Before conducting the first treatment, participants were asked to select a sealed envelope containing a unique random number. Only the acupuncturist knew the assignment group.

6.3.2 Blinding

A double-blind, placebo-controlled clinical trial is considered as the gold standard for evaluating the therapeutic effects of a treatment (Feinstein, 1984). However, it is not feasible for acupuncture studies, as the acupuncturist cannot be blinded. In the current clinical trial, performance bias of the participants was minimised by employing sham acupuncture as the controlled-intervention. Furthermore, independent assistants in charge of data entry or assessing PPT were unaware of the treatment allocation. Any discussion related to treatment between the participants and the acupuncturist was restricted to a minimum of necessary explanations in order to ensure the allocation concealment. Describing this procedure as a
dummy or modified double-blind (patient/evaluator) trial is acceptable when the intervention characteristics preclude investigator blinding (Jadad et al., 1996).

After the first treatment week, credibility of the sham acupuncture procedure was assessed with a questionnaire (Appendix 8) completed by the participants.

6.3.3 Drop-Outs

Participants were informed that they could withdraw from this study at any time. The time of and the reason for drop-out and the allocation of drop-out participants were recorded.

6.4 Materials

6.4.1 Selection of Needles

Individually wrapped, sterilized, disposable needles with guide tubes (Hwato, Suzhou Medical Instrument Factory, China) were used. This brand of needles is listed by the Therapeutic Goods Administration (TGA) of Australia. All the needles used on local (head) and distal (limb) areas were 0.25 mm in diameter. According to the location of the acupoints, the length of the needles used was either 30 mm or 40 mm. Furthermore, short needles of 13mm in length with 0.22 mm in gauge were used for sham acupuncture, so that only a short body part of the needle was above the skin (for detailed information, see section 6.4.4 Sham Acupuncture for Control Groups). Similar number of needles was used in both groups (RA: 10-12 needles; SA: 8-10 needles), as the SA group had less needling in the head than the RA group. Medical swabs were used for sterilization and used needles were placed into a sharps disposal bin.
6.4.2 Pressure Algometer

A handheld pressure algometer (Wagner, Electronic Engineering Corporation of India) (Figure 20) was used to measure pressure pain thresholds twice, before and after the treatment (the 4\textsuperscript{th} week and 24\textsuperscript{th} week from baseline). The apparatus consists of a 1-cm in diameter hard rubber tip, attached to the plunger of a pressure (force) gauge. The dial of the gauge is calibrated in kg/cm\textsuperscript{2}. The reliability and validity of algometer have been demonstrated by several studies (List et al., 1989, Nordahl and Kopp, 2003). Furthermore, the reliability is enhanced when PPT is assessed by one examiner (Antonacci et al., 1998).

Figure 20: The algometer used to test the pressure pain threshold
6.4.3 Real Acupuncture (RA) Treatment

For RA, needles were inserted either transversely, obliquely or perpendicularly to a depth of 10-30 mm depending on the specific locations of acupoints. The treatment consisted of local and distal points. De Qi sensation was induced, which is a patient’s feeling of soreness, numbness, distension, heaviness or even an electric shock either around the needles or going up or down along the meridian, elicited by the acupuncture needles. Needles were retained for 25 minutes, with further stimulation given every 10 minutes.


The same acupuncturist, registered with the Chinese Medicine Registration Board of Victoria, Australia, performed all acupuncture treatments consistently throughout the trial.

6.4.3.1 Mandatory Acupoints

Mandatory acupoints included bilateral Fengchi (GB20) and bilateral Taiyang (EX-HN5) as well as Shuaigu (GB8), and Hegu (LI4) at the side with pain or the side with pain in last migraine attack. These acupoints were used for all the participants and were illustrated in the following diagram (Figure 21).
6.4.3.2 Supplementary Acupoints

The selection of the supplementary acupoints was based on the diagnosis according to Chinese medicine theory. In terms of syndrome differentiation, there are four types of migraine, namely Ascending Hyperactivity of Liver Yang, Deficiency of Qi and Blood, Phlegm Retention, and Blood Stasis. Table 15 shows the typical symptoms and signs of these different syndromes and selected supplementary acupoints. Figure 22 illustrates the location of each supplementary acupoint.

Table 15: Typical symptoms and supplementary acupoints for different syndromes
<table>
<thead>
<tr>
<th>SYNDROMES</th>
<th>TYPICAL SYMPTOMS</th>
<th>SUPPLEMENT ACUPOINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending</td>
<td>Hyperactivity of Liver Yang</td>
<td>Baihui (DU20), Xingjian (LR2), Taichong (LR3), Taixi (KI3), Xuanzhong (GB39), Sanyinjiao (SP6)</td>
</tr>
<tr>
<td>Deficiency of Both Qi and Blood</td>
<td>Pale or sallow complexion; shortness of breath after slight physical exertion; weak limbs; pale tongue with white and thin coating; deep, thready and feeble pulse</td>
<td>Baihui (DU20), Shangxing (DU23), Zusanli (ST36), Sanyinjiao (SP6)</td>
</tr>
<tr>
<td>Wind Phlegm blocking the meridians</td>
<td>Chest distress; corpulence tongue body with tooth-prints; white and greasy tongue coating; deep and taut or deep and slippery pulse</td>
<td>Fenglong (ST40), Zhongwan (CV12), Yinlingquan (SP9)</td>
</tr>
<tr>
<td>Blood Stasis</td>
<td>Stabbing pain; cyanotic lips and nails; purplish tongue body with thin white coating; deep, thready or thready-sluggish pulse</td>
<td>Sanyinjiao (SP6), Xuehai (SP10) and Ashi point</td>
</tr>
</tbody>
</table>
Figure 22: Location of supplementary acupoints
6.4.4 Sham Acupuncture (SA)

For sham acupuncture treatment, a combined insertion and non-insertion procedure were used, and is illustrated in Table 16.

Table 16: Method of sham acupuncture

<table>
<thead>
<tr>
<th>Sham point</th>
<th>Distal sham acupuncture</th>
<th>Local sham acupuncture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2 cm away from the real individual distal supplementary points according to the syndrome differentiation</td>
<td>1-2 cm away from the real acupoint of DU20 and GB17, on both side</td>
</tr>
<tr>
<td>Technique</td>
<td>Minimal acupuncture, 2 mm depth insertion</td>
<td>Non-invasive, using a blunted cocktail-stick</td>
</tr>
<tr>
<td>Stimulation</td>
<td>No needling manipulation</td>
<td>The stick was tapped</td>
</tr>
</tbody>
</table>

For distal acupoints needles were inserted gently into the distal sham points, which were 1-2 cm away from the exact acupoint locations. Depth of insertion was about 2 mm, which was just sufficient to make the needle stand vertically (Vincent, 1989b). For sham needling, short needles of 13 mm in length were used, such that after insertion only a short body part of the needle was above the skin, giving an impression of much of the needle having been inserted. Such method was named minimal acupuncture and illustrated by Figure 23. No needling manipulation was carried out for sham points. A non-invasive technique was carried out for local sham points in the head, (1-2 cm away from the real acupoint of DU20 and GB17). A blunted cocktail-stick was tapped on the site to produce some discernible prick to simulate needling sensation. Table 17 compares the methods applied in the RA and SA, respectively.
Figure 23: The method of minimal sham acupuncture
Table 17: Treatment methods for real and sham acupuncture groups

<table>
<thead>
<tr>
<th></th>
<th>Real group</th>
<th>Sham group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Point selection</strong></td>
<td>Standard acupoints plus supplementary acupoints according to differentiation of syndromes</td>
<td>1-2 cm away from the standard acupoint.</td>
</tr>
<tr>
<td><strong>Stimulation</strong></td>
<td>Needling to obtain “De Qi” sensation</td>
<td>For distal points, needles were inserted about 2 mm depth without manipulation. For local points, a blunted cocktail-stick was used to simulate needling sensation</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>25 mins with stimulation every 10 minutes</td>
<td>25 mins without stimulation. But the acupuncturist visited participants every 10 minutes.</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Twice per week for four weeks followed by once per week for another four weeks, then once per fortnight for four weeks, then once per month for another two months</td>
<td>Twice per week for four weeks followed by once per week for another four weeks, then once per fortnight for four weeks, then once per month for another two months</td>
</tr>
<tr>
<td><strong>Number of needles</strong></td>
<td>10-12</td>
<td>8-10</td>
</tr>
</tbody>
</table>
6.5  Outcome Measures

6.5.1  Primary Outcome Measures

The primary endpoints were 1) Frequency: number of days with migraine per four weeks (assessed with headache diaries); 2) Intensity: mean severity of average migraine per four weeks (assessed with headache diaries); and 3) Duration: hours of migraine per four weeks. 4) Respondent rate; 5) Numbers of accompanying symptoms, including nausea, vomiting, light sensitivity, sound sensitivity, pain with movement and other specific symptoms that were described by individual participants. All of these were assessed using a Headache Diary (Appendix 9). The daily Headache Diary took about five minutes to complete. In the first interview, the investigator taught the participants how to complete the Diary step-by-step. During baseline and the treatment period participants were requested to complete the diary every day and hand the completed form to the investigator (or a research assistant) fortnightly. During the three-month follow-up I and another one-month follow-up II period, the diaries were required to be posted back to the investigators every four weeks.

**Frequency of Migraine:** In the headache diary, participants were required to indicate whether they had migraine or not every day. The number of days having migraine every 4-weeks were calculated.

**Intensity of Migraine:** The intensity of migraine was assessed with measurements that consisted of two parts, the 10-cm Visual Analogue Scales (VAS) which designates “no pain” and “pain as bad as it could be” at the two ends. Three VASs were conducted for rating highest, lowest and average migraine of that day. The other measurement is the Likert Scale of Headache Severity, which has six numbers (0-5) to describe the pain. 0 means no headache, 5 means intense, incapacitating headache. Means of the VAS value and the Likert Scale per four weeks were calculated.
**Duration of Migraine:** Participants were required to indicate the times and duration of each migraine headache on a 24-hour scale. In some cases, patients reported to have two headaches per day, as the first headache could be eliminated by medication, and onset again once the effect of medication ran out. The total hours of the two headaches represented the duration of migraine on that day. Mean hours of migraine per four weeks were calculated. If a participant had 3 days with migraine of different duration within a 4-week period, we calculated the mean duration of the migraine attacks during the 4-week period.

**Respondent Rate:** The 50% or greater improvement in the days with migraine per four weeks compared with the baseline period was considered as positively responding to the treatment.

**Accompanying Symptoms:** Some common symptoms that accompany migraine were listed for the participants to choose, such as light sensitivity, vomiting, and nausea. Furthermore, participants were asked to write down the signs and symptoms they experienced if they were not listed.

### 6.5.2 Secondary Outcome Measures

Secondary outcome measures included anti-migraine and pain relief medication consumption (assessed with the diary), severity and quality of migraine assessed with the McGill pain questionnaire (MPQ) (Appendix 10), quality of life assessed with Migraine Specific Quality of Life questionnaire (MSQOL) (Appendix 11) and pressure pain threshold (Appendix 12). MPQ and MSQOL were given to the participants every four weeks. Pressure pain thresholds were tested twice, prior to the first and last treatment sessions.
**Medication Quantification**: The name and dosage of any migraine medication for daily use or for acute attacks were recorded by the participants, such as Sandomigrain and Noten for prophylaxis; and Tramal and Nurofen for acute pain. These medications were divided into three groups for analysis, namely, medication for acute pain, migraine specific medication and prophylaxis medication. The medications for acute pain are quite complex with different drug classes, dosage and detriment weight, hence, the Medication Quantification Scale (MQS) version III was used. The sum of four-week scores of MQS was calculated for further analysis. As to the latter two subgroups, the mean pill count per four weeks was adopted for comparison.

The score of each acute pain medication in MQS was calculated through multiplying individual detriment weight and a score for dosage level. The detriment weights range from 1.1 to 4.5 (Appendix 13). A score of dosage level ranges from 1 to 4 (Table 18), as stated in the drug manufacturer package inserts or the physicians desk reference (PDR, 2004).

Table 18: Relative dosage scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subtherapeutic dose or occasional use</td>
</tr>
<tr>
<td>2</td>
<td>Low 50% of the therapeutic dose rang</td>
</tr>
<tr>
<td>3</td>
<td>Upper 50% of the therapeutic dose rang</td>
</tr>
<tr>
<td>4</td>
<td>Supratherapeutic dose</td>
</tr>
</tbody>
</table>

Take Aspirin and Tramal as examples, whose detriment weights were 3.4 and 2.3 respectively. If a migraine patient took 15 tablets of Aspirin (325 mg / tab) per day and 50 mg Tramal for the migraine relief, the score of dosage was given four to Aspirin and one for Tramal, according to Table 4. The score of MQS of that day is indicated in Figure 24.
### MQS III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (Mg/day)</th>
<th>Dosage level</th>
<th>Detriment weight</th>
<th>=</th>
<th>MQS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>15 tab/day 325 mg * 15</td>
<td>4 * 3.4</td>
<td>= 13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramal</td>
<td>100 mg</td>
<td>1 * 2.3</td>
<td>= 2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.9</td>
</tr>
</tbody>
</table>

Figure 24: Sample MQS III computation sheet.

**Adverse Events (AEs) of Acupuncture**: Participants were asked to record in Headache and Medication Diaries any AEs associated with acupuncture treatments and the management of these AEs at the end of each week throughout the treatment period. They were also asked to indicate the severity of AEs by selecting one of the three words “mild”, “moderate” or “severe”. Participants have been notified about the common adverse events including fainting, infection, dizziness, bruising, pain and lethargy. During analysis, AEs were classified into three types: by event, by risk and by causation according to the WHO Draft Guidelines for Adverse Event Reporting and Learning Systems (WHO, 2005). For instance, the wrong diagnosis and wrong practices belong to “event”, such as pneumothorax; infection, bruising or pain caused by needling can be classified as “risk”; and tingling sensation belongs to “causation”. Any disagreement on the classification was solved by discussion among researches.

**Quality of Pain** was assessed with the McGill Pain Questionnaire, which consists of three major categories of word descriptors – sensory, affective and evaluative. These words describe patients’ subjective experience of pain. There are 20 subclasses with three to six
words in each subclass. Participants were requested to pick one word only from each subclass. The scoring method of the MPQ questionnaire followed the instructions described in Melzack’s study (1975b). Four types of data are obtained from the questionnaire. Pain rating index (PRI) was calculated based on the rank values of the words-PRI. In this scoring system, the word in each subclass implying the least pain (first word) was given a value of 1, the next word was given a value of 2, etc. The values of the words chosen by a patient were then added up to obtain a score for each dimension. The score of subclasss 1-10 to assess sensory components (PRI-S); 11-15 to assess affective components (PRI-A); 16 assess evaluative components (PRI-E); 17-20 to assess miscellaneous components (PRI-M) and PRI–T to investigate the overall performance, subclass 1-20.

**Quality of Life** was measured by Migraine Specific Quality of Life Questionnaire (MSQOL), which is designed specifically to assess the health related quality of life of migraine sufferers during the previous four weeks. It consists of three dimensions, namely, role function-restrictive (FR) (questions 1-7), role function-preventive (FP) (questions 8-11) and emotional function (EF) (questions 12-14). Each dimension is scored from 0-100 and a higher score indicates better health.

**Pressure Pain Threshold** was assessed with a manual algometer. Eleven points were tested and these are illustrated in Figure 25. They included the point A: located 2 cm inferior to the external occipital protuberance and 2 cm lateral from the midline, on both side; point B: bilateral GB20: in a depression between the upper portion of the sternocleidomastoid muscle and the trapezius; point C: bilateral points at 2 cm lateral to GV20: which is located on the head, 5 cun directly above the midpoint of the anterior hairline; point D: bilateral EX-HN5 (Taiyang): at temple, in a depression about 1 cun posterior to the midpoint between the lateral end of the eyebrow and the outer canthus of the eye; point E: bilateral ST6: one finger width
anterior and superior to the angle of the mandible at the belly of the masseter muscle with teeth clenched and point F: EX-HN3 (Yintan), which is located midway between the medial ends of the eyebrows. When testing for the pain threshold, the blinded investigator placed the rubber tip on the selected point and applied a steady gentle pressure at a rate of 1 kg/cm²/sec (Nussbaum and Downes, 1998). The participants were informed that the investigation was aiming to determine pain threshold, but not pain tolerance. Participants were asked to tell the investigator when pain was induced. A reading was made and recorded. The procedure was repeated twice and the mean of the two ratings represented the pressure pain threshold (PPT) of the point. The difference between the two groups in PPT after treatment was calculated.

![Diagram showing measuring points of PPT](image)

Figure 25: Location of measuring points of PPT

### 6.6 Procedure of the Trial

The overall procedure is illustrated in Figure 26.

![Flowchart showing procedure](image)
Figure 26: A diagram of the procedure of the clinical trial
6.6.1 Initial Examination and Assessment

After receiving the Expression of Interest Form (EIF) from potential participants, the assessor and investigator went through the forms together based on the selection criteria to identify the eligible participants. This step was followed by individual phone calls to those potential participants for a face-to-face interview.

The first interview was conducted at the Chinese Medicine Clinical Trial Laboratory, Bundoora Campus of RMIT University. During the first interview, the following procedures were undertaken.

The assessor and investigator together greeted the potential participants, and then explained the procedure of the trial as well as the right of the participant to withdraw at any time. The assessor / investigator assessed the migraine situation of the potential participants according to the IHS criteria to ensure they were eligible for the trial. Any questions were comprehensively answered prior to the signing of the Consent Form (CF).

The Consent Form (CF) was signed and witnessed by a third person. A copy of the signed CF was provided to the participants for their own record. Another two forms, “Attitude to Acupuncture” (Appendix 14) and “Knowledge of Acupuncture” (Appendix 15) were given and participants were asked to complete these at that time.

Assessor / investigator explained to the participants how to complete the diary, MPQ and MSQOL.

6.6.2 Run-in Period

After explaining the instructions for the diary, a four-week baseline Headache Diary was given to the potential participants. During this stage, they were asked to record their migraine
condition as well as the medication dosage daily in the diaries. These baseline diaries were brought back on their next visit.

### 6.6.3 Treatment Stage

Before conducting the treatment, the investigator checked the four-week baseline diaries to calculate the days with migraine. Potential participants, who had less than five days with migraine during the baseline period, were excluded from this trial. The remaining eligible participants were then randomly allocated to either RA group or SA group and treated for a total of 16 sessions during the following twenty weeks. As described in Section 6.5 Outcome Measures, the frequency, duration and intensity of migraine as well as the pain medication, adverse events of acupuncture, quality of pain and quality of life were monitored.

### 6.6.4 Follow-up Stage

After completion of the treatment period, the participants were asked to record their migraine condition using the daily diaries for three months. MPQ and MSQOL were completed every four weeks for three months. The follow-up procedure was designed to evaluate any potential long-term effect of acupuncture for migraine.

### 6.7 Data Collection and Analysis

#### 6.7.1 Sample Size Calculation

For this clinical trial, the sample size was calculated based on an acupuncture trial on migraine compared with sham acupuncture and waiting list (Linde et al., 2005b) of which statistical significance was achieved with 221 participants of two groups (treatment \( n = 145 \), waiting list \( n = 76 \)) based on the frequency of headaches. The mean frequency (standard deviation) of headaches in the treatment and control groups were 1.5 (1.2) and 2.3 (1.1). Using this data, we calculated the following:
ES (Effect Size) = (Mean of acupuncture – Mean of control) / pooled SD

Pooled SD = \( \sqrt{(n_1 - 1) \cdot SD_1^2 + (n_2 - 1) \cdot SD_2^2} / (n_1 + n_2) \) = 1.17

ES = \( \frac{1.5 - 2.3}{1.17} \) = -.68

Significance level \( \alpha \) = (Two-tailed) = 0.05

\( \beta = 1 - \text{power} = 0.2 \), i.e. power was set at 0.80 (80%)

Hence, using sample size tables (David, 1995) it was estimated that the trial required a sample size of 33 per group for each of the two groups with statistical power of 80%. As the intention-to-treat analysis was used, no additional participants were needed to compensate the drop-outs. Consequently, a total of 66 participants was needed in this study.

6.7.2 Data Collection and Treatment of Missing Data

The diaries were returned and then passed on to one of the independent research assistants for data entry. Whenever the research assistant found there was a report of an adverse event of acupuncture, the adverse events sheet was allowed to be provided to the acupuncturist to ensure safe practice.

The research assistants entered all raw data into Excel spreadsheets. Mean values per four weeks were then calculated and saved in a separate Excel spread sheet, which was then exported to Statistical Package (SPSS, version 15.0 for Windows) for data analysis. The MPQ and MSQOL were calculated according to the relevant manuals.

Any missing data in the Headache Diary was replaced by using the Missing Value Analysis function in SPSS. As to the Six-Point Likert Scale for assessing the intensity, if more than one box are marked, the higher one was chosen. Moreover, the data missed in the MPQ and MSQOL were dealt with according to the instructions for these two questionnaires,
respectively. In MPQ, the missing data are replaced with the median values of the total sample (Stevinson et al., 2003). As to MSQOL, in the event that responses on one or more items within a dimension are missing, the missing item values are estimated using the average of the other items within the same dimension (Medical Outcomes Trust, 1998).

6.7.3 Data Analysis

All the data were summarised as mean (standard deviations, SD). Intention-to treat analysis was performed for all the outcome measurements. Per protocol (PP) analyses of primary outcome measurements were conducted with data from participants who completed the 20-week treatment.

Chi-square or t-test was adopted to test the comparability between two groups in socio-demographic characteristics and primary and secondary outcome measure data. Tests for short-term effects of acupuncture employed repeated measures of General Linear Model (ANOVA) to test the main effects of treatment group of time and group by time interaction. Paired-samples t-test and independent-sample t-tests with Bonferroni correction were used for post-hoc analyses. The long-term effects were analysed using the paired sample t-tests. The scores of sub-categories of MPQ and MSQOL were analysed separately. The number and percentage of AEs were summarised and analysed using Chi-square to investigate the safety of acupuncture.

When the probability value achieved 0.05 or less, the difference was considered to be statistically significant. In the event when more than one comparison was made, significant p value was calculated by dividing 0.05 with the number of comparison.
This chapter presents the analysis of data obtained from the 20-week treatment period of the study. Per protocol analysis was employed to analyse both the primary and secondary outcomes. Results in the study have demonstrated a statistically significant short-term prophylactic effect of acupuncture, as well as improvement with respect to severity, medication consumption and quality of life, when compared with sham acupuncture. Furthermore, there were no any serious adverse events that necessitated withdrawal of participants from the trial. The incidence and severity of minor adverse effects were comparable between two groups.

7.1 Short-term Results

7.1.1 Subject Recruitment

Between October 2005 and April 2007, a total of 179 phone calls were received from the public to express an interest in participating in this clinical trial. Fifty-nine respondents were excluded because they did not meet the selection criteria. The Plain Language Statement and Expression of Interest Form were sent to the remaining 120 respondents. A total of 95 of these completed and returned the Form. Furthermore, 37 respondents were excluded for reasons outlined in Table 19. The remaining 58 potential participants were invited to RMIT University for a face-to-face interview. Four potential participants did not attend the interviews. One was excluded because he had a mixed migraine and tension-type headache and he could not distinguish between the two types of headaches. Finally, a total of 53 respondents signed the informed consent form and entered into the run-in period of the study, in which they completed the migraine diaries to record the frequency, intensity and duration of migraine. At the end of four weeks, all volunteers returned for further assessment and treatment. Three were excluded as they had less than 5 days with migraine in a four-week
run-in period. A total of 50 participants were randomly allocated into either the real acupuncture (RA) or the sham acupuncture (SA) groups. The whole process is illustrated in Figure 27.

Table 19: Number of potential participants being excluded from the trial.

<table>
<thead>
<tr>
<th>Item</th>
<th>Reason</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not met the IHS definition of migraine.</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Had less than five days with migraine in four weeks</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Had acupuncture experience for headache in the last six months</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Preparing to get pregnant</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>
Contact by phone from people who were interested in this study, \( n = 179 \)

Sending Plain Language Statement, \( n = 120 \)

Patients who returned Expression of Interest Form, \( n = 95 \)

Phone call to make a face to face interview, \( n = 58 \)

Further assessments @ RMIT Chinese Medicine Research Clinic, \( n = 54 \)

Signed informed consent
Four weeks baseline diaries were handed out, \( n = 53 \)

Included in clinical trial, \( n = 50 \)

Excluded, \( n = 59 \)

\( n = 25 \), did not return form back

Excluded, according to inclusion criteria, \( n = 37 \)

Did not attend interview, \( n = 4 \)

Excluded, as cannot distinguish tension-type headache, \( n = 1 \)

Excluded, as attack days < 5 @ baseline \( n = 3 \)

Figure 27: A flowchart illustrating the process of recurring participants
7.1.2 Allocation of Participants

Among the 50 participants, 26 were randomly allocated to receive RA and 24 to receive SA. Forty-eight participants completed the treatment, with one withdrawing from each treatment group. One in the RA group could not tolerate acupuncture needling; one in the SA group had work commitments preventing him from receiving treatment regularly. One more participant in the SA group withdrew during the follow-up period without giving any reason. The number of participants at each stage of the clinical trial is illustrated in Figure 28. Intention-to-treat (ITT) analysis was used when comparing the treatment groups on all variables.
Participants were randomly assigned to either treatment or control group
n = 50

Treatment: acupuncture
n = 26

16 sessions of treatment during a 20-week period:
2/wk for 4wks → 1/wk for 4wks
→ 1/2wks for 4wks → 1/4wks for 8wks
Treatment: n = 25
Dropout: n = 1 (can not tolerate acupuncture needling)

12 weeks follow-up period
n = 25

ITT analysis n = 26
PP analysis n = 25

Control: sham acupuncture
n = 24

16 sessions of treatment during a 20-week period:
2/wk for 4wks → 1/wk for 4wks
→ 1/2wks for 4wks → 1/4wks for 8wks
Control: n = 23
Dropout: n = 1 (work commitments)

12 weeks follow-up period
n = 22

ITT analysis n = 24
PP analysis n = 23

Allocation

Analysis

Figure 28: Number of participants in different stages of trial
7.1.3 Socio-demographic Data

The 50 included participants had an age range from 19 to 68 years with a mean age of 42.6 and a standard deviation of 14.10 years. Thirty-seven of the participants were females and 13 were males. The migraine history of all participants corresponded to a mean time of 19.7 years with a standard deviation of 12.90 years. Thirty-seven of the 50 participants were currently married or partnered. Twenty-six participants had an acupuncture experience more than six months ago, and these 26 participants were nearly evenly allocated into the two groups, 12 in RA and 14 in SA. The education level of participants was high with 22 having a degree or higher education; 26 having 9 years formal education; one having less than nine years education and the remaining one not providing relevant data.

The socio-demographic data of each treatment group are presented in Table 20. There were no significant differences between the RA and SA groups with respect to age, migraine history, gender, acupuncture experience, marital status and education level.

As to the knowledge and attitude to acupuncture, 82% of the participants agreed that acupuncture should be used as a complementary medicine; and 74% of the participants indicated that they felt more anxiety about using acupuncture than taking medication indicating a lack of knowledge of acupuncture. Moreover, 48% of the participants consulted with their doctors about acupuncture before joining this study. 62% of participants had heard about acupuncture from friends or relatives. Overall, on the 18 questions regarding the attitude to acupuncture and the 14 questions investigating the knowledge of acupuncture, the two treatment groups showed no significant differences.
Table 20: Comparisons of demographic variables at baseline in the RA and SA groups

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>RA (n = 26)</th>
<th>SA (n = 24)</th>
<th>(\chi^2) or (t) - value</th>
<th>(p) - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (Mean ± SD)</td>
<td>41.6 (14.91)</td>
<td>43.8 (13.40)</td>
<td>-.55</td>
<td>.58</td>
</tr>
<tr>
<td>Migraine History (yrs) (Mean ± SD)</td>
<td>18.4 (12.67)</td>
<td>21.1 (13.28)</td>
<td>-.74</td>
<td>.47</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (26.93%)</td>
<td>6 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (73.07%)</td>
<td>18 (75%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acupuncture Experience (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (53.85%)</td>
<td>10 (41.67%)</td>
<td></td>
<td>.74</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (46.15%)</td>
<td>14 (58.33%)</td>
<td></td>
<td>.39</td>
</tr>
<tr>
<td>Marital Status (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partnered</td>
<td>17 (65.38%)</td>
<td>17 (70.83%)</td>
<td></td>
<td>.17</td>
</tr>
<tr>
<td>Single</td>
<td>9 (34.62%)</td>
<td>7 (29.17%)</td>
<td></td>
<td>.68</td>
</tr>
<tr>
<td>Education level (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H: University or higher</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S: 9 or more years of formal education</td>
<td>14</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L: less than 9 years</td>
<td>0</td>
<td>1</td>
<td></td>
<td>2.26</td>
</tr>
<tr>
<td>M: Miss data</td>
<td>0</td>
<td>1</td>
<td></td>
<td>.52</td>
</tr>
</tbody>
</table>
7.1.4 Clinical Characteristics Between RA and SA Groups at Baseline

Baseline clinical characteristics of the RA and SA groups are presented in Table 21. The two groups are comparable in the frequency, duration, intensity and accompanying symptoms of migraine. A typical participant had migraine attacks for 12 days per four weeks with each attack lasting for more than eight hours, the highest pain intensity being 5.5 out of 10 on a 10-cm VAS and 3 on a Six-Likert scale and with more than two accompanying symptoms, such as nausea and photophobia. Per protocol analysis with 48 participants who completed the study confirmed this finding.

The two groups were also comparable on four items of the MPQ, QoL scales and medication consumption measured with MQS and pill count.

Eighteen of 50 participants were diagnosed as Ascending Hyperactivity of Liver Yang according to differentiation of syndromes in Chinese Medicine. Sixteen were in the Deficiency of Qi and Blood sub-group. Ten and six participants had the diagnosis of Phlegm Retention and Blood Stasis, respectively. No group difference regarding the Chinese Medicine syndromes was detected (Table 22).
Table 21: Comparison of baseline clinical characteristics variables of participants

<table>
<thead>
<tr>
<th></th>
<th>RA Mean (SD)[range]</th>
<th>SA Mean (SD)[range]</th>
<th>t-value</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack days (Number of days with migraine per 4 weeks)</td>
<td>11.81 (5.76) [5, 28]</td>
<td>12.41 (6.40) [5, 28]</td>
<td>-.35</td>
<td>(-4.07, 2.85)</td>
<td>.73</td>
</tr>
<tr>
<td>Duration (Hours /attack)</td>
<td>8.99 (3.57) [1.7, 15.43]</td>
<td>8.86 (4.82) [0.92, 22.71]</td>
<td>.11</td>
<td>(-2.27, 2.53)</td>
<td>.91</td>
</tr>
<tr>
<td>Highest of Pain-VAS</td>
<td>6.03 (1.08) [3.63, 8.17]</td>
<td>5.30 (2.04) [1.27, 9.66]</td>
<td>1.64</td>
<td>(-.17, 1.64)</td>
<td>.11</td>
</tr>
<tr>
<td>Lowest of Pain-VAS</td>
<td>3.12 (1.82) [.18, 7]</td>
<td>2.66 (1.90) [0, 7.64]</td>
<td>.88</td>
<td>(-.60, 1.53)</td>
<td>.39</td>
</tr>
<tr>
<td>Average of Pain-VAS</td>
<td>4.62 (1.35) [1.94, 7.5]</td>
<td>4.01 (1.99) [1.7, 8.32]</td>
<td>1.28</td>
<td>(-.35, 1.57)</td>
<td>.21</td>
</tr>
<tr>
<td>Severity of Pain (Six-point Likert Scale)</td>
<td>3.20 (.39) [2.11, 3.89]</td>
<td>3.24 (.62) [2.02, 4.20]</td>
<td>-.27</td>
<td>(-.34, .26)</td>
<td>.79</td>
</tr>
<tr>
<td>Accompanying symptoms (Number of symptoms per attack)</td>
<td>2.70 (0.96) [1, 8]</td>
<td>2.32 (0.96) [1, 7]</td>
<td>1.41</td>
<td>(-.16, .93)</td>
<td>.16</td>
</tr>
<tr>
<td>McGill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRI-S</td>
<td>21.26 (7.5)</td>
<td>18.27 (8.87)</td>
<td>1.29</td>
<td>(-1.67, 7.64)</td>
<td>.20</td>
</tr>
<tr>
<td>PRI-A</td>
<td>6.68 (3.20)</td>
<td>5.40 (2.74)</td>
<td>1.51</td>
<td>(-.42, 2.98)</td>
<td>.14</td>
</tr>
<tr>
<td>PRI-E</td>
<td>3.63 (1.12)</td>
<td>3.51 (1.34)</td>
<td>.34</td>
<td>(-.58, .82)</td>
<td>.73</td>
</tr>
<tr>
<td>PRI-M</td>
<td>7.59 (3.22)</td>
<td>6.74 (2.95)</td>
<td>.97</td>
<td>(-.91, 2.61)</td>
<td>.34</td>
</tr>
<tr>
<td>MSQOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>46.70 (18.93)</td>
<td>54.17 (17.23)</td>
<td>-1.45</td>
<td>(-17.79, 2.86)</td>
<td>.15</td>
</tr>
<tr>
<td>FP</td>
<td>61.73 (20.64)</td>
<td>71.04 (18.97)</td>
<td>-1.66</td>
<td>(-20.61, 1.99)</td>
<td>.10</td>
</tr>
<tr>
<td>EF</td>
<td>48.50 (24.15)</td>
<td>54.72 (24.77)</td>
<td>-.85</td>
<td>(-20.99, 8.55)</td>
<td>.40</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MQS</td>
<td>87.01 (110.15)</td>
<td>93.76 (81.11)</td>
<td>-.25</td>
<td>(-62.14, 48.64)</td>
<td>.81</td>
</tr>
<tr>
<td>Pill Account</td>
<td>7.27 (13.50)</td>
<td>13.50 (20.27)</td>
<td>-.62</td>
<td>(-12.70, 6.74)</td>
<td>.54</td>
</tr>
</tbody>
</table>

PP: indicates the data are based on the per protocol analysis
PRI-S: sensory components
PRI-A: affective components
PRI-E: evaluative components
PRI-M: miscellaneous components
FR: Function-restrictive in Migraine Specific Quality of Life questionnaire
FP: Function-preventive in Migraine Specific Quality of Life questionnaire
EF: Emotional function in Migraine Specific Quality of Life questionnaire
PPT: Pressure Pain Threshold
MQS: Medication Quantification Scale
Table 22: Chinese medicine differentiation syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>RA</th>
<th>SA</th>
<th>Total</th>
<th>$\chi^2$ - value</th>
<th>$p$ - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending Hyperactivity of Liver Yang</td>
<td>7</td>
<td>11</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency of Both Qi and Blood</td>
<td>11</td>
<td>5</td>
<td>16</td>
<td>4.13</td>
<td>.25</td>
</tr>
<tr>
<td>Phlegm Retention</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Stasis</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>24</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.1.5 Effects of Acupuncture on the Primary Outcomes During the Treatment Period

All of the primary outcomes data sampled between Week 17 to 20 (last phase of treatment) were analysed using the Independent-Samples $t$-test, and the results are summarised in Table 23.

Table 23: Primary outcome measurements between Week 17 and 20.

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th></th>
<th>SA</th>
<th></th>
<th>$t$-value</th>
<th>95% CI for difference</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack days (Number of days with migraine per 4 weeks)</td>
<td>5.17 (5.02)</td>
<td></td>
<td>10.08 (7.11)</td>
<td></td>
<td>-2.80</td>
<td>(-8.45, -1.37)</td>
<td>.008*</td>
</tr>
<tr>
<td>Duration (Hours /attack days)</td>
<td>5.96 (3.30)</td>
<td></td>
<td>7.99 (4.49)</td>
<td></td>
<td>-1.83</td>
<td>(-4.26, .20)</td>
<td>.073</td>
</tr>
<tr>
<td>Highest of Pain-VAS</td>
<td>4.96 (1.76)</td>
<td></td>
<td>4.48 (1.89)</td>
<td></td>
<td>1.61</td>
<td>(-.17, 1.64)</td>
<td>.35</td>
</tr>
<tr>
<td>Lowest of Pain-VAS</td>
<td>2.34 (1.92)</td>
<td></td>
<td>2.47 (1.73)</td>
<td></td>
<td>-.24</td>
<td>(-1.16, .92)</td>
<td>.82</td>
</tr>
<tr>
<td>Average of Pain-VAS</td>
<td>3.01 (1.82)</td>
<td></td>
<td>3.24 (1.80)</td>
<td></td>
<td>-.45</td>
<td>(-1.26, .80)</td>
<td>.65</td>
</tr>
<tr>
<td>Severity of Pain (Six-point likert Scale)</td>
<td>2.18 (1.05)</td>
<td></td>
<td>2.93 (.61)</td>
<td></td>
<td>-3.05</td>
<td>(-1.24, -.26)</td>
<td>.004*</td>
</tr>
<tr>
<td>Accompanying symptoms (Number of symptoms per attack)</td>
<td>2.03 (1.41)</td>
<td></td>
<td>1.86 (.87)</td>
<td></td>
<td>.52</td>
<td>(-.49, .84)</td>
<td>.60</td>
</tr>
</tbody>
</table>

Note: * statistical significance assessed at $0.05/6 = 0.0083$ (Bonferroni Correction) for both intention to treat and per protocol analysis

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7.1.5.1 The Effect of Acupuncture on the Frequency of Migraine

The data regarding migraine frequency collected from six phases, including baseline and five phases of treatment were analysed with the General Linear Model (GLM) for repeated measures. There was a significant time effect $[F (5, 240) = 18.372, p < .001]$ and treatment group by time interaction $[F (5, 240) = 4.53, p = 0.002]$ indicating that the number of days with migraine was reduced in both groups over the 20-week treatment period and the reduction was faster in the RA group than in the SA group (Figure 29). During the first eight weeks of treatment, the number of attack days was reduced quickly in the RA and continued to reduce throughout the rest of the treatment period. In contrast, the frequency of migraine in the SA group did not change greatly through the whole 20 weeks treatment period.

Post-hoc analyses were conducted using Independent sample t-tests with a Bonferroni correction. The significance level was adjusted at $\alpha = 0.0083$. A significant difference in the number of days with migraine was found between the two groups ($p = 0.008$) at the end of the 20-week treatment.
Figure 29: The number of days with migraine per four weeks in each group across all treatment time points (Mean and SEM)
Tw4, Tw8, Tw12, Tw16 and Tw20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20 respectively * indicated that at the end of treatment, the mean number of attack days 5.92(0.66) in RA was significantly less than those in SA, 7.99 (0.92).

At the end of 20-week treatment, the number of participants who achieved more than a 50% reduction in the days with migraine is summarised in Table 24. A significant group difference (\(p = 0.002\)) was detected, which indicates that more participants in the RA group responded to the RA treatment than those in the SA.

Table 24: The number of participants responded to the treatment

<table>
<thead>
<tr>
<th></th>
<th>RA (n, %)</th>
<th>SA (n, %)</th>
<th>Total</th>
<th>(\chi^2) value</th>
<th>(p) - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent</td>
<td>19 (73.08%)</td>
<td>7 (9.17%)</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-respondent</td>
<td>7 (16.92%)</td>
<td>17 (70.83%)</td>
<td>24</td>
<td>9.64</td>
<td>.002</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>24</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 25 lists the number of participants in each of the four categories of Chinese medicine syndromes. The Chi-square test indicates there was no significant difference between the treatment groups \( (p = 0.248) \). Table 26 lists the number of respondent and non-respondents in each category of Chinese medicine syndromes. Spearman correlation indicates that was no significant correlation between the two sets of data, \( (p = 0.387) \).

Table 25: The number of participants in each of the four categories of Chinese medicine syndromes

<table>
<thead>
<tr>
<th>Chinese Medicine diagnosis</th>
<th>RA</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending Hyperactivity of Liver Yang</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Deficiency of Both Qi and Blood</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Phlegm Retention</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Blood Stasis</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Chi-square (df)</td>
<td>4.132 (3,50)*</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.248</td>
<td></td>
</tr>
</tbody>
</table>

*3 cells (37.5%) have expected count less than 5. The minimum expected count is 2.88.

Table 26: The number of respondent in each of the four categories of Chinese medicine syndromes

<table>
<thead>
<tr>
<th>Chinese Medicine diagnosis</th>
<th>Respondents</th>
<th>Non-respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending Hyperactivity of Liver Yang</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Deficiency of Both Qi and Blood</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Phlegm Retention</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Blood Stasis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Chi-square (df)</td>
<td>4.132 (3,50)*</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.248</td>
<td></td>
</tr>
<tr>
<td>Spearman Correlation</td>
<td>-.125</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.387**</td>
<td></td>
</tr>
</tbody>
</table>

* 3 cells (37.5%) have expected count less than 5. The minimum expected count is 2.88.

** Based on normal approximation.
7.1.5.2 The Effect of Acupuncture on the Duration of Migraine

GLM analysis was conducted, and the result revealed a significant time effect of duration \( F (5, 240) = 3.77, p = 0.006 \), demonstrating that during the 20-week treatment period, the duration of each migraine attack was reduced in both groups. However, no significant difference was detected between the two groups in terms of duration of time \( F (5, 240) = 2.11, p = 0.082 \) (Figure 30).

![Figure 30: The reduction of migraine duration in each group across all treatment time points (Mean and SEM)](image)

Tw4, 8, 12, 16 and 20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20

7.1.5.3 The Effect of Acupuncture on the Intensity of Migraine

The means of highest, lowest and average pain for every four weeks were measured using VASs. The average pain was also measured with a Six-Point Likert Scale.

GLM analyses revealed that the highest, average and lowest pain were reduced during the treatment period (time effect: highest pain \( F (5, 240) = 6.80, p < 0.001 \); average pain \( F (5, 240) = 10.13, p = 0.082 \); lowest pain \( F (5, 240) = 0.74, p = 0.55 \)). However there was no significant difference between groups by time interaction in the three measures of the
intensity of migraine during the 20 weeks. The time course of the intensity of migraine measured with VASs are illustrated in Figure 31.

Figure 31: The time course of the highest, lowest and average levels of pain measured with VASs over the five treatment phases (Mean and SEM)
Tw4, 8, 12, 16 and 20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20
On the other hand, when pain was measured with the Six-point Likert Scale (Figure 32), GLM analysis indicated there was a significant time effect difference for average pain \( F (5, 240) = 10.15, p < .001 \) induced by the active treatment group by time interaction \( F (5, 240) = 3.14, p = 0.02 \) indicating that the RA group experienced a faster reduction of migraine pain when compared with the SA group.

Figure 32: The time course of the average pain measured with a Six-point Likert Scale over the five treatment phases (Mean and SEM) Tw4, 8, 12, 16 and 20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20 * indicated that at that time point, the mean of average pain measured with Six-point Likert Scale in RA was significantly less than those in SA using a Bonferroni correction on the \( t \)-test

7.1.5.4 The Effect of Acupuncture on the Reduction of Accompanying Symptoms of Migraine

The number of accompanying symptoms per attack was analysed with the GLM, and there was a time effect \( F (5, 240) = 5.80, p < 0.001 \), however, without a treatment group by time interaction \( F (5, 240) = 0.69, p = 0.58 \) (Figure 33), indicating the number of accompanying symptoms decreased in both RA and SA groups to a similar degree.
Figure 33: No significant difference in number of accompanying symptoms was detected between two RA and SA groups in treatment period. Tw4, 8, 12, 16 and 20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20.

7.1.6 The Effect of Acupuncture on the Secondary Outcomes During the Treatment Period

All the secondary outcome data at the last phase of treatment (week 17 to week 20) were analysed using Independent-sample t-tests, and the summary is presented in Table 27.
Table 27: Secondary outcome measurements at the week 17 to 20 (last phase of treatment)

<table>
<thead>
<tr>
<th></th>
<th>RA Mean (SD)</th>
<th>SA Mean (SD)</th>
<th>t-value</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRI-S</td>
<td>13.07 (8.80)</td>
<td>15.83 (11.55)</td>
<td>-953</td>
<td>(-8.57,3.06)</td>
<td>.35</td>
</tr>
<tr>
<td>PRI-A</td>
<td>3.96 (3.01)</td>
<td>4.79 (2.75)</td>
<td>-1.02</td>
<td>(-2.48,.81)</td>
<td>.32</td>
</tr>
<tr>
<td>PRI-E</td>
<td>2.08 (1.26)</td>
<td>2.83 (1.46)</td>
<td>-1.96</td>
<td>(-1.53,.02)</td>
<td>.056</td>
</tr>
<tr>
<td>PRI-M</td>
<td>5.62 (3.39)</td>
<td>6.13 (3.49)</td>
<td>-.52</td>
<td>(-2.47,1.45)</td>
<td>.60</td>
</tr>
<tr>
<td>McGill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRI-M</td>
<td>5.62 (3.39)</td>
<td>6.13 (3.49)</td>
<td>-.52</td>
<td>(-2.47,1.45)</td>
<td>.60</td>
</tr>
<tr>
<td>MSQOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>72.20 (16.37)</td>
<td>57.98 (21.00)</td>
<td>2.68</td>
<td>(3.56,24.89)</td>
<td>.010</td>
</tr>
<tr>
<td>FP</td>
<td>77.12 (16.80)</td>
<td>68.33 (22.73)</td>
<td>1.54</td>
<td>(-2.70,20.27)</td>
<td>.130</td>
</tr>
<tr>
<td>EF</td>
<td>78.31 (19.25)</td>
<td>60.53 (25.55)</td>
<td>2.79</td>
<td>(4.98,30.58)</td>
<td>.007*</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MQS</td>
<td>20.81 (46.43)</td>
<td>68.92 (81.19)</td>
<td>-2.60</td>
<td>(-85.35,-10.87)</td>
<td>.012</td>
</tr>
<tr>
<td>Pill</td>
<td>4.54(12.21)</td>
<td>10.54 (19.31)</td>
<td>-1.32</td>
<td>(-15.12,3.11)</td>
<td>.192</td>
</tr>
<tr>
<td>Account</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: * statistical significance assessed at 0.05/6 = 0.0083 (Bonferroni Correction).
PRI-S: sensory components
PRI-A: affective components
PRI-E: evaluative components
PRI-M: miscellaneous components
FR: Function-restrictive in Migraine Specific Quality of Life questionnaire
FP: Function-preventive in Migraine Specific Quality of Life questionnaire
EF: Emotional function in Migraine Specific Quality of Life questionnaire
PPT: Pressure Pain Threshold
MQS: Medication Quantification Scale
7.1.6.1 Pain Assessed with McGill Questionnaire

The MPQ contains four domains, and a low score reflects a milder level of pain. GLM analysis showed that time effects were detected in all four sub-categories (PRI-S \( F (5, 240) = 7.41, p < 0.001 \); PRI-A \( F (5, 240) = 8.87, p < 0.001 \); PRI-E \( F (5, 240) = 10.34, p < 0.001 \) and PRI-M \( F (5, 240) = 4.50, p = 0.001 \)). However, a treatment group by time interaction was found in PRI-A \( F (5, 240) = 2.82, p = 0.017 \) only (Figure 34).
Figure 34: The trend over time of four domains of MPQ over five treatment phases
Tw4, 8, 12, 16 and 20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20
Post-hoc analysis was conducted using a $t$-test to examine the effects on PRI-A in the treatment week 8 and last treatment phase. However, no significant differences between two groups were detected (TW8: $p = 0.40$; TW20: $p = 0.32$).

7.1.6.2 Quality of Life

Three dimensions of MSQoL, namely, role function-restrictive (FR), role function-preventive (FP) and emotional function (EF) were analysed individually with the GLM for repeated measures.

There were statistically significant time effects in FR [$F (5, 240) = 8.60, p < 0.001$] and EF [$F (5, 240) = 10.83, p < 0.001$] and treatment group by time interaction (FP [$F (5, 240) = 2.97, p = 0.023$] and EF [$F (5, 240) = 596, p < 0.001$]). Both groups improved on FR and EF, however EF and FP showed faster improvement in the RA group when compared to those in the SA group (Figure 35).
Figure 35: Comparisons of MSQOL between two groups at baseline and last phase of treatment (Mean and SEM)

* indicated that at the end of treatment, the EF of MSQOL 78.31 (19.25) in RA was significantly better than those in SA, 60.53 (25.55).
7.1.6.3  Medication Consumption

Medication used by the participants included those for reducing acute migraine headache and those for prophylactic purposes. Their consumption was recorded by the participants in the Headache Diaries during the whole study period. Medications for acute pain, including Aspirin, Brufen, Cafergot, Codiene, Deseril, Panaderine, Panaderine Forte and Tramal, etc, were quantified using MQS. The number of pills of preventive medication including specific anti-migraine and prophylactic drugs, such as Endep, Noten, Sumatripton, Sandomigrain, Valium, Imigrain and Zomig was analyzed. The numbers of participants who took medication during the baseline period and at the end of treatment are listed in Table 28 and Table 29 respectively.

Table 28: Number of participants took different types of medication during the baseline period

<table>
<thead>
<tr>
<th></th>
<th>RA n=26 (n)</th>
<th>SA n=24 (n)</th>
<th>$\chi^2$ - value</th>
<th>$p$ - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants who took pain killers</td>
<td>23</td>
<td>22</td>
<td>.14</td>
<td>.71</td>
</tr>
<tr>
<td>Number of participants who took specific anti-migraine drugs</td>
<td>3</td>
<td>4</td>
<td>.27</td>
<td>.60</td>
</tr>
<tr>
<td>Number of participants who took prophylactic drugs</td>
<td>11</td>
<td>12</td>
<td>.30</td>
<td>.59</td>
</tr>
</tbody>
</table>

Table 29: Number of participants took different types of medication at the end of treatment

<table>
<thead>
<tr>
<th></th>
<th>RA n=26 (n)</th>
<th>SA n=24 (n)</th>
<th>$\chi^2$ - value</th>
<th>$p$ - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants who took pain killers</td>
<td>9</td>
<td>18</td>
<td>8.2</td>
<td>.004*</td>
</tr>
<tr>
<td>Number of participants who took specific anti-migraine drugs</td>
<td>1</td>
<td>4</td>
<td>2.28</td>
<td>.13</td>
</tr>
<tr>
<td>Number of participants who took prophylactic drugs</td>
<td>7</td>
<td>9</td>
<td>.64</td>
<td>.42</td>
</tr>
</tbody>
</table>

* indicated that there was a significant group difference.
There was no statistically significant difference between two groups with respect to the numbers of participants adopting anti-migraine drugs, preventive control drugs or using pain killers during baseline period. However, at the end of treatment fewer participants in the RA group took pain-killers than the SA group did ($p = 0.004$).

The MQS was reduced in both groups during the treatment period (time effects [$F (5, 240) = 7.14$, $p < 0.001$]). Furthermore, there was a trend for a quicker reduction in the RA group when compared with the SA group (treatment group by time interaction [$F (5, 240) = 2.54$, $p = 0.064$]) (Figure 36). Results of the post-hoc $t$-tests demonstrated that at the end of treatment, the participants in the RA group took less pain killers for acute pain than SA group did. Although the group difference achieved significant level ($p = 0.012$), as under the Bonferroni Correction test, the $p$ value less than $0.05/6 = 0.0083$ was considered as a result that showed statistical significance.

![Figure 36: The changed trend of MQS over five treatment phases](image)

$Tw4$, 8, 12, 16 and 20 correspond to the treatment week 1-4; week 5-8; week 9-12; week 13-16 and week 17-20
There were neither time effects \[ F (5, 240)= 1.53, \ p = 0.18 \] nor treatment group by time interaction \[ F (5, 240)= 0.85, \ p = 0.52 \] in the pill account (Figure 37). The number of tablets of preventive medication was slightly reduced in both groups, without reaching statistical significance when comparing the two treatment groups.

![Pill Account](image)

Figure 37: Comparisons of pill account between the two groups

### 7.1.7 Summary of the Short-term Effects of Acupuncture

In summary, at the end of the 20-week treatment period, the frequency of migraine was significantly reduced in both groups. Moreover, there was a more rapid reduction in the RA than in the SA group. In the first eight weeks of treatment, the number of attack days was reduced more quickly in the RA, and this effect was maintained during the remaining treatment period.

The two groups were similar in the reductions of the duration and intensity of migraine when measured with VASs or MPQ and accompanied symptoms. However, the RA group reported a more rapid decline of the intensity of migraine measured with a Six-point Likert Scale, and also improved emotional function and role function-preventative.
Real acupuncture treatment effectively reduced the medication consumption for acute pain when compared with SA, but not preventive medication or specific anti-migraine medications.

### 7.1.8 Adverse Events of Acupuncture

Fifty participants completed 774 sessions of treatment, comprising 400 RA sessions and 374 SA sessions. Fifty adverse events (AE) were recorded, 36 in the RA group and 14 in the SA group. The rates of AE incidences per treatment in the two groups were 9% and 3.74%, respectively. The most frequently reported AE by the RA group was the tingling sensation, recurrent headache followed by cold and sweaty feelings (Table 30). In the SA group, cold and sweaty feelings and then dizziness were more frequent than other AEs.

Most of the AEs were reported as mild or moderate, except for one case. One participant in the RA group experienced severe tingling sensation after a needle was inserted into Hegu (LI4) on the right hand. The participant described that the tingling could be felt on the right side of the face, lasted for one hour, and disappeared after some rest. She withdrew from the study. AEs reported by other participants disappeared after rest. There was no incidence in which special medical management or intervention was required or causing withdrawal of participants from the trial except for the case mentioned above.

Among the total 50 AEs, 37 cases had dizziness, cold and sweaty feelings, bruising, needling pain or headache. These AEs were likely due to being nervous, treatment position or low blood sugar, and acupuncture was defined as risk of these patients. Twelve cases involved tingling sensation, and acupuncture was classified as being the cause. In one case, the participant developed mild spasm in the calf muscle induced by tapping on the thigh after. This AE was classified as not assessable for cause.
Table 30: The adverse events reported by participants in each treatment group.

<table>
<thead>
<tr>
<th>Type of event</th>
<th>RA</th>
<th></th>
<th></th>
<th></th>
<th>SA</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Degree of Severity of Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td>Degree of Severity of Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Total</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Total</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>1</td>
<td></td>
<td>4</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Bruising</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Cold and sweaty</td>
<td>4</td>
<td>4</td>
<td></td>
<td>8</td>
<td>3</td>
<td>2</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Tingling</td>
<td>5</td>
<td>2</td>
<td></td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Recurrent Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total incidents of A.E.</td>
<td></td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total treatment</td>
<td></td>
<td>400</td>
<td></td>
<td></td>
<td></td>
<td>374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidences per treatment</td>
<td></td>
<td>9%</td>
<td></td>
<td></td>
<td></td>
<td>3.74%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.1.9 Credibility of Blinding Process

Credibility of the blinding process was assessed with the Participants’ Perception of Acupuncture Treatment at the end of the first treatment week. All 50 participants completed this three-item questionnaire, which was designed to detect whether the participants could tell the allocation of groups. Data from the two groups are presented in Table 31. No statistically significant differences were detected between the two groups ($p = 0.88$), indicating the blinding was successful.
Table 31: Number of participants’ perception of treatment in each group at the end of first week of treatment

<table>
<thead>
<tr>
<th></th>
<th>Guessing in the RA (n, %)</th>
<th>Guessing in the SA (n, %)</th>
<th>Do not know (n, %)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RA group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 26</td>
<td>14 (53.85%)</td>
<td>4 (15.38%)</td>
<td>8 (30.77%)</td>
<td>26</td>
</tr>
<tr>
<td><strong>SA group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 24</td>
<td>11 (45.84%)</td>
<td>4 (16.67%)</td>
<td>9 (37.5%)</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>8</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
</tbody>
</table>

The participants were asked the reason for their guess. Seventeen participants who could not tell which group they were in and did not select any reason. The majority of the remaining 33 participants made the guess based on the result of the treatment or the manner, attitude or the words of other personnel in the research (Table 32). There was no group difference in the reasons.

Table 32: The reason of guessing group location

<table>
<thead>
<tr>
<th></th>
<th>RA group n = 26</th>
<th>SA group n = 24</th>
<th>Total</th>
<th>$\chi^2$ - value</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No selection</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manner, attitude or words of</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acupuncturist</td>
<td></td>
<td></td>
<td></td>
<td>1.88</td>
<td>.76</td>
</tr>
<tr>
<td>Manner, attitude or words of</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the personnel in the clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results of the treatment</td>
<td>8</td>
<td>4</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26</td>
<td>24</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.1.10 Results of Media Promotion and Participants Recruitment

From October 2005 to September of 2006, a series of methods were used to promote the trial and to recruit the participants. In October 2005, the first media story was released in the MX newspaper in Melbourne. News about the Division of Chinese Medicine and the current trial were published in the major newspapers including the Age and the Herald Sun. Interviews of the main investigators were broadcasted or published on television (Channel Nine), radio (3LO) and local newspaper interviews (Leaders Newspapers). News about the trial was also distributed to the RMIT University staff and students via RMIT internet and to all the members of the Australian Acupuncture and Chinese Medicine Association (AACMA) through email, and the newsletter of AACMA. Advertisements were placed in the local Leader newspaper. The numbers of participants who were enrolled into this study through the above methods are listed in Table 33 and Figure 38. Taking “Radio and MX” as an example, these two promotions were released at the same time. Sixty phone calls were received after that, 26 volunteers returned the Expression of Interest Form after reading the Plain Language Statement. Fourteen participants met the selection criteria and were included into the study.

In this research study, interviews and news in the newspaper and interview with the local radio station are the most effective way to recruit participants.
Table 33: Participants allocation of media release

<table>
<thead>
<tr>
<th></th>
<th>Radio and MX</th>
<th>The Age</th>
<th>Leader newspaper (interview)</th>
<th>Herald Sun</th>
<th>RMIT website</th>
<th>Channel Nine and others</th>
<th>AACMA newsletter</th>
<th>Leader (Ads)</th>
<th>Referred by other participants</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone Enquiries</td>
<td>60</td>
<td>10</td>
<td>32</td>
<td>25</td>
<td>5</td>
<td>15</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>178</td>
</tr>
<tr>
<td>Returned the Questionnaires</td>
<td>26</td>
<td>5</td>
<td>18</td>
<td>13</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>21</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>Included</td>
<td>14</td>
<td>3</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>50</td>
</tr>
</tbody>
</table>
Figure 38: The numbers of participants recruited through various media sources
7.2 Discussion

7.2.1 Population Sample

Participants of the study were volunteers, recruited from the local community around Melbourne, and identified as the migraine with aura and without aura, the two major sub-groups of migraine patients. Furthermore, these participants all experienced at least five days of migraine or more during the four-week baseline period. No upper limit on the maximum migraine days or attacks per month was set. This population sample of high migraine attacks was chosen because the effect of acupuncture on migraine of such high frequency has not been studied previously. Current published migraine trials included patients with 2-6 migraine attacks per month (Diener et al., 2006, Alecrim-Andrade et al., 2008); 2-8 migraine attacks per month (Streng et al., 2006, Lind et al., 2005a) and 2 attacks per month (Allais et al., 2002, Alecrim-Andrade et al., 2006, Vickers et al., 2004a). Part of them reported the mean of days with migraine, ranged from 5 (Linde et al., 2005) to 6.1 days (Diener et al., 2006). The mean attack days at baseline in the current study was about 12 days per four week, much higher than previous published studies.

Among the 50 participants, 37 were females and 13 were males. This conforms with other clinical studies (Demirkirkan et al., 2006, Alecrim-Andrade et al., 2006) and epidemiological studies (Rasmussen, 1999, Aygul et al., 2005), which have shown that migraine is more prevalent in women than in men. This gender difference might also be a consequence of that women seek medical care for headaches more often than men do (Celentano et al., 1990). The migraine history of all participants was 19.68 (12.90 in SD) years, which is similar to other studies (Alecrim-Andrade et al., 2006, Vickers et al., 2004b, Alecrim-Andrade et al., 2008).
The participants of current study aged between 19 and 68 years old, and with the mean of 42.64 (14.10 in SD) years, consistent with a survey conducted in the USA that the peak prevalence of migraine occurs between ages 25 and 55 years (Lipton et al., 2001). The marital status of migraine sufferers has not been widely reported (Abramson et al., 1980, Lafata et al., 2004). In the current study 68% participants of the study were partnered. Similar percentage was also reported by one other study (Aygul et al., 2005).

7.2.2 Blinding Procedure

Randomised, double blind and controlled study is recognised as the gold standard design for clinical study. However, blinding the acupuncturist has been proven unfeasible for acupuncture studies. Employing independent assistants who are in charge of randomisation, data entry and checking was recommended to minimize bias (Margolin et al., 1998). Describing this procedure as a modified double-blind (patient/evaluator blinded) trial is acceptable when the intervention characteristics preclude investigator blinding (Jadad et al., 1996). In this study, independent assistants were employed for randomisation, data entry and assessing pressure pain thresholds.

Furthermore, two sham procedures were conducted to ensure the success of sham acupuncture and to minimize the non-specific effects of needling. This is discussed in the following Section 10.3. In addition, the success of blinding was measured. From the literature, there are two methods to assess this item in acupuncture studies. The first operates as a surrogate for testing blinding, and tests for psychological impact of the real and sham interventions. The credibility of the interventions is assessed by questions, such as whether the participant would
recommend the treatment to other friends (Vincent and Lewith, 1995). The second method, employed by the current study, asks the participants directly, which group they think they were in. In order to minimize the perception from the treatment effects, we chose the second week of the treatment period to assess the credibility of the intervention. The result showed that blinding of participants was successful, as there was no difference between the two groups in the participants’ perception of group allocation and reasons.

7.2.3 Sham Acupuncture Control

The purpose of employing control intervention in a clinical trial is to elicit the belief in participants that they have received a real intervention. Various strategies were adopted in the trial to mimic real acupuncture procedure and make sham acupuncture indistinguishable from real acupuncture by participants.

7.2.3.1 Selection of Acupuncture Points

Sham points were 1-2 cm away from the real acupuncture points to avoid stimulating the meridians. This method attempts to mimic acupuncture technique and minimize afferent stimulation along the same meridians with the real acupoints. This method has been used by acupuncture trials on various diseases (Xue et al., 2004, Vincent, 1989a, Xue et al., 2007), including migraine studies (Linde et al., 2005a). A systematic review reported almost half (27 out of 47) studies employed this technique (Dincer and Linde, 2003). Because the head has a high density of real acupoints, therefore, in the present trial only two sham points were used in the head. In some trials, no head sham points were chosen (Diener et al., 2006).
7.2.3.2 Selection of Needles

The thickness of needles is considered as an important factor for inducing therapeutic effect in acupuncture, as the stimulus strength would increase with the thickness of needles (Marcus, 1994). Therefore needles used in the sham acupuncture group are often thinner and shorter than those used in real acupuncture group (Xue et al., 2002). Although, some trials still employed same needles in two acupuncture groups (Alecrim-Andrade et al., 2006), in the present study, thinner needles with 0.22 mm in diameter were used in the SA group rather than the needles with 0.25 mm in diameter used in the RA group, in order to minimize the specific effects of sham acupuncture.

7.2.3.3 Selection of Stimulation Mode

In acupuncture trials, it is difficult to establish a true placebo intervention, as sham acupuncture is not an inert treatment (Le Bars et al., 1991), and may produce non-specific effects (Birch, 2006), such as the analgesic effects produced via diffuse noxious inhibitory control (DNIC) by simply piercing the skin (Le Bars et al., 1991). Even though conducting standardised sham needling method on non-acupoints by the same acupuncturist, it is impossible to eliminate the non-specific effects of sham acupuncture, because there are other variables considered as potential modifiers of needling effects, such as depths of insertion, manipulation of the needle, etc. For these reasons, sham acupuncture often involves shallow needling and without eliciting Deqi, which is a level of stimulation essential to traditional Chinese acupuncture. The results of previous clinical trials supported that success was higher in patients who reported feeling of Deqi (Lundeberg et al., 1988).
Two methods of stimulation were employed in the current study. For distal points on the arms and legs, needles were shallowly inserted to a 2 mm depth as the depth of insertion is considered as an important factor for inducing therapeutic effect in acupuncture, and has been demonstrated to be in proportion to the stimulus strength (Marcus, 1994). It is the most popular method of sham acupuncture (Dincer and Linde, 2003).

For the two sham points on the head, blunt acupuncture without insertion of needles into the skin was used. This method of non-invasion is reported as the second popular sham technique in acupuncture trials by a review (Dincer and Linde, 2003) and used by other acupuncture studies for migraine (Linde et al., 2004) and for tension-type headache (Karst et al., 2001). Especially, in some trials for pain related conditions, where penetration of the skin is commonly thought of as the single most important mechanism, the blunt acupuncture method was widely employed (Linde et al., 2004, Streitberger and Kleinhenz, 1998). The validity of this method has been demonstrated by White’s study (2003). Furthermore, a systematic review showed that shallow invasive sham needling within the dermatome of the diseased area was almost as effective as RA (Sánchez Aranjo, 1998), indicating non-invasive procedure should be used on the head points when studying the effect of acupuncture on headache.

Finally, in order to ensure the credibility of the sham acupuncture, participants with few acupuncture experience were recruited, therefore they could not identify the sham acupuncture according to the past experience. Such criterion has been used in most acupuncture studies (Berman et al., 2004, Xue et al., 2007, Alecrim-Andrade et al., 2008).
7.2.4 Acupuncture Protocol

Number and frequency of treatment sessions are of considerable concern as they may be reasons for negative outcomes of acupuncture studies (White et al., 2001). Although, to date there is no standard treatment protocol available for acupuncture studies. A systematic review on chronic pain revealed that studies in which participants received six sessions or more were significantly more likely to have positive findings than the studies with fewer sessions did (Ezzo et al., 2000). Ceccherelli and his colleagues (2000) suggested that the study with twice per week treatment was more successful than those with weekly treatment. This option was supported by the result of the systematic review of Chinese literature (Chapter Five).

In the current clinical study, twice per week treatment was applied for the first four weeks, then frequency of treatment gradually reduced to once per month. This gradual reduction in treatment frequency is commonly used in clinical practice to consolidate the effects achieved by the first eight weeks, and to avoid recurrent headache from abrupt withdrawal of acupuncture. Totally, 16 sessions of treatment were delivered in 20 weeks, which is a quite long treatment period.

This method has been used in an acupuncture study for osteoarthritis in the knee (Berman et al 2004), which consisted of a total of 23 treatments during 26 weeks (eight weeks of twice treatments per week, then once per week for another two week followed by four weeks of once per fortnight, then monthly treatment for another 12 weeks). However, such long treatment period was seldom applied by other acupuncture studies for migraine except for one study (Allais et al., 2002). For instance, in Linde (2005a) and Alecrim-Andrade’ studies
(2008), 12 and 16 treatment-sessions were conducted in 8 and 12 weeks respectively. In Allais’ study (2002), 24-week treatment period was used, and acupuncture was compared with western medication and their study findings revealed acupuncture was adequate for migraine prophylaxis. One limitation of Allais’ study is that once-a-week treatment was conducted for the first 8 weeks, which may weaken the effect of acupuncture compared with twice per week treatment.

Point selection is also important element in successful treatment. Commonly acupuncturists should make the treatment plan based on individual situation, including the choice of points, or method of stimulation (Sun, 1998). However the superiority of individual treatment in comparison with formula acupuncture has not been demonstrated in clinical trials (White et al., 2001).

In the present study the treatment method adopted a semi-structured acupuncture prescription which included four mandatory acupoints plus up to six supplementary acupoints chosen according to the individual’s syndrome differentiation based on signs and symptoms. All four mandatory acupoints are most commonly used points for migraine as identified from systematic review of Chinese literature (Chapter Five), and three of them are in the top five frequently used acupoints of the systematic review of English literature (Chapter Four).
7.2.5 Effectiveness of Acupuncture

7.2.5.1 The Effect of Acupuncture on the Frequency of Migraine

The results of the present clinical trial show that acupuncture could reduce the frequency of migraine during the treatment period. Accordingly, the numbers of respondents was higher in the RA group than that in the SA group. During the first eight weeks of treatment, the number of attack days reduced quickly in the RA group and continued to reduce throughout the rest of the treatment period, which is in agreement with those of Alecrim-Andrade (2008) in their study on acupuncture for migraine. However, in Alecrim-Andrade’s study, the respondent rate which is more than 50% improvement in the frequency, was used. Such outcome measure is not so sensitive as the mean and SD. According to the Guidelines for Controlled Trials of Drugs in Migraine (2000), respondent rate is a relatively insensitive measurement. It can only be used to identify a subgroup of respondents in *post hoc* analysis.

The findings on migraine frequency of the current study demonstrated that the RA is significantly better than SA, which was different with some other studies (Linde et al., 2004, Linde et al., 2005a, Alecrim-Andrade et al., 2006). These authors reported that RA and SA both contributed to the reduction of frequency, thus, resulting in no significant difference in frequency reduction between RA and SA groups. The success of frequency reduction in the current study may be due to the fact that all recruits in this study had higher frequency of migraine per month at baseline than other studies. They had five days or more per month. A study with 284 migraineurs and 17 tension-type headache patients found that obvious improvement in the number of days with migraine appeared in the participants with more than four days with headache per month (Vickers et al., 2004a). Our study seems to support this
claim. A second reason for producing positive results may be our treatment regime. To this
date, our study of acupuncture for migraine has the longest treatment period of 20 weeks
among all previous studies. The treatment protocol started with higher number of acupuncture
sessions of twice per week and then gradually decreased to once a week, then once a fortnight
and finally once a month towards the end. Such regime is quite different from previous
published trials of less than 12 weeks treatment-period (Streng et al., 2006, Diener et al.,
2006). Further, the sham acupuncture in this study which had been designed to optimally
minimize non-specific effects might also contribute to the success (detailed see Section 7.2.8
Placebo Effects).

7.2.5.2 The Effect of Acupuncture on the Duration of Migraine

Although RA acupuncture reduced duration of each migraine attack in the RA group, there
was no group different on this measure in this study. Two studies conducted by
Alecrim-Andrade and her colleagues (2008, , 2006) demonstrated that acupuncture reduced
the total hours in pain per four weeks. However, these studies employed the widely used
measurement method of Headache Index (Liguori et al., 2000, Wylie et al., 1997). Results
obtained from Headache Index should be considered with care because they combined the
duration of each attack with the frequency of migraine attack. It is important to understand
that decrease in the frequency of attack alone can contribute to a reduction of the total number
of hours in pain per four weeks. This assessment method is different from our single measure
of hours per attack. We chose this approach since in most cases where a decrease in total
hours of pain is found, this is due to a decrease in frequency attacks (International Headache
Society Clinical Trials Subcommittee, 2000). To date, there is only one other study (Hesse et
al., 1994) that also used the same single measurement of duration of migraine alone as in our study. They also reported no significant difference in total hours of pain per four weeks between the two groups. This difference of results by the two different measurement methods clearly demonstrates possible bias due to assessment methodology.

7.2.5.3 The Effect of Acupuncture on the Intensity of Migraine

The severity of migraine tested by VAS slightly decreased in both groups, without significant group difference being detected. Such findings are consistent with other migraine studies (Linde et al., 2004, Melchart et al., 2003a, Hesse et al., 1994), as well as tension-type headache studies (Karst et al., 2001, White et al., 2000). However, severity assessed by a Six-Point Scale revealed significant group difference in current study. This anomaly in the results in severity between VAS and Six-Point Scale could be explained by the higher sensitivity and user-friendly nature of the latter scale. Generally, the six-point scale was described by words, such as “0” means no headache; “4” means very severe headache: I find it difficult to concentrate and can do only undemanding tasks. This scale is easier to use than the VAS. Moreover, the VAS are likely to be too complicated to use in long-lasting prophylactic RCTs (International Headache Society Clinical Trials Subcommittee, 2000). Vickers and his colleagues (2004a) used the Six-Point Scale for chronic headache patients and found that the scores were significantly lower in the acupuncture group. Some studies (Alecrim-Andrade et al., 2008, Alecrim-Andrade et al., 2006) chose a brief Four-Point Scale, and found no significance between the two groups.
7.2.5.4 **Quality of Life**

Recent population-based studies have demonstrated that migraine impairs quality of life due to high frequency of attack and compromised physical, mental and social functioning (Terwindt et al., 2000). The SF-36 questionnaire is a commonly used outcome measure instrument for evaluating the efficacy of an intervention on quality of life. In this study, we used MSQOL questionnaire, based on the SF-36, but specifically for the migraine sufferers, assessed three aspects, namely, role function-restrictive, role function-preventive and emotional function. MSQOL was introduced in 1997, and has been widely used for migraine studies involving various therapies other than acupuncture (Shevel, 2007, Spigt et al., 2005) and survey based studies (Vos and Passchier, 2003), but has not been used in acupuncture studies for migraine.

The effectiveness of acupuncture in improving QoL of pain conditions in certain aspects has been supported through RCTs (Jena et al., 2008, Coeytaux et al., 2005). On the other hand, some studies stated that acupuncture cannot achieve significant improvement when compared with sham acupuncture (Jubb et al., 2008, Grant et al., 1999). In the present study, the role function – preventive and emotional function in RA group demonstrated a significant improvement when compared with SA group. This may be due to the reduction of frequency alone.


7.2.5.5 **Medication Consumption**

The first line of anti-migraine agents normally taken by migraine sufferers for acute pains and prophylaxis are the analgesics. The type of rescue medication took by migraineurs are analgesia for acute pain, anti-migraine agents normally taken when the first symptoms of migraine occur. Alecrim-Andrade (2008) pointed out that most migraineurs used more than two types of medication. In the current study, 90% participants took either simple or compound analgesics, which is consistent with figures in other migraine studies (Streng et al., 2006) which reported 76% with simple and 19% with compound analgesics.

Our study is among the few acupuncture studies using the MQS to measure consumption of analgesics, rather than by pill counts or by number of patients who take analgesics. At present, there are numerous different types of pain killers with various analgesic strengths. Therefore, simple pill counts of analgesics do not tell the types of medication nor the total medication weight. Thus, the patient’s strength of medication consumption is not truthfully reflected. In our study real acupuncture treatment achieved reduction of analgesics more quickly for acute pain as assessed by MQS, than did sham acupuncture. Similar findings were also detected by other studies (Allais et al., 2002, Vickers et al., 2004b) in which treatment effects were measured by pill counts and MQS respectively. This reduction included all types of medications. This can be explained by our finding that the frequency of attack was significantly reduced in the RA group. Consequently, a lower number of days with migraine would result in a reduced demand for medication consumption, simple or compound analgesics included.
Around half of participants took anti-migraine drugs or prophylactic drugs in this study. However, we could not compare our results with other relative migraine studies, as these published studies did not report the consumption of each type of medications as discussed above.

7.2.6 Safety

The safety of acupuncture treatment is an important consideration in the practice of Chinese medicine (White, 2004). Some surveys (Ernst and White, 2001, Melchart et al., 2004b) have shown that acupuncture is well tolerated and that serious complications are rare events. Although a number of AEs like pneumothorax have been reported by other studies, such events are rare and generally associated with poorly trained and unlicensed acupuncturists (Birch, 2004). In our study only minor AEs were encountered. The type of AEs and their incident rate of 9% in the RA group is lower than the 15% reported in a survey conducted in the United Kingdom, further confirming that acupuncture is a relatively safe form of treatment technique (MacPherson et al., 2001).

Apart from the common AEs associated with acupuncture such as needling pain and bruising, a peculiar AE, a recurrent headache in the first couple of treatment sessions, was reported nine times by our participants. The headache, however, did not lead to a real migraine onset, and disappeared after resting. Such AE phenomenon was also reported by one other acupuncture study for migraine (Allais et al., 2002). Furthermore, according to the record of diary, some participants actually experienced more migraine attacks in the first four-weeks after
acupuncture. Whether this observation was a reaction to acupuncture or simply a coincidence of the individual’s migraine development is unclear.

7.2.7 Drop-out Rate

Although our study has the longest acupuncture treatment period compared to other migraine prophylactic studies (Streng et al., 2006), the drop-out rate was low at 6%, a figure similar to a recently published study of acupuncture for migraine (Alecrim-Andrade et al., 2008). This result indicates that a long-term treatment protocol can be well tolerated and accepted by most of the patients.

7.2.8 Placebo Effect

Some improvements in the SA group had been observed in certain outcome measures during the treatment period although this response did not negate the overall statistical significance group difference. This SA improvement is most likely the consequences of the placebo effects and non-specific effect of acupuncture, such as the analgesic effect resulting from skin piercing. Pervious studies have argued that needling the sham points located outside of meridian but within the same dermatome as the treatment acupoints have some treatment effects, as even the shallow insertion can activate the diffuse noxious inhibitory control (DNIC) (Berman, 2001). Linde et al.(2005a) used invasive sham acupuncture in migraine patients, and found that the results showed a meaningful improvement of pain, although statistically insignificant. And most trials comparing real acupuncture with such sham acupuncture technique (i.e., needling slightly away from the active acupoint, but within the same dermatome) have very often yielded negative results between the RA and SA groups for
various conditions. This may lend support to the argument to the involvements of DNIC. Furthermore, Sanchez Aranjo (1998) reviewed 100 clinical trials and revealed that putting needling close to active acupoints but outside of the meridians can produce greater placebo effect than putting needles on different nerve segment, or dermatome. On the other hand, if sham acupuncture without puncture were employed, acupuncture clinical trials showed positive results more frequently (Richardson and Vincent, 1986). The current study has adopted the non-puncture method by using blunt needling for the sham points in the head. Undoubtedly, such blunt sham method could minimize the non-specific effects of invasive needling even though no scientific evidence is yet available to support that it is inert. Nevertheless, it must be pointed out that, the participants’ belief in positive results of the acupuncture treatment, the regular visits to the acupuncturist and the subjective belief of the magic power of the non-conventional therapies may all be the contributing factors to placebo effect and all could enhance the therapeutic effect. In the current study, nearly 30% SA participants responded positively to the sham treatment. This is comparable to data by other studies (Linde and Rossnagel, 2004, Diener et al., 2002, Brandes et al., 2004). Furthermore, there is some evidence that medical devices induced a much higher placebo effect than medications did (Kaptchuk et al., 2000). Especially the subcutaneous placebo had higher efficacy (34%) than oral application does (26%) (Diener, 2001). Even the blunt needling was still greater than placebo pills (Kaptchuk et al., 2006). A systematic review reported that there was a 46% placebo response for pain relief and 21% for pain-free in pharmacological pediatric migraine trials (Fernandes et al., 2008).
However, these placebo effects also exist in the RA group. Our significant results were based on difference between the two groups. Therefore, the placebo effects do not invalidate our conclusion of statistically significant positive outcomes.

### 7.2.9 Limitations and Implications for Future Studies

There are several limitations in the present study, which need to be addressed in future studies.

The main limitation is the small sample size. Inadequate sample size can skew the findings (Moher et al., 1994) and this has been a common problem for acupuncture trial (ter Riet et al., 1990, Melchart et al., 2001). The originally targetted sample size of the present study was a total of 66 participants, based on a migraine study which achieved statistical significance between acupuncture and waiting list groups on the frequency of headaches. In the end, our study only managed to recruit fifty participants. There are several reasons, which may contribute to the difficulties of recruiting participants. First of all, with the increasing popularity of acupuncture, it is difficult to enroll participants who have no previous acupuncture experience. Surveys revealed that headache sufferers accounted for about 10% of visits to acupuncturists in USA (Burke et al., 2006), and more than 25% in Germany (Endres et al., 2007b). In order to ensure the success of the blinding of participants, we recruited only subjects who had not received acupuncture treatment for headache in the last six months. Secondly, our criterion of recruiting only participants who had five days or more of migraine per month excluded many interested migraine sufferers who had a lower frequency of attack, thus limiting our recruitment capability. Finally, the long-treatment
period might also be an obstacle or impediment. Some people were unwilling and or unable to
commit themselves for such a long period of time.

The Oxford Pain Validity Scale, which is designed to assess the quality of clinical trial for
pain conditions, has defined trials with 40 or more participants as satisfactory sample size.
Nevertheless, a small sample size is still possible if more disease-specific primary outcome
measures, such as frequency or intensity of migraine headaches, are chosen (Melchart et al.,
2001). Consequently, in the current study, there was still sufficient power to detect significant
changes in frequency and intensity of migraine.

In addition, sham acupuncture method is still a controversial issue. So far no universal
agreement on an inert method of sham acupuncture is available (Birch, 2006). The
non-specific effects produced by shallow needling may reduce the difference in effect size of
real and sham acupuncture.

Another potential limitation is that frequent migraine sufferers might have a higher
expectation for acupuncture than normal migraineur do. Previous studies have shown that the
expectation caused greater activation than skin prick (Pariente et al., 2005). In this project all
participants were volunteers. One of the reasons that they joined the study was that they learnt
from others’ experience that acupuncture was helpful. 62% participants are in this category.
They might have expected a good treatment response. Although one would argue that the
same expectation also occurred in the sham acupuncture group. The exact contribution of this
factor is unknown in the present study. Future studies should include a measurement of expectations.

In conclusion, acupuncture is potentially effective in preventing migraine attacks in short term. Its long-term effect is presented and discussed in the following chapter.
CHAPTER EIGHT: LONG TERM EFFECTS OF ACUPUNCTURE TREATMENT ON MIGRAINE

This chapter presents the analysis of data collected during the 12-week follow-up I period of the study and the 12-month follow-up II period. Independent-sample $t$-tests were used to detect the differences between the two groups in weeks 4, 8 and 12, and at the end of 12 months. Furthermore, paired-sample $t$-tests were used to compare data sampled in weeks 4, 8 and 12 of follow-up I, as well as data from the end of follow-up II, with data from the end of treatment. This data was used to assess the long-term effects of acupuncture. The significant $p$ value was set at $0.05/3=0.0167$ with Bonferroni correction.

For the follow-up I data, ITT analyses were used. The data of three drop-out participants was replaced using the Missing Value Analysis function in SPSS, except for MPQ and MSQOL. A detailed description of data handling is presented in section 6.7.3. In total, 50 participants were included.

For follow-up II, the data of 25 participants who sent their dairies back was analyzed. Thus per protocol analyses were employed.
8.1 Results of Twelve-week Follow-up I Period

8.1.1 The Effects of Acupuncture on the Primary Outcomes During the Follow-up Period

The results of the primary outcomes data during the last phase of follow-up I are presented below in Table 34.

Table 34: Primary outcome measurements at the end of the 12-week follow-up I period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RA Mean (SD)</th>
<th>SA Mean (SD)</th>
<th>t-value</th>
<th>95% CI for difference</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack days (Number of days with migraine per 4 weeks)</td>
<td>5.12 (3.67)</td>
<td>9.47 (6.20)</td>
<td>-2.99</td>
<td>(-7.20, -1.40)</td>
<td>.005*</td>
</tr>
<tr>
<td>Duration (Hours /attack days)</td>
<td>8.17 (2.81)</td>
<td>8.81 (4.05)</td>
<td>-.65</td>
<td>(-2.61, 1.33)</td>
<td>.52</td>
</tr>
<tr>
<td>Highest of Pain-VAS</td>
<td>4.79 (1.39)</td>
<td>4.66 (2.03)</td>
<td>.25</td>
<td>(-.86, 1.11)</td>
<td>.80</td>
</tr>
<tr>
<td>Lowest of Pain-VAS</td>
<td>2.55 (1.10)</td>
<td>2.62 (1.65)</td>
<td>-.18</td>
<td>(-.86, .72)</td>
<td>.86</td>
</tr>
<tr>
<td>Average of Pain-VAS</td>
<td>3.90 (1.03)</td>
<td>3.60 (1.89)</td>
<td>.72</td>
<td>(-.55, 1.16)</td>
<td>.48</td>
</tr>
<tr>
<td>Severity of Pain (Six-point Likert Scale)</td>
<td>2.63 (.39)</td>
<td>2.87 (.56)</td>
<td>-1.76</td>
<td>(-.52, .04)</td>
<td>.087</td>
</tr>
</tbody>
</table>

Note: * indicates statistically significant difference at the 0.05 level (2-tailed)
8.1.1.1 The Effect of Acupuncture on the Reduction of Frequency of Migraine

During the 12-week follow-up I period, the RA group had fewer numbers of migraine days when compared with the SA group. At the end of this follow up period, the RA group had 5.12 (3.67) days with migraine, which was significantly less than the SA group 9.47 (6.20) days with migraine ($p = 0.005$).

Within-group analysis using the paired-sample $t$–tests showed the numbers of days with migraine in the RA or SA did not change significantly during the 12-week follow-up period when compared with the end of treatment (Figure 39). This indicates the effects of acupuncture were maintained throughout the follow-up period.

![Figure 39: The time course of the number of days with migraine in the two groups during the follow-up I period (Mean and SEM)](image)

Pw4, 8 and 12 correspond to the post-treatment week 1-4; week 5-8 and week 9-12

* indicates that at the Pw4, Pw8 and Pw 12, the mean number of attack days 5.87 (1.07), 5.62 (0.88) and 5.12 (0.73) in RA was significantly less than those in SA, 9.85 (1.45), 9.32 (1.2) and 9.47 (1.27).
At the end of the 12-week follow-up period, the number of participants who achieved more than a 50% reduction from the baseline, i.e., the respondent is listed in Table 35. Significant group difference was revealed ($p = 0.002$) with the RA having more respondents.

Table 35: The number of participants who respond to the treatment at end of follow-up period

<table>
<thead>
<tr>
<th></th>
<th>RA ($n, %$)</th>
<th>SA ($n, %$)</th>
<th>Total</th>
<th>$\chi^2$- value</th>
<th>$p$ - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent</td>
<td>17 (65.38%)</td>
<td>5 (20.83%)</td>
<td>22</td>
<td>10.05</td>
<td>.002*</td>
</tr>
<tr>
<td>Non-respondent</td>
<td>9 (34.62%)</td>
<td>19 (79.17%)</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>24</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* indicates there was a significant difference between the two groups

The numbers of respondents at the end of follow-up I period in each category of Chinese medicine diagnosis is listed in Table 36. The Spearman correlation indicates the significant relationship between the respondent rates at the end of follow-up I and the different Chinese medicine syndromes ($p = 0.034$). The participants who experienced migraine from Ascending Hyperactivity of Liver Yang had the poorest response rates.
Table 36: Number of participants who respondent to the acupuncture in each group of Chinese medicine syndrome at the end of follow-up period I

<table>
<thead>
<tr>
<th>Chinese Medicine diagnosis</th>
<th>Respondent</th>
<th>Non-respondent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending Hyperactivity of Liver Yang</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Deficiency of Both Qi and Blood</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Phlegm Retention</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Blood Stasis</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Chi-square (df) 5.84 (3,50)*

* 3 cells (37.5%) have expected count less than 5. The minimum expected count is 2.64.

Spearman Correlation -.30

P .034**

8.1.1.2 The Effect of Acupuncture on the Reduction of Duration of Migraine

No significant difference in the duration of migraine was detected between the two treatment groups at the end of the 12-week follow-up period ($p = 0.52$).

Paired-sample t–tests showed that the duration of migraine in the RA group increased rapidly during the follow-up period, from 5.96 (3.31) hours at the end of the treatment to 8.17 (2.81) hours at the end of the follow-up period. There was a significant difference in the duration measured at the end of the follow-up period when compared with the data from the end of treatment ($p < 0.001$). Contrary to this, the changes in the SA group were not statistically
significant during the same period [7.99 (4.49) to 8.81(4.05) hours] (Figure 40). Such data illustrates the reduction of duration of migraine observed during the treatment period in the RA group was maintained for eight weeks after treatment.

![Figure 40: The trend of duration of migraine in two groups during follow-up period (Mean and SEM)](image)

Pw4, 8 and 12 correspond to the post-treatment week 1-4; week 5-8 and week 9-12
+ indicates that, the mean of duration of migraine attacks at the end of Pw 12 was 8.17 (0.56) in RA was significantly more than those at the end of Tw20 5.92 (0.66).

### 8.1.1.3 The Effect of Acupuncture on the Reduction of Intensity of Migraine

There were no significant differences between the RA and SA groups in terms of highest ($p = 0.80$), lowest ($p = 0.86$) and average ($p = 0.48$) VAS pain and the average pain on the Six-Point Likert Scale ($p = 0.087$) at the end of the follow-up period.

In the RA group, the highest and lowest level of pain on VAS, and average pain in the six-point Likert Scale, slightly fluctuated without reaching statistical significance during the follow-up period ($p = 0.45$; 0.49 and 0.027 respectively) when compared with the last phase...
of treatment. The average pain levels measured using VAS significantly increased ($p = 0.006$) after the termination of the acupuncture treatment.

In the SA group, no significant differences were detected with respect to any of the highest, lowest and average levels of pain on VAS, or the average value pain on the six-point Likert Scale at any stage of the follow-up period when compared with the end of treatment data. See the following graphs in Figure 41.

Figures 41: The intensity of migraine of the two groups during the 12-week follow-up period, presented using mean (SEM)
Continued Figures 41: The intensity of migraine of the two groups during the 12-week follow-up period, presented using mean (SEM) Pw4, 8 and 12 correspond to the post-treatment week 1-4; week 5-8 and week 9-12 + indicates the intensity of migraine significantly changed within the RA group at the Pw12 3.90 (0.21) when compared with Tw20 3.01(0.36) (p < 0.0167).
8.1.1.4 The Effect of Acupuncture on the Reduction of Accompanying Symptoms of Migraine

There were no significant differences between the RA and SA groups at the end of the follow-up period. Results of paired-sample $t$-tests showed that there were no significant changes in either group during any stage of the 12-week follow-up period (Figure 42).

Figure 42: The number of accompanying symptoms of the two groups during the 12-week follow-up period, presented using mean (SEM)

Pw4, 8 and 12 correspond to the post-treatment week 1-4; week 5-8 and week 9-12
8.1.2 The Effect of Acupuncture on the Secondary Outcomes During the Follow-up Period

All the secondary outcomes data from the last phase of follow-up were analysed and are presented in Table 37.

Table 37: Secondary Outcome measurements at post-treatment weeks 8 to 12 (last phase of follow-up period)

<table>
<thead>
<tr>
<th></th>
<th>RA Mean (SD)</th>
<th>SA Mean (SD)</th>
<th>t-value</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRI-S</td>
<td>11.13 (4.24)</td>
<td>14.09 (8.99)</td>
<td>-1.47</td>
<td>(-7.07, 1.13)</td>
<td>.15</td>
</tr>
<tr>
<td>PRI-A</td>
<td>3.30 (2.13)</td>
<td>4.36 (3.10)</td>
<td>-1.42</td>
<td>(-2.56, .44)</td>
<td>.163</td>
</tr>
<tr>
<td>PRI-E</td>
<td>1.58 (.86)</td>
<td>2.59 (1.32)</td>
<td>-3.23</td>
<td>(-1.64, -.38)</td>
<td>.002*</td>
</tr>
<tr>
<td>PRI-M</td>
<td>5.50 (.86)</td>
<td>5.85 (2.85)</td>
<td>-.46</td>
<td>(-1.92, 1.21)</td>
<td>.651</td>
</tr>
<tr>
<td>MSQOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>74.18</td>
<td>56.31</td>
<td>3.19</td>
<td>(6.52, 29.21)</td>
<td>.003*</td>
</tr>
<tr>
<td>FP</td>
<td>80.77</td>
<td>63.13</td>
<td>2.87</td>
<td>(5.08, 30.21)</td>
<td>.007*</td>
</tr>
<tr>
<td>EF</td>
<td>79.33</td>
<td>58.80</td>
<td>3.08</td>
<td>(7.06, 33.99)</td>
<td>.004*</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MQS</td>
<td>10.99</td>
<td>54.27</td>
<td>-3.19</td>
<td>(-69.79, .002*</td>
<td>.002*</td>
</tr>
<tr>
<td>Pill</td>
<td>3.46 (9.84)</td>
<td>10.10</td>
<td>-1.63</td>
<td>(-14.93, 1.64)</td>
<td>.113</td>
</tr>
</tbody>
</table>

Note: * indicates statistically significant difference at the 0.05 level (2-tailed)
8.1.2.1 Pain Assessed with McGill Questionnaire

For MPQ, the only significant difference between the two groups was PRI-E measured at the end of the follow-up period ($p = 0.002$). (Table 38),

Table 37: Pain assessed with MPQ in each group at the Tw 20 and Pw 12

<table>
<thead>
<tr>
<th></th>
<th>Treatment week 20</th>
<th>Post-treatment week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA $n = 26$</td>
<td>SA $n = 24$</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>PRI-A</td>
<td>3.96 3.01</td>
<td>4.79 2.75</td>
</tr>
<tr>
<td>PRI-E</td>
<td>2.08 1.26</td>
<td>2.83 1.46</td>
</tr>
<tr>
<td>PRI-M</td>
<td>5.62 3.40</td>
<td>6.13 3.49</td>
</tr>
</tbody>
</table>
Results of paired-sample $t$-tests for within group effects showed that there were no significant changes in either group at any stage of the 12-week follow-up period when compared with the end of treatment data (Figure 43).

Figure 43: The trend of four dimensions of MPQ in two groups during follow-up period (Mean and SEM)
Pw4, 8 and 12 correspond to the post-treatment week 1-4; week 5-8 and week 9-12.
* indicates that at the end of follow-up period I, the mean PRI-E 1.58(0.17) in RA was significantly less than those in SA, 2.59 (0.27).
Continued Figure 42: The trend of four dimensions of MPQ in two groups during follow-up period (Mean and SEM). Pw4, 8 and 12 correspond to the post-treatment week 1-4; week 5-8 and week 9-12. * indicates that at the end of follow-up period, the mean PRI-E 1.58(0.17) in RA was significantly less than those in SA, 2.59 (0.27).

8.1.2.2 Quality of Life

Statistically significant differences in all of the three categories were detected between the two groups at the end of the follow-up period (FR $p = 0.003$, FP $p = 0.007$, EF $p = 0.004$), which indicated the QoL of the participants in the RA group maintained after discontinuation of treatment.

Paired-sample $t$-tests revealed a statistically significant increase in FP for the RA group, but not in FR or EF dimensions between the end of treatment and the follow-up periods ($p = 0.03$) (Figure 44), indicating the effect of RA on FR and EF of QoL lasted for 12 weeks.
Figure 44: The trend of three dimensions of MSQOL in two groups during follow-up period
* indicates significant difference between two groups at that time point. + indicates significant change within the RA group at the time points when compared with tw20 (at the end of treatment)
8.1.2.3 Medication Consumption

Mean and SD of medication consumption are presented in Table 39. Figure 45 illustrates the changes in medication consumption as measured with the MQS and pill counts. Whilst the consumption of both acute and preventative medication in the RA group was stable during the follow-up period, the SA use of medications for acute pain reduced. Nevertheless, there was no within-group difference in these two measures during the follow up periods ($p > 0.0167$). The significant group difference in MQS was revealed at the eighth week of the follow-up period ($p = 0.013$).

Table 39: The medication consumption in each group at the tw 20 and pw 12

<table>
<thead>
<tr>
<th></th>
<th>Treatment week 20</th>
<th></th>
<th>Post-treatment week 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA $n = 26$</td>
<td>SA $n = 24$</td>
<td>RA $n = 26$</td>
<td>SA $n = 24$</td>
</tr>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>MQS</td>
<td>20.81 46.43</td>
<td>68.92 81.19</td>
<td>10.99 24.26</td>
<td>54.27 62.36</td>
</tr>
<tr>
<td>Pill Account</td>
<td>4.54 12.21</td>
<td>10.54 19.31</td>
<td>3.46 9.84</td>
<td>10.10 17.63</td>
</tr>
</tbody>
</table>

Paired-sample t-tests did not identify any within-group difference indicating that the reduction of MQS observed at the end of the treatment period in the RA group continued to improve for 12 weeks after treatment.
Figures 45: Trends in medication scale of two groups during follow-up period
* indicates significant difference between two groups at that time point.

8.2 Results of Follow-up Period II

At the 12th month after the termination of treatment, four-week diaries were sent out to participants to record their migraines. Only 25 of our 47 participants sent their questionnaire back, 16 from the RA group and nine from the SA group. All the available data was summarised into mean and SD and is presented in Table 40. No significant group difference was detected in any outcome measures.
Table 40: Primary and secondary outcome measurements at the end of the one-year follow-up period II

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>RA Mean (SD)</th>
<th>SA Mean (SD)</th>
<th>t - value</th>
<th>95% CI for difference</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack days (Number of days with migraine per 4 weeks)</td>
<td>11.31 (5.47)</td>
<td>12.33 (5.57)</td>
<td>-.45</td>
<td>(-5.77, 3.73)</td>
<td>.66</td>
</tr>
<tr>
<td>Duration (Hours /attack days)</td>
<td>7.51 (2.60)</td>
<td>7.61 (3.50)</td>
<td>-.09</td>
<td>(-2.64, 2.43)</td>
<td>.93</td>
</tr>
<tr>
<td>Highest of Pain-VAS</td>
<td>5.81 (1.01)</td>
<td>4.91 (2.44)</td>
<td>1.06</td>
<td>(-1.75, 1.12)</td>
<td>.71</td>
</tr>
<tr>
<td>Lowest of Pain-VAS</td>
<td>2.77 (1.45)</td>
<td>3.04 (2.12)</td>
<td>-.38</td>
<td>(-1.00, 2.82)</td>
<td>.31</td>
</tr>
<tr>
<td>Average of Pain-VAS</td>
<td>4.21 (1.08)</td>
<td>3.39 (2.08)</td>
<td>1.10</td>
<td>(-.83, 2.47)</td>
<td>.29</td>
</tr>
<tr>
<td>Severity of Pain (Six-point Likert Scale)</td>
<td>3.11 (0.46)</td>
<td>3.31 (0.71)</td>
<td>-.83</td>
<td>(-.68, .29)</td>
<td>.42</td>
</tr>
<tr>
<td>McGill PRI-S</td>
<td>21.56 (8.11)</td>
<td>19.67 (10.82)</td>
<td>.50</td>
<td>(-5.98, 9.78)</td>
<td>.62</td>
</tr>
<tr>
<td>PRI-A</td>
<td>6.5 (2.45)</td>
<td>6.22 (3.40)</td>
<td>.23</td>
<td>(-2.18, 2.74)</td>
<td>.82</td>
</tr>
<tr>
<td>PRI-E</td>
<td>3.56 (1.15)</td>
<td>3.75 (1.18)</td>
<td>-.40</td>
<td>(-1.19, .81)</td>
<td>.70</td>
</tr>
<tr>
<td>PRI-M</td>
<td>7.25 (2.52)</td>
<td>8.11 (2.89)</td>
<td>-.78</td>
<td>(-3.15, 1.43)</td>
<td>.44</td>
</tr>
<tr>
<td>MSQOL FR</td>
<td>46.36 (15.21)</td>
<td>50.07 (18.97)</td>
<td>-.54</td>
<td>(-18.03, 10.61)</td>
<td>.60</td>
</tr>
<tr>
<td>FP</td>
<td>61.97 (15.39)</td>
<td>64.28 (17.80)</td>
<td>-.34</td>
<td>(-16.33, 11.71)</td>
<td>.74</td>
</tr>
<tr>
<td>EF</td>
<td>49.52 (16.98)</td>
<td>56.63 (21.05)</td>
<td>-.92</td>
<td>(-23.06, 11.23)</td>
<td>.37</td>
</tr>
<tr>
<td>Medication MQS</td>
<td>78.18 (79.06)</td>
<td>75.06 (50.77)</td>
<td>.10</td>
<td>(-59.50, 67.74)</td>
<td>.92</td>
</tr>
<tr>
<td>Pill Account</td>
<td>10.56 (14.81)</td>
<td>7 (9.90)</td>
<td>.64</td>
<td>(-7.91, 15.03)</td>
<td>.53</td>
</tr>
</tbody>
</table>

Furthermore, the paired-sample t-tests were conducted between the data of baseline and follow-up II, and revealed that no within-group difference was detected in either RA or SA group; this indicated the effects of acupuncture ceased after one-year (Table 41) with the migraine of participants returning to baseline situation. However, after 12 months, the number of days with migraine in the RA was slightly better than baseline data.
Table 41: Comparisons between baseline and follow-up II in the RA and SA groups

<table>
<thead>
<tr>
<th></th>
<th>Within RA Group Mean (SD)</th>
<th>p-value</th>
<th>Within SA Group Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack days (Number of days with migraine per 4 weeks)</td>
<td>.94 (1.77)</td>
<td>.051</td>
<td>.33 (1.4)</td>
<td>.50</td>
</tr>
<tr>
<td>Duration (Hours /attack days)</td>
<td>.29 (1.01)</td>
<td>2.76</td>
<td>-.10 (.48)</td>
<td>.57</td>
</tr>
<tr>
<td>Highest of Pain-VAS</td>
<td>.17 (.43)</td>
<td>.13</td>
<td>.04 (.58)</td>
<td>.83</td>
</tr>
<tr>
<td>Lowest of Pain-VAS</td>
<td>.10 (.67)</td>
<td>.54</td>
<td>-.17 (.84)</td>
<td>.55</td>
</tr>
<tr>
<td>Average of Pain-VAS</td>
<td>.29 (.87)</td>
<td>.20</td>
<td>.54 (1.06)</td>
<td>.16</td>
</tr>
<tr>
<td>Severity of Pain (Six-point Likert Scale)</td>
<td>.10 (.50)</td>
<td>.45</td>
<td>-.08 (.25)</td>
<td>.34</td>
</tr>
<tr>
<td>McGill</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRI-S</td>
<td>-.19 (1.22)</td>
<td>.55</td>
<td>-.17 (2.19)</td>
<td>.82</td>
</tr>
<tr>
<td>PRI-A</td>
<td>-.01 (1.2)</td>
<td>.97</td>
<td>-.46 (1.77)</td>
<td>.46</td>
</tr>
<tr>
<td>PRI-E</td>
<td>-.17 (.70)</td>
<td>.34</td>
<td>-.49 (1.39)</td>
<td>.32</td>
</tr>
<tr>
<td>PRI-M</td>
<td>.31 (1.0)</td>
<td>.24</td>
<td>.09 (1.3)</td>
<td>.84</td>
</tr>
<tr>
<td>MSQOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>-.65 (6.55)</td>
<td>.70</td>
<td>.57 (12.04)</td>
<td>.89</td>
</tr>
<tr>
<td>FP</td>
<td>.84 (6.55)</td>
<td>.61</td>
<td>2.39 (6.24)</td>
<td>.28</td>
</tr>
<tr>
<td>EF</td>
<td>-1.77 (11.28)</td>
<td>.54</td>
<td>.04 (11.11)</td>
<td>.99</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MQS</td>
<td>4.23 (24.06)</td>
<td>.49</td>
<td>11.39 (28.54)</td>
<td>.26</td>
</tr>
<tr>
<td>Pill Account</td>
<td>-2.38 (8.87)</td>
<td>.30</td>
<td>0 (3)</td>
<td>1</td>
</tr>
</tbody>
</table>

8.3 Summary of the Long-term Effects of Acupuncture

In summary, during the 12-week follow-up I period, the anti-migraine effect of acupuncture on the frequency of attack days and QoL was maintained for at least 12 weeks after the discontinuation of the treatment in both the RA and SA groups. The RA group also experienced a continuous reduction in the consumption of medication. The duration and intensity of migraine increased after the end of the treatment in both groups, and the effect was maintained for eight weeks only in the RA group. After the one-year follow-up II period, all the effects of acupuncture ceased.
8.4 Discussion

Our study demonstrated the long-term effects of acupuncture lasted up to three months after the cessation of treatment. The effects depend on the type of measures utilized with frequency, medication consumption and QoL having better outcomes in the RA group. Such long-term effects of acupuncture are also observed in most well-designed, recently-published migraine studies which show a four month follow-up period reducing analgesics taken (Allais et al., 2002) and a six month follow-up period reducing the intensity and days with migraine (Diener et al., 2006) respectively. Furthermore, similar findings on the long-term effect (up to 12 months) of acupuncture in reducing frequency, analgesics taken and headache index were also reported in some tension-type headache studies (Tavola et al., 1992).

Except for the number of days with migraine in the RA group, all the features of migraine went back to the baseline situation 12 months after the termination of treatment. However, such findings conflict with Vickers’ study (2004a) where the effect of acupuncture lasted for 12 months in frequency, intensity and prophylactic medication consumption. Similarly, in Vincent’s study (1989a), the group difference in pain scores (combination of frequency and intensity) still remained substantial at the 1-year follow-up. Moreover, the same measurements were used to assess the frequency, intensity and medication in both our study and Vickers’ study. The larger sample size of 379 participants and “avoid acupuncture” control intervention of Vincent’s study may have contributed to the contrasting findings.

The discrepancy in outcomes might be explained by a high drop-out rate from the follow-up period II in the current study. As described in Section 7.2.7, we had a low drop-out rate at 6%
until the end of follow-up period I. However, during the second phase of the follow-up, half of participants dropped-out from the study. This situation was probably due to the rebound symptoms of migraine, which may have disappointed participants, and patients suffering severe migraine might be less likely to complete the diary. In the two other studies, the drop-out rate at one year was 13.3% and 17.9%, respectively (Vincent, 1989a, Vickers et al., 2004a), much lower than the current study.
CHAPTER NINE: PRESSURE PAIN THRESHOLD

9.1 Background of Pressure Pain Threshold (PPT)

Individual pain threshold and tolerance may affect people’s experience of the pain. The common method of assessment of threshold is pressure pain threshold (PPT) measured with an algometry. Many trials have demonstrated the high reliability and validity of algometry in assessing the PPT (Nussbaum and Downes, 1998, List et al., 1989, Nordahl and Kopp, 2003). This instrument has excellent inter-examiner reliability (Antonaci et al., 1998). Nussbaum and Downes’ trial (1998) indicates that the reliability of algometry is enhanced when measured by one examiner only.

The correlation between PPT and migraine is not clear. Jensen and his colleagues (1988) demonstrated that PPT of temporal muscle did not change during the attacks of common migraine nor during headache-free intervals, which is contradictory to another study (Sandrini et al., 1994) reporting a lower PPT during migraine attacks compared to healthy people. Moreover, a recent study revealed significant differences in PPTs of the neck region between the patients with unilateral migraine and healthy volunteers, and between symptomatic and non-symptomatic sides (Fernández-de-Las-Peñas et al., 2008). One other study also reported the lower PPTs on the symptomatic side than on the non-symptomatic side in the cranial area of migraine patients (Smith et al., 2006).
The above mentioned studies had some flaws. For example, there was no consistency of measuring sites between studies. The values of PPTs were measured on the neck and in the cephalic area in 25 migraineurs (Fernández-de-Las-Peñas et al., 2008); on the temporal muscles in 26 patients (Jensen et al., 1988); on the frontalis muscles in 22 patients (Sandrini et al., 1994) and in the cranial area in 10 migraineurs (Smith et al., 2006). PPT measured at different areas makes it difficult to compare between studies. Moreover none of these studies explored the relationship between PPTs and features of migraine. Among those few PPTs studies on migraine, no studies assessed the effectiveness of acupuncture on PPTs for migraine sufferers, although some RCTs had reported acupuncture improved PPTs in tension-type headache patients (Karst et al., 2000, Xue et al., 2004).

Therefore, there is a need to assess the PPTs on migraine patients, investigate the effectiveness of acupuncture on PPTs via a well-designed RCT and explore the relationship between the PPTs and features of migraine.

### 9.2 Objectives

To determine whether manual acupuncture could change the PPT of migraine sufferers;

To determine if there was a correlation between migraine reduction and changes in PPT.
9.3 Methods

9.3.1 Subjects

In the current study, 50 participants with migraine were recruited from local community by a series of media release. They took part in a randomised, sham acupuncture controlled trial as described in Section 6.1 and Chapters 7 and 8.

9.3.2 Intervention

Subjects were blinded to the allocation of treatment groups throughout the intervention period, and received either real acupuncture or sham acupuncture treatment, with a total of 16 sessions during 20 weeks (Please see Sections 6.4.3 and 6.4.4 for detailed information).

9.3.3 Regional PPT Measurement Sites

In total, PPTs at 11 sites were measured, including 7 acupoints and 4 non-acupoints. These points are located in the head, face and neck area, and are listed in Table 42, and have been illustrated in Section 6.5.2.
Table 42: The points used for testing pressure pain threshold

<table>
<thead>
<tr>
<th>No.</th>
<th>Side</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>2 cm inferior to the external occipital protuberance and 2 cm lateral to the midline</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>GB20: In a depression between the upper portions of the sternocleidomastoid muscle and the trapezius</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>2 cm lateral to GV20, which locates on the head, 5 cun(^#) directly above the midpoint of the anterior hairline, at the midpoint of the line connecting the apexes of both ears</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>EX-HN5: In the temple region, in a depression about 1 cun posterior to the midpoint between the lateral end of the eyebrow and the outer canthus of the eye</td>
</tr>
<tr>
<td>5</td>
<td>Left</td>
<td>ST6: One finger width anterior and superior to the angle of the mandible at the belly of the masseter muscle when teeth clenched</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>EX-HN3: At the midpoint of the line connecting the medial ends of the eyebrows</td>
</tr>
</tbody>
</table>

\(^\#\)cun, is a Chinese word that translates to "anatomical inch". The length of one cun is individualized. For instance, the distance from the eyebrow to the forehead hairline is defined as 3 cun.

9.3.4 PPT Measurement

PPT was measured before the first real or sham acupuncture treatment and after the last treatment during the trial. Within each session, PPT of each site was measured twice, and the mean of the two measurements represented the PPT value of that site.
PPT was measured in a standard sequence from the No. 1 site to the No. 11 site with 1 kg/cm² increasing rate. The research assistant who measured PPT was blinded to the treatment allocation. Detailed methods have been described in Section 6.5.2 Pressure Pain Threshold.

9.3.5 Statistical Analysis

The percentage change in the mean PPT scores at each site before and after treatment of each session was used for statistical analyses.

\[
\text{Percentage change at each site} = \frac{(\text{mean PPT post-treatment} - \text{mean PPT pre-treatment})}{(\text{mean PPT pre-treatment})} \times 100\%
\]

This computation was applied because of the wide variation in the PPT values, both between and within subjects and across the 11 measurement sites. Moreover, no standard PPT value exists for migraine patients at the present time, and the PPT values cannot be compared between studies. The General Linear Model (GLM) was used to perform analysis of variance of PPT percentage change scores. Post-hoc analyses using \(t\)-tests were performed when examining the significant treatment effects at each site. This method of analysis has been used in other studies to test the effects of acupuncture on PPTs (Zaslawski et al., 2003). Furthermore, bivariate Pearson correlation analysis was adopted for investigating the correlation between PPTs and other clinically related outcomes.
9.4 Results

9.4.1 Baseline PPT

The baseline values of PPT at different sites are listed in Table 43 and the two groups were comparable. The PPT values were also analysed with GLM via SPSS, and a significant site difference was detected \( F (10, 480) = 37.60, p < 0.001 \), indicating that the mean PPTs at different sites varied widely. The lowest PPT values were reported at sites No.7, No.8, No.9 and No.10. No significant site by treatment group interaction was detected \( F (10, 480) = 1.74, p = 0.15 \). Testing for group differences across the different sites showed no significant differences (see Figure 46).

Table 43: Baseline PPT at different sites

<table>
<thead>
<tr>
<th>Site No.</th>
<th>RA Mean (SD) Kg / cm(^2)</th>
<th>SA Mean (SD) Kg / cm(^2)</th>
<th>( t ) - value</th>
<th>95% CI for difference</th>
<th>( p ) - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.35 (2.13)</td>
<td>2.95 (1.42)</td>
<td>.77</td>
<td>(-.64, 1.43)</td>
<td>.45</td>
</tr>
<tr>
<td>2</td>
<td>3.30 (2.05)</td>
<td>3.28 (1.74)</td>
<td>.05</td>
<td>(-1.06, 1.11)</td>
<td>.96</td>
</tr>
<tr>
<td>3</td>
<td>2.70 (1.31)</td>
<td>2.78 (1.27)</td>
<td>-.24</td>
<td>(-.82, .65)</td>
<td>.81</td>
</tr>
<tr>
<td>4</td>
<td>2.59 (1.45)</td>
<td>2.79 (1.38)</td>
<td>-.49</td>
<td>(-1.00, .61)</td>
<td>.63</td>
</tr>
<tr>
<td>5</td>
<td>3.03 (1.72)</td>
<td>3.09 (1.87)</td>
<td>-.12</td>
<td>(-1.08, .96)</td>
<td>.91</td>
</tr>
<tr>
<td>6</td>
<td>3.01 (1.71)</td>
<td>2.92 (1.64)</td>
<td>.20</td>
<td>(-.86,1.04)</td>
<td>.85</td>
</tr>
<tr>
<td>7</td>
<td>1.82 (1.19)</td>
<td>2.20 (1.00)</td>
<td>-1.21</td>
<td>(-1.00, .25)</td>
<td>.23</td>
</tr>
<tr>
<td>8</td>
<td>1.81 (1.06)</td>
<td>2.28 (0.90)</td>
<td>-1.67</td>
<td>(-1.03, .10)</td>
<td>.10</td>
</tr>
<tr>
<td>9</td>
<td>1.52 (0.88)</td>
<td>1.74 (0.88)</td>
<td>-.89</td>
<td>(-.72, .28)</td>
<td>.38</td>
</tr>
<tr>
<td>10</td>
<td>1.58 (0.91)</td>
<td>1.80 (0.89)</td>
<td>-.88</td>
<td>(-.74, .29)</td>
<td>.38</td>
</tr>
<tr>
<td>11</td>
<td>2.60 (1.56)</td>
<td>2.38 (1.01)</td>
<td>.59</td>
<td>(-.53, .98)</td>
<td>.56</td>
</tr>
</tbody>
</table>
Meanwhile, the PPT values were also analysed using GLM via SPSS using gender as the grouping variable. Although females had lower PPTs than the males \[F(1, 48) = 1.91, p = 0.17\], no site by gender interaction was revealed \[F(10, 480) = 0.91, p = 0.45\]. There was no statistically significant difference between males and females across all sites (Figure 47). This is summarised in Table 44.
Figure 47: PPTs measured at the 11 sites for males and females (Mean and SEM, Female n = 37, Male, n = 13)

Table 44: A comparison of baseline PPT by gender.

<table>
<thead>
<tr>
<th>Site No.</th>
<th>Female ( n = 37 ) Mean (SD) Kg/cm(^2)</th>
<th>Male ( n = 13 ) Mean (SD) Kg/cm(^2)</th>
<th>( t ) - value</th>
<th>95% CI for difference</th>
<th>( p ) - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.99 (1.80)</td>
<td>3.66 (1.83)</td>
<td>-1.15</td>
<td>(-1.84, .50)</td>
<td>.26</td>
</tr>
<tr>
<td>2</td>
<td>3.12 (1.90)</td>
<td>3.79 (1.83)</td>
<td>-1.11</td>
<td>(-1.89, .55)</td>
<td>.27</td>
</tr>
<tr>
<td>3</td>
<td>2.58 (1.28)</td>
<td>3.20 (1.19)</td>
<td>-1.55</td>
<td>(-1.44, .19)</td>
<td>.13</td>
</tr>
<tr>
<td>4</td>
<td>2.48 (1.28)</td>
<td>3.28 (1.62)</td>
<td>-1.80</td>
<td>(-1.69, .10)</td>
<td>.08</td>
</tr>
<tr>
<td>5</td>
<td>2.82 (1.76)</td>
<td>3.75 (1.68)</td>
<td>-1.65</td>
<td>(-2.06, .20)</td>
<td>.11</td>
</tr>
<tr>
<td>6</td>
<td>2.81 (1.70)</td>
<td>3.42 (1.50)</td>
<td>-1.15</td>
<td>(-1.68, .46)</td>
<td>.26</td>
</tr>
<tr>
<td>7</td>
<td>1.92 (1.09)</td>
<td>2.24 (1.16)</td>
<td>-.91</td>
<td>(-1.04, .40)</td>
<td>.37</td>
</tr>
<tr>
<td>8</td>
<td>1.93 (1.02)</td>
<td>2.35 (0.92)</td>
<td>-1.30</td>
<td>(-1.06, .23)</td>
<td>.20</td>
</tr>
<tr>
<td>9</td>
<td>1.55 (0.87)</td>
<td>1.84 (0.90)</td>
<td>-1.02</td>
<td>(-.86, .28)</td>
<td>.31</td>
</tr>
<tr>
<td>10</td>
<td>1.60 (0.93)</td>
<td>1.93 (0.77)</td>
<td>-1.13</td>
<td>(-.91, .26)</td>
<td>.27</td>
</tr>
<tr>
<td>11</td>
<td>2.40 (1.16)</td>
<td>2.79 (1.70)</td>
<td>-.94</td>
<td>(-1.25, .45)</td>
<td>.35</td>
</tr>
</tbody>
</table>
Tests of correlations were conducted on baseline data involving frequency, duration and intensity of migraine and PPT values at the 11 sites. Statistically significant, but very weak correlations were found between the duration of migraine and PPTs measured in the neck at site No.3 ($r = -0.30, p = 0.033$), No.4 ($r = -0.304, p = 0.016$) and No.5 ($r = -0.28, p = 0.047$). No other significant correlations were identified.

9.4.2 Percentage Changes in PPT after Treatment

Percentage changes in PPT were analysed with the General Linear Model (GLM). There was a significant site difference [$F (10, 480) = 4.50, p = 0.026$] without a site by treatment group interaction [$F (10, 480) = 2.41, p = 0.11$] indicating that the changes in PPTs varied significantly among the 11 sites. Generally, the two groups showed similar trends in the PPTs changes across the sites (Figure 48).

![Figure 48: The percentage change of PPTs at 11 sites in the two groups after the treatment (Mean and SEM, RA n = 26, SA, n = 24)](image_url)

* indicates that at the end of treatment, the mean percentage changes in PPTs of site No.7 and 8 in RA was significantly larger than those in SA.
Post-hoc analyses were conducted using Independent sample $t$-tests. The percentage changes in PPT are summarised in Table 45.

Table 45: The percentage changes in PPTs in the two treatment groups

<table>
<thead>
<tr>
<th>Site No.</th>
<th>RA Mean (SD) %</th>
<th>SA Mean (SD) %</th>
<th>$t$ - value</th>
<th>95% CI for difference</th>
<th>$p$ - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.78 (50.99)</td>
<td>8.63 (39.53)</td>
<td>.84</td>
<td>(-16.99, 41.30)</td>
<td>.406</td>
</tr>
<tr>
<td>2</td>
<td>16.06 (41.66)</td>
<td>7.16 (53.46)</td>
<td>.66</td>
<td>(-18.23, 36.04)</td>
<td>.512</td>
</tr>
<tr>
<td>3</td>
<td>26.88 (67.06)</td>
<td>17.40 (63.66)</td>
<td>.51</td>
<td>(-27.77, 46.74)</td>
<td>.611</td>
</tr>
<tr>
<td>4</td>
<td>30.09 (65.51)</td>
<td>10.64 (41.96)</td>
<td>1.26</td>
<td>(-11.69, 50.60)</td>
<td>.215</td>
</tr>
<tr>
<td>5</td>
<td>33.73 (67.66)</td>
<td>4.29 (40.34)</td>
<td>1.89</td>
<td>(-2.10, 60.97)</td>
<td>.067</td>
</tr>
<tr>
<td>6</td>
<td>42.39 (18.88)</td>
<td>81.50 (70.77)</td>
<td>1.09</td>
<td>(-20.06, 67.08)</td>
<td>.283</td>
</tr>
<tr>
<td>7</td>
<td>228.48 (565.45)</td>
<td>-.66 (36.86)</td>
<td>2.06</td>
<td>(.328, 457.95)</td>
<td>.050*</td>
</tr>
<tr>
<td>8</td>
<td>92.69 (173.82)</td>
<td>-2.52 (30.13)</td>
<td>2.75</td>
<td>(24.09, 166.33)</td>
<td>.011*</td>
</tr>
<tr>
<td>9</td>
<td>190.19 (445.64)</td>
<td>66.87 (202.89)</td>
<td>1.24</td>
<td>(-76.42, 323.06)</td>
<td>.220</td>
</tr>
<tr>
<td>10</td>
<td>227.77 (451.18)</td>
<td>65.46 (196.64)</td>
<td>1.67</td>
<td>(-34.98, 359.61)</td>
<td>.104</td>
</tr>
<tr>
<td>11</td>
<td>15.84 (55.53)</td>
<td>4.15 (29.83)</td>
<td>.92</td>
<td>(-13.97, 37.35)</td>
<td>.364</td>
</tr>
</tbody>
</table>

* indicates significant difference between the two treatment groups

After the treatment, PPTs increased at all sites in both groups except for those at sites No. 7 and 8 in the SA group. In the RA group, mean increases in PPTs ranged from 15.84% at No. 11 to 229.48% at No. 7. In the SA group, the range was from a decrease of 0.66% at No. 7 to an increase of 66.86% at No. 9.
A significant difference between the two treatment groups on the percentage change in PPTs was obtained at sites No. 7 and 8, which are the left and right EX-HN5, located at the temporal region of the head.

No significant correlations were detected between changes in frequency, duration or intensity of migraine and changes of PPTs (Table 46). Two-way ANOVA was used to detect the difference in changes of PPTs between respondents and non-respondents. There is neither site difference [$F(10, 480) = 1.02, p = 0.34$], nor group by site interaction [$F(10, 480) = 0.16, p = 0.77$].

Table 46: Correlation between changes of PPTs and frequency, duration and intensity of migraine

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th></th>
<th>Duration</th>
<th></th>
<th>Intensity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson’s r</td>
<td>P</td>
<td>Pearson’s r</td>
<td>P</td>
<td>Pearson’s r</td>
<td>P</td>
</tr>
<tr>
<td>PPT1%</td>
<td>-.20</td>
<td>.18</td>
<td>-.08</td>
<td>.60</td>
<td>.17</td>
<td>.23</td>
</tr>
<tr>
<td>PPT2%</td>
<td>-.11</td>
<td>.44</td>
<td>.06</td>
<td>.66</td>
<td>.26</td>
<td>.07</td>
</tr>
<tr>
<td>PPT3%</td>
<td>.00</td>
<td>.98</td>
<td>.06</td>
<td>.70</td>
<td>-.04</td>
<td>.79</td>
</tr>
<tr>
<td>PPT4%</td>
<td>-.24</td>
<td>.10</td>
<td>-.11</td>
<td>.45</td>
<td>.08</td>
<td>.60</td>
</tr>
<tr>
<td>PPT5%</td>
<td>-.17</td>
<td>.25</td>
<td>-.02</td>
<td>.91</td>
<td>.05</td>
<td>.74</td>
</tr>
<tr>
<td>PPT6%</td>
<td>-.14</td>
<td>.34</td>
<td>.03</td>
<td>.84</td>
<td>.06</td>
<td>.66</td>
</tr>
<tr>
<td>PPT7%</td>
<td>-.08</td>
<td>.60</td>
<td>-.07</td>
<td>.62</td>
<td>-.11</td>
<td>.45</td>
</tr>
<tr>
<td>PPT8%</td>
<td>-.08</td>
<td>.58</td>
<td>-.00</td>
<td>.99</td>
<td>.14</td>
<td>.33</td>
</tr>
<tr>
<td>PPT9%</td>
<td>.05</td>
<td>.74</td>
<td>-.03</td>
<td>.86</td>
<td>.19</td>
<td>.20</td>
</tr>
<tr>
<td>PPT10%</td>
<td>.12</td>
<td>.43</td>
<td>-.05</td>
<td>.73</td>
<td>-.10</td>
<td>.47</td>
</tr>
<tr>
<td>PPT11%</td>
<td>.15</td>
<td>.32</td>
<td>.21</td>
<td>.14</td>
<td>-.05</td>
<td>.76</td>
</tr>
</tbody>
</table>
9.5 Discussion

Manual acupuncture changed PPTs of migraine sufferers in the temporal and facial muscles, especially in the temporal area. No correlation between migraine reduction and changes in PPTs was detected. As no participant had any migraine during the two sessions of test, the correlation between PPT during an attack and migraine features is unknown.

At baseline, the four sites located on the bilateral temporalis and the belly of the masseter muscles, were reported to have the lowest PPTs. This finding is in agreement with Bono’s study which tested the PPTs of 10 symmetrical points on each side of the head and at the deltoid in cluster headache patients. The researcher found that the lowest PPTs were at the anterior and intermediate levels of the temporal muscle on the symptomatic side (Bono et al., 1996).

In our current PPT trial/tests, there are weak correlations between the PPTs on the neck and the duration of migraine. Given such correlation was not assessed by other migraine studies, no comparison can be made. It is unknown whether the relationship can be explained by the finding that the most sensitive region of migraine sufferers is the nape area (Kosek et al., 1993).

In the current study, 19 of 22 PPT values in both two groups increased after the treatment. Furthermore, eight of total 11 PPTs in the RA group increased by 30% or more from baseline data; whereas only three of 11 PPTs in the SA group increased by more than 30%. Acupuncture seemed to increase PPTs better than SA did, although significant group
differences were found at two sites only. The results are somewhat consistent with one study (Karst et al., 2000), finding that acupuncture improved the PPTs in the temporal region of chronic tension-type headache than SA did.

Three factors might explain why PPTs at two sites No. 7 and 8 were statistically significantly higher than those in the SA group. Firstly, increases in PPT varied from site to site, but the temporalis has been considered to be the most reliable site when the repeatability of PPT was assessed at a few sites, including 13 sites located in anterior, upper, posterior and temporal areas of the head. (Sand et al., 1997). Secondly, the significant increase in PPT might be due to the local effect of acupuncture since the two sites were needled in the trial. Finally, testing on healthy volunteers, Zaslawski and his colleagues (2003) stated that PPTs changed more significantly on the acupoints compared with the non-acupoints. No. 7 and No. 8 are two commonly used acupoints for headache.

It is not a co-incidence that the PPTs increased significantly at No. 7 and No. 8, namely, Tai Yang, which is located on either side of the temporal regions, in the m. temporalis, on the superficial temporal artery and vein, and near the second and third branches of the trigeminal nerve. The temporal artery (Lipton, 2004) and trigeminal nerve are associated with the development of migraine (Moskowitz, 2007). The neurovascular theory considers that the vasodilatation activates the stretch receptors in the wall of the temporal artery, stimulating the peri-vascular trigeminal nerves, and leading to neurogenic inflammation. The inflammation in turn activates the trigeminal nuclei and further enhances the sensitivity of the nervous system prior to a migraine attack (Maassenvandenbrink and Chan, 2008). Acupuncture has been
shown to increase pain threshold in many other studies (Zaslawski et al., 2003, Chapman et al., 1976, Berlin et al., 1975), however it is unknown about the relationship between the enhanced PPT in the temporal area and the sensitivity of stretch receptors in the wall of the temporal artery. It is possible that acupuncture reduces the sensitivity of these receptors, and therefore prevents the activation of trigeminal nerves. This hypothesis should be explored in the future and it might help us understand the anti-migraine mechanisms of acupuncture.

Nevertheless there is no correlation between percentage increases in PPTs and the features of migraine. The present results suggest that the changes of laboratory-derived measurement PPT were unrelated to the clinical outcomes, frequency, duration and severity of migraine. Other studies also indicated that the reduced PPT did not correlate with illness duration and side of pain in cluster headache sufferers (Bono et al., 1996). However heat or cold pain thresholds were not assessed in the current study, and correlation between thermal pain threshold and migraine cannot be concluded.

Our observations of baseline data confirm the findings of previous publications regarding the range of PPT values (Fernández-de-Las-Peñas et al., 2007) as well as the lower PPT in women in healthy populations (Chesterton et al., 2003, Jensen et al., 1992) and in migraine groups (Fernández-de-Las-Peñas et al., 2007). However, such data were from studies, including the current study, with a small sample size and different gender proportions, which is probably due to the higher prevalence in the females than the males. Gender imbalance could have affected our results. Therefore, further investigations of clinically relevant changes in PPT for both gender groups are still required (Chesterton et al., 2003).
As noted earlier, this study involved 50 participants only; this small sample size may have underestimated the effects of acupuncture. Furthermore, participants suffering from bilateral migraine or unilateral migraine with side shift might also complicate the results. However these data were not collected in this study.

In conclusion, future studies need to assess both thermal and mechanical pain thresholds in the neck and cranial regions, in particular the temporal area, to further understand the correlation between pain threshold and migraine features. More importantly, the relationship between the increased pain threshold in temporal area after acupuncture and temporal artery pressure / neurogenic inflammation should be explored.
CHAPTER TEN: DISCUSSION

10.1 A summary

The aims of the project were to: 1) systematically review the current state of evidence from English and East Asian literature of acupuncture for migraine headache; and 2) design and conduct a RCT that addresses the key methodological problems identified from the systematic reviews (SR) to determine the short- and long-term effect and safety of acupuncture for patients with frequent migraine headache.

Fifteen English and 17 Chinese published studies were identified in two separate literature review through searching major English, Chinese, Japanese and Korean databases. Overall, findings of these two reviews supported the value of acupuncture in the treatment and prevention of migraine headache when compared with standard western prophylaxis medications, including beta blockers (Metoprolol), selective calcium channel antagonist (Flunarizine, Nimodipine), 5-HT\textsubscript{1A} receptor agonists (Dihydroergotamine) and anticonvulsant (valproic acid) (English studies: RR 1.19; 95% CI 0.98 to 1.46; Chinese studies: RR 1.55; 95% CI 1.27 to 1.88). However, there was insufficient data for a meta-analysis to determine the effectiveness of acupuncture when compared with no treatment. Furthermore, conflicting findings were reported in respect of the specific effect of acupuncture for migraine headache in studies involving a comparison between real and “sham/placebo” acupuncture (English studies: RR 1.07, 95% CI 0.93 to 1.25). Overall it was difficult to perform a meta-analysis to assess the efficacy of acupuncture due to the highly heterogeneous data, differences in outcome measures and insufficient reporting of study details.
A randomised, sham acupuncture controlled trial built on findings of the above literature reviews were conducted. Fifty participants were recruited. The results demonstrated a statistically significant preventative effect of acupuncture on migraine, as well as improvement in medication consumption and quality of life, when compared with sham acupuncture. The effect lasted up to three months and ceased one year after the termination of the treatment. The results demonstrated that manual acupuncture could be effective and safe prophylaxis for frequent migraine sufferers. Because the findings of the present study were based on self-selected and community-based participants, the results discussed here are limited to this specific sub-group. Furthermore, there were no adverse events that necessitated withdrawal of participants from the trial. The incidents and severity of minor adverse effects were comparable between the two groups.

10.2 Strengths of This Project

Our systematic review (SR) is the first review to assess the East Asian data of acupuncture RCTs for migraine. Such literature has been neglected in previous SRs (Melchart et al., 2001, Scott and Deare, 2006). It is surprising to find that no RCTs in acupuncture for migraine have been reported in Korea and Japan where acupuncture has been widely used. In comparison, Chinese researchers have conducted a few dozens of trials in this area. Half of them were however observational studies. The remaining RCTs were of poor reporting quality.

Our SR is also the first study evaluating the efficacy of acupuncture in various features of migraine, such as intensity and the numbers of migraine attacks. This is different from two existing reviews in which only respondent rates were analyzed.
The current RCT is unique when compared with previous studies of acupuncture for migraine in the following four aspects. First, only patients having a minimum migraine frequency of 5 days per month were included. Other studies typically included patients having two – five or two – eight migraine attacks per month. Second, it has the longest treatment period of 20 weeks with a gradual decrease in treatment frequency. This treatment regime follows how acupuncture is practiced in a clinical setting, and has been shown to be effective in one acupuncture trial of osteoarthritis in the knee (Berman et al., 2004). The current study also has the longest follow-up period at one year. Third, according to the potency of analgesics, we used the MQS to assess medication consumption, rather than the simple pill account used in many other studies. This method is sensitive and more meaningful to patients. Finally, our sham acupuncture procedure has minimised the non-specific effect of acupuncture by using non-invasive procedure on the points in the cranial area.

In addition, we have also conducted a study to examine the effect of acupuncture on cranial pressure pain threshold (PPT) and its relationship with features of migraines, such as headache intensity, and number of days with migraine. Such correlation has never been assessed before. The findings may contribute to further understanding of the mechanism of migraine and the anti-migraine mechanisms of acupuncture.

10.3 Limitations

Due to a lack of accessibility to databases in other languages, our search and studies were limited to those published in Chinese, English, Japanese and Korean. With the increased use of acupuncture globally, more and more migraine sufferers seek complementary therapies
including acupuncture for relief. A recent Italian study reported that the percentages of complementary and alternative medicines used in chronic migraine and episodic migraine sufferers were 50% and 27%, respectively (Rossi et al., 2005). RCTs published in French, Italian and Russian databases have not been searched and assessed. This could have impacted on our conclusion.

As discussed in the limitation part of Chapter Seven, like many acupuncture studies, this study also suffers from a small sample size, a common problem due to frequent treatment regime, invasive needling and a lack of understanding of acupuncture by the public. A small sample size could over-estimate the results by 30% (Bandolier Professional, 2003). This could have happened in the current study.

Furthermore, a high expectation to acupuncture treatment could also contribute to the outcome of this study. A low back pain study showed that patients with a high expectation of acupuncture often had a better outcome than those with a low expectation (Kalauokalani et al., 2001). Another study that examined four acupuncture trials for painful conditions reported a significant association between better improvement and a higher expectation (Linde et al., 2007b). Although not assessed in the current study, expectation is less likely to be the reason underlying the group differences. The participants were successfully blinded from the treatment allocation as indicated by the credibility questionnaire. Nevertheless such factor should be assessed in future studies. A newly developed Acupuncture Expectancy Scale (Mao et al., 2007) can be used.
10.4    Implications for Further Studies

Based on the findings of the SRs and the current clinical study, further studies should be conducted to address the following four aspects, including trials with various control interventions, trials examining more real life events, understanding respondents and exploring the anti-migraine mechanisms of acupuncture.

10.4.1    Studies with Various Comparisons

The effect achieved by acupuncture consists of specific, non-specific and placebo elements (Paterson and Dieppe, 2005). The following four types of studies should be conducted to address the above three elements.

10.4.1.1    Acupuncture VS. Standard Drugs

Control method plays an important role in a successful acupuncture RCT. The choice of control is determined according to the research question. The first of all strategies in acupuncture research is to assess its overall efficacy (including specific, non-specific and placebo effects), when compared with standard pharmacology treatment. Studies assessing the effect of acupuncture on acute migraine attacks should be conducted as currently there was only one such study. A direct comparison of the cost-effectiveness of acupuncture with prophylactic medications should also be studied. Furthermore, most patients who are taking prophylactic medications might also use acupuncture. Given the mechanisms of these drugs such as enhancing central inhibition and dilating blood vessels that are also involved in the actions of acupuncture, the interactions between the two therapies need to be explored.
10.4.1.2 Acupuncture VS. Sham Acupuncture

Comparison between active acupuncture and sham acupuncture is the only way to evaluate the specific effect of acupuncture. Identifying an ideal placebo/sham acupuncture device or procedure is an important initial step to acupuncture RCTs for evaluating its specific effects. However to date, no existing evidence supports that placebo intervention, such as mock TENS, placebo tablets or inactivated laser apparatus can produce the same psychological impact as acupuncture does (Kaptchuk et al., 2000). The commonly used sham procedure involves needles being inserted deeply or superficially into either inappropriate acupoints or sham acupoints outside of traditional acupoint / meridians. Such points are often within the same region within which the points used for real acupuncture treatment and the location of the diseases reside.

A review (Sánchez Aranjo, 1998) on methodology of sham acupuncture found that placing needles in the same dermatome or myotome of the disease often produced a strong therapeutic effect. Once the needles are inserted, the spinal gate control is activated thereby producing pain relief in the same and adjunct spinal nerve segment. Hence, the placebo needles have been developed and they have been proven to be credible (White et al., 2003, Kleinhenz et al., 1999, Park et al., 2002). Blunt needling could be used to replace the placebo needle. Lao and colleagues employed such blunt needling in patients with pain after oral surgery (Lao et al., 1999).
To assess the specific acupuncture effect, using sham acupuncture as the control intervention is inevitable. It seems blunt stimulation at the region of the disease could be one of the ideal sham acupunctures.

10.4.1.3 Comparing Different Treatment-Regime

Treatment regime includes the length of the trial and the frequency of the treatment. The current clinical study revealed a marked improvement in several variables within the RA group occurring after eight or 12 weeks’ treatment. The effect continued to improve in the remaining 8 treatment weeks and in the 12-week follow-up period. Silberstein and Goadsby (2002) have also found that in the controlled clinical trials evaluating migraine prophylaxis, the efficacy was often noted in the first four weeks and continued to increase for three months. However, in most of the available acupuncture studies, the treatment period lasted eight to 12 weeks only. Before the acupuncture showed its furthest effect, the treatment already ceased. In the future, treatments with various treatment lengths should be compared.

Moreover, this clinical study is one of the acupuncture studies using a gradual decrease in the treatment frequency, starting with twice per week. As discussed in Chapter Four, nearly half of the studies conducted in Western countries treated participants once per week then the treatment stopped abruptly. Such regime might not be sufficient to maintain the effect of acupuncture on migraine. A SR of acupuncture on chronic pain conditions revealed that the patients who received more than six sessions were significantly more likely to show positive effect of the treatment than those with fewer sessions (Ezzo et al., 2000). The frequent and
number of treatment may contribute to the positive results of the current clinical trial. We suggest future researches should focus on exploring the most effective treatment regime.

10.4.1.4 Assessing Combined Interventions

In real practice, acupuncture is often combined with other Chinese medicine therapies, such as herbal medicine, Chinese massage (Tuina), Qi Gong or Tai Chi. Five of the total 15 Chinese studies employed acupuncture plus other therapies. None of the English studies used acupuncture in combination with other types of Chinese medicine as the treatment. With appropriate design such combined intervention studies can tell us the specific effect of acupuncture in the combined therapy.

10.4.2 Conducting “real life” Acupuncture Treatment

In any RCTs, there is always a trade off between internal and external validity. Well-designed and well-organised sham-acupuncture controlled trials limit the potential to assess the effectiveness of acupuncture treatment. One of the main draw back in these trials is being inflexible in the delivery of acupuncture.

In a clinical setting, acupuncturists change the treatment according to the conditions of the patients on the day in addition to individualised treatment plan. Such flexibility is not permitted in RCTs. Treatments in RCTs have to follow the protocol as strictly as possible. For instance, one patient reported lower back pain in one session in the current trial. The patient reported that the low back pain seemed to be associated with the migraine. The trial acupuncturist had to decide whether to treat this acute low back pain or not, given this
deviation was not written in the protocol. The patient’s low back pain was treated on that day. In total there were three such incidents during the trial. The trial acupuncturist controlled this deviation to a minimum.

From the trial point of view, this limitation is successful and important. However from the point of view of assessing the real effect of acupuncture, such limitation interferes with the results. Indeed, from Chinese medicine point of the view, the blockages of Qi flow in the low back can cause a blockage of Qi in the upper stream of meridians, causing headache or migraine. A review has also showed a connection between migraine/headache and low back pain (Hestbaek et al., 2003). Some acupuncture trials have planned a number of non-trial related treatments in the protocol thus introducing some flexibility (Melchart et al., 2005). This practice needs to be included, documented and analysed in future trials. Associated with this problem is a better understanding of the comorbidity of migraine so that we can determine what types of conditions can be treated in an acupuncture trial for this type of headache.

A second problem is about the holistic approach of acupuncture and its actual practice in clinical trials. Although in many trials, including the current study, the researchers select complementary acupoints according to Chinese medicine differential diagnosis, the trial participants are not treated holistically as in clinical practice. This is mainly due to the limited communication between participants and the trial acupuncturists. As shown in the current trial (Paterson et al., 2008), when interviewed, participants found that the whole experience was not like what they expected how acupuncture should have been practiced. The trial
acupuncturist tried to limit the communication with the participants in order to avoid practitioner-patient interaction. Meanwhile the participants also tried to play their part of being “subjects” and not asking questions to have their problem, treatment and weekly experienced of migraine explained.

Acupuncture is a complex intervention, involving flexibility in treatment delivery, body contact of practitioners and patients, patients trust in needling and communication between the two parties. These elements of practice can work synergistically to achieve a great effect (Paterson and Britten, 2004). How to address these elements of practice and their complex interaction remains a challenge to acupuncture clinical trials. However these elements cannot be ignored or dismissed. Introducing some degree of flexibility in the trial and a standard recording system of any deviation is the first step to address these problems.

10.4.3 Understanding the Respondents

The current clinical trial has found that the RA group had a greater number of respondents than the SA group did. During the follow-up period, participants who had a migraine pattern of Ascending Hyperactivity of Liver Yang had the lowest respondent rate. From Chinese Medicine point of view, such patients are prone to mental stress and their migraine is associated with life events and a lack of restful sleep. Could this result indicate that acupuncture alone is not sufficient and additional psychological interventions, Chinese herbal medicine, relaxation therapy, meditation or Tai Chi are needed? Furthermore, both in the current study and one other study, the migraine of a small proportion of patients worsened
after acupuncture. Unfortunately, to date, there is no way to tell who will respond to acupuncture and who will not. Future studies need to explore this area.

10.4.4 Studying the Mechanism

The underlying mechanism of acupuncture for its prophylactic effect requires investigation. Almost all of the studies in our two reviews used acupuncture points located on the temporal region and the nape. Both regions are innervated by the trigeminal nerves. The significance of the increase in PPTs in these regions observed in the current study should be examined in the context of migraine reduction. It is possible that acupuncture has reduced the sensitivity of “stretch receptors” in the wall of temporal arteries therefore preventing the activation of trigeminal nerves and further migraine attacks. Previous studies have shown that acupuncture can modulate or change the pain threshold in the viscera by stimulating the body wall (Cui et al., 2005). Whether this action also explains the current finding is yet to be studied. Other possible mechanism is its effect of sympathetic inhibition. A recent study shows that acupuncture reduces the sympathetic tonus in the migraine respondents (Bäcker et al., 2008), which might have caused a long-term vasodilatation, therefore preventing the development of migraine.

The involvement of well-established anti-inflammation and anti-central sensitization actions of acupuncture in animals is yet to be confirmed in migraine prevention.
10.5 Implication for Clinical Practice

Acupuncture can be used as alternative prophylaxis for frequent migraine. Practitioners are recommended to treat migraine sufferers twice per week for at least eight weeks. Regular follow-up treatments at a monthly or bimonthly interval are needed for the long-term maintenance. Practitioners should also encourage the impatient individuals to have at least six sessions of treatment before assessing whether they are respondents to acupuncture. Other therapies can be combined with acupuncture, in particular, when treating patients with a pattern of Ascending Hyperactivity of Liver Yang. Reduced medication usage is expected during acupuncture treatment. Patients need to be informed that acupuncture sometime worsens migraine.
Reference


DAVID, A. (1995) Statistical considerations for a parallel trial where the outcome is a measurement.


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LINDE, K., STRENG, A., HOPPE, A., WEIDENHAMMER, W., WAGENPFEIL, S. & MELCHART, D. (2007a) Randomized trial vs. observational study of acupuncture for migraine found that patient characteristics differed but outcomes were similar. *Journal of Clinical Epidemiology*, 60, 280-287.


MEDICAL OUTCOMES TRUST (1998) Scoring and interpretation information of Migraine Specific Quality of Life. Waltham, Medical Outcomes Trust.


APPENDICES

Appendix 1: Diagnosis of Migraine

<table>
<thead>
<tr>
<th>Migraine without aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
</tbody>
</table>
| C                     | Headache has at least two of the following characteristics:  
1. Unilateral location  
2. Pulsating quality  
3. Moderate or severe pain intensity  
4. Aggravation by or causing avoidance of routine physical activity (e.g. Walking or climbing stairs) |
| D                     | During headache at least one of the following:  
1. Nausea and/or vomiting  
2. Photophobia and phonophobia |
| E                     | Not attributed to another disorder |

<table>
<thead>
<tr>
<th>Migraine with aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
</tbody>
</table>
| B                   | Aura consisting of at least one of the following, but no motor weakness:  
1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision)  
2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)  
3. Fully reversible dysphasic speech disturbance |
| C                   | At least two of the following: Unilateral location:  
1. Homonymous visual symptoms and/or unilateral sensory symptoms  
2. At least one aura symptom develops gradually 5 minutes or more and/or different aura symptoms occur in succession over 5 or more minutes |
| D                   | Headache fulfilling criteria for migraine without aura beginning during the aura or follows the aura within 60 minutes. |
## Appendix 2: Pre-planed Form for Extracting Data in Systematic Review

<table>
<thead>
<tr>
<th>Author and Date</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>Sample Conditions</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td>Study Intervention</td>
<td></td>
</tr>
<tr>
<td>Control Intervention</td>
<td></td>
</tr>
<tr>
<td>Type of Acupuncture Treatment</td>
<td></td>
</tr>
<tr>
<td>Acupuncture points &amp; Needling</td>
<td></td>
</tr>
<tr>
<td>Other treatment</td>
<td></td>
</tr>
<tr>
<td>Treatment Regime</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
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<tr>
<td>Follow-up</td>
<td></td>
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<tr>
<td>Drop-out</td>
<td></td>
</tr>
<tr>
<td>Practitioner Background</td>
<td></td>
</tr>
<tr>
<td>Authors conclusion</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3: Examples of Media Advertisement

Appendix 3.1: “The Age” Newspaper

Research points to drug-free migraine relief

It is estimated that that up to 12 per cent of the Australian population suffers from migraine headaches. And if RMIT University’s new clinical research study is successful, migraine sufferers may soon have a viable drug free alternative to treating the debilitating condition.

The study will investigate whether acupuncture can alleviate the symptoms of migraine headaches and assess its potential role in reducing treatment by medication. RMIT’s Head of Chinese Medicine, Associate Professor Charlie Xue, said the study was an important part of finding a drug free alternative to treating the condition.

“Acupuncture takes a holistic approach to understanding normal function and disease processes and focuses as much on the prevention of illness as on the treatment,” he said.

Working in tandem with the study is Dr Charlotte Paterson, a GP for 20 years and visiting scholar from the University of Bristol medicine faculty.

She will spend the next six months investigating what it is like to be a patient participating in an acupuncture research trial.

“It is important for us to know if acupuncture in a trial setting is the same as in the real world, and it is vital we understand how participants feel about the experience. We can then use this information to improve the design of future trials for patients,” she said.

Patients with chronic illnesses were seeking help from a variety of sources, Dr Paterson said. “It makes much more sense that we learn to combine both western and complementary medicine in order to treat people in the best possible way.”

RMIT is to host an international symposium exploring the “harmonisation of traditional and modern medicine” later this year. More information is at www.rmit.edu.au/rid/harmonisation. The university is encouraging migraine sufferers to contact Ms Yanli Wang on 9925 7584.
Acupuncture: a new cure for migraine?
Volunteers needed

More than 10% of Australians suffer from migraines - are you one of them? Help us find an effective cure.

RMIT University is looking for volunteers to take part in a clinical study investigating whether acupuncture can alleviate the symptoms of migraine headaches.

With extensive experience using acupuncture to treat headaches, our aim is to now scientifically determine its effectiveness in treating this debilitating condition.

Participants need to be between 18 and 80 years of age. Research is carried out at the Chinese Medicine Clinical Trial Laboratory at RMIT University, Bundoora West Campus, Plenty Road, Bundoora.

If you suffer from frequent migraines and would like to be part of the cure, please contact: Ms Yanyi Wang, Registered Chinese Medicine Practitioner.
Ph: 9925 7002 or Email: s3042947@student.rmit.edu.au

The Division of Chinese Medicine also provides treatment to the general public of a wide range of health conditions using safe and holistic methods with herbs, acupuncture and Chinese massage. Appointment: 9925 7866.

→ www.rmit.edu.au
Appendix 3.3: “GoodMedicine” Magazines

MIGRAINE STUDY

RMIT University, Melbourne, researchers are looking for volunteers to take part in a clinical study which is examining the benefits of using acupuncture to treat migraines. “It has been shown to have positive effects on tension headaches and evaluating its impact on migraine headaches means that this study could have a significant impact on the treatment available to chronic sufferers of the condition,” says Professor Charlie Xue of RMIT.

Contact: Ms Yanyi Wang
(03) 9925 7584.
## Appendix 4: Initial Screening Form

<table>
<thead>
<tr>
<th>Question</th>
<th>Option A</th>
<th>Option B</th>
<th>Option C</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you suffer from migraine or have been diagnosed as migraine?</td>
<td>A: Yes</td>
<td>B: Do not know</td>
<td>C: No</td>
<td>Go to question 2</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>2. How old are you</td>
<td>A: 18-80 years old</td>
<td>B: less than 18 or older than 80 years old</td>
<td></td>
<td>Exclude</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>3. Are you current pregnant or plan to pregnant in the next 12 months</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Exclude</td>
</tr>
<tr>
<td>(if you are female)?</td>
<td></td>
<td></td>
<td></td>
<td>Go to question 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. Do you have history of head injury or whiplash?</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Go to question 5</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>5. Do you have severe arrhythmia or heart failure, brain tumor, epilepsy</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Go to question 6</td>
</tr>
<tr>
<td>or hemophiliac?</td>
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<tr>
<td>6. Have you used acupuncture to treat your migraine in the last months?</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Go to question 7</td>
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<td></td>
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<tr>
<td>7. Had participated in another clinical trial in the past six months?</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Go to question 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you also suffer from tension-type headache?</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Go to question 9</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>9. If answer “Yes” for question 8, can you distinguish between migraine</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Go to question 10</td>
</tr>
<tr>
<td>attacks and additional tension-type headache?</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. If answer “Yes” for question 9, do you usually have tension-type</td>
<td>A: Yes</td>
<td>B: No</td>
<td></td>
<td>Exclude</td>
</tr>
<tr>
<td>headache more than six days per month?</td>
<td></td>
<td></td>
<td></td>
<td>Go to question 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. How many days do you usually have migraine per month?</td>
<td>A: Less than five days</td>
<td>B: five days or more</td>
<td></td>
<td>Successful in Initial screen, sending PLS</td>
</tr>
</tbody>
</table>

PLS
Appendix 5: Plain Language Statement (PLS)

Information about Acupuncture and Migraine Study

Project Title: Evaluation of effectiveness and safety of acupuncture in the treatment of migraine (CM)

Investigator: Ms. Yanyi Wang, Registered Chinese Medicine Practitioner, MappSc candidate

Dear Volunteer,

My name is Yanyi Wang, a Master of Applied Sciences (in Chinese Medicine, by research) candidate in the School of Health Sciences, RMIT University. My study is supervised by Dr. Zhen Zheng; Associate Professor Charlie Xue, Dr. Lin Dong and Prof. Robert Helme. I am the principal investigator of this proposed clinical trial which will determine the effectiveness and safety of acupuncture in the treatment of migraine. This letter is to give you relevant information about this study.

1. Research Project

Acupuncture is commonly used in Chinese medicine practice worldwide and is regularly used in everyday practice. This research is about using acupuncture for the treatment of migraine headache. The study will involve approximately 78 migraine participants. To date, there have been only a few clinical trials that have been conducted into acupuncture treatment of migraine and they have suggested effective outcome, although the results of these studies are not yet conclusive. Therefore, it is necessary to conduct a more comprehensive clinical trial to verify whether acupuncture is useful for the management of migraine headache.

We are looking for volunteers who have a minimum of 5 or more migraines or migraine related headache per month. If you fall into this category, then you are invited to participate in our study together with the other 77 participants. However, if you have any of the following conditions you are not eligible for this study. Please see the following exclusion criteria:
a) Current pregnancy or malignancy.
b) History of head injury or whiplash.
c) Severe arrhythmia or heart failure, brain tumour or epilepsy.
d) Haemophilia.
e) Do not comprehend English.

Once you are recruited into this study, you will then be assigned by chance to either a sham or real acupuncture treatment. That is, you will have a 50% chance of being randomly assigned to either the real or control group.

2. Purpose of the study

The aim of the study is to examine whether acupuncture reduces the intensity, frequency of migraine and the consumption of medications as well as improving the quality of life.

3. The real or sham treatment

The sham treatment is used to demonstrate if the real acupuncture treatment has a true effect for migraine. Theoretically the sham acupuncture should produce minimal acupuncture efficacy, apart from placebo effects, if any. Once you have met the inclusion criteria you will be allocated randomly into one of the two groups. If the results of this study show that acupuncture is effective in the treatment of migraine headache, then we will be happy to provide free real treatment at the completion of the study to those who were in the control group.

4. What you will be asked to do during the study

If you agree to participate in the study, which includes a four-week baseline, a twenty-week treatment period and three-month follow up, you will be asked to:

- Come to the clinic for an initial assessment.
- Visit the clinic for a total of 16 acupuncture treatments.
- Complete a daily record for intensity and frequency of headache, medication consumption chart, and monthly record of quality of life questionnaire for 7 times.
- Have pain thresholds tested twice, once prior to commencement of acupuncture treatment, and once at the completion of the study.
- Record adverse event of acupuncture, if any.

5. Safety issues of acupuncture

Acupuncture procedure is widely used in everyday practice with an excellent safety profile. Only disposable needles will be used and they are much thinner than needles used for injections. However, acupuncture has been reported to be associated, in a very few cases, with minor risks, such as fainting,
infection, small bleeding and bruises. In this trial, the principal investigator is an experienced acupuncturist registered with the Chinese Medicine Registration Board of Victoria. Great precaution will be taken to minimise any possible unpleasant adverse effect. Furthermore, the acupuncturist and all staff in the Division of Chinese Medicine possess First Aid, level II training.

6. Potential discomfort of acupuncture

Some people may experience minor pricking sensations when acupuncture needle was first inserted. However, this sensation is only brief. Generally there is no pain or discomfort involved in acupuncture.

7. Potential benefits to you and the community

The benefit of participating in the study is that your migraine symptoms and well-being will be monitored closely. This trial will further contribute towards a growing body of scientific knowledge about the effects of acupuncture for the treatment of migraine. Your involvement will help to determine whether acupuncture might be used as an alternative drug-free treatment to the debilitating migraine condition. Any new findings from this study may be taken into account when planning for future studies. Furthermore, all findings will be made available to all participants in a summary format.

8. About discontinuation and termination of your participation

Involvement in this study is voluntary, and you may ask for the procedure to be discontinued at any time.

9. Confidentiality of information you provide

All information provided by you and the data collected through this study will be stored in a password protected computer program. All files are kept securely in a locked filing cabinet. Your records may be inspected only by authorised persons for the purpose of original data audit. In any form of publication, all your personal information will be removed. You have the right to view or request a copy of your personal data.

10. Answering any question concerning the procedure of this research

Any question that you may have about the procedure will be answered and explained. Please contact Ms. Yanyi Wang on 9925 7002 or 0423427330, if you have any question about the research.

This project has been reviewed and approved by the Human Research Ethics Committee of RMIT University. The project is covered by RMIT University, Broadform Public Product Liability Insurance.

Any Questions or complaints about your participation in this project may be directed to the Secretary, RMIT Human Research Ethics Committee, University Secretariat, RMIT, GPO Box 2476V, Melbourne, VIC 3001. Tel: 9925 1745
Appendix 6: Acupuncture Study-Expression of Interest

(To be completed by the patient)

Dear Participants,

Thank you for your interest in participating in the study of acupuncture for migraine. Please find enclosed some information about the study.

It contains a number of questions to be completed. Your answers will help us assess whether you are suitable to participate in our study.

In order to provide accurate information for this initial assessment, please read the information carefully prior to completing the forms on pages 1, 2, 3 and 4.

Please return the completed Expression of Interest form in the enclosed prepaid envelope. Upon receipt of your information I will contact you to arrange an appointment for further assessment to confirm your suitability for this research.

I look forward to your participation and thank you for taking time to fill in this form.

Yours Sincerely

Ms. Yanyi WANG

Tel: 9925 7584 or 0423427330 or email: s3042947@student.rmit.edu.au

1. Title: □ Mr □ Mrs □ Miss

2. Family Name: ___________ First name: ______________________

3. Date of birth: ________________ Gender: □ Male □ Female

4. Address: Street___________________________________________

   Suburb___________________ Postcode:____________________

   Email:______________________________________________

5. Telephone No: (home) ________________ (work): _____________
Best time to call you ________________________________________________

Which one do you prefer to contact with:  □  Home phone;
□  Work phone;  □  Mobile

6. Emergency Contact:

Name: _____________________________________________________________

Address: ___________________________________________________________

Telephone No: (home) _______________    (work) _______________

(mobile) ____________________________________________

7. Currently married/ partnered?  □  Yes  □  No

8. Occupation (current): _____________________________________________

9. Education attained: ______________________________________________


11. Are you of Aboriginal and/or Torres Strait Island descent?  □ Yes  □ No

If Yes, please tick one:  □  Aboriginal and Torres Strait
□  Aboriginal not Torres Strait
□  Torres Strait

12. How long have you suffered from headache?  _______________________

13. Do you use any pain medication for headache control?

□  Yes  □  No

If Yes, please list the medication that you have used

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Dosage</th>
<th>Frequency (times/day or week)</th>
<th>How long have you been taking it?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. Please tick (√) how many times you usually have a headache per month.
15. Please tick (✓) the symptoms that happen while you have headache. y

- Unilateral location
- Plusating quality
- Aggravated by routine physical activity; or avoiding physical activity
- Nausea
- Vomiting
- Light Sensitive
- Sound Sensitive
- Other ________________________________

16. Can you visit the clinic 16 times in the future 6 months?

- Yes
- No
- Not sure

17. Do you plan to move to other city during the next 5 months?

- Yes
- No

18. Have you been diagnosed to be a haemophilia?

- Yes
- No

19. Are you pregnant (if you are female)?

- Yes
- No

20. Are you currently breast-feeding (if you are female)?

- Yes
- No

21. Do you suffer from any heart disease?

- Yes
- No

If yes, Please specify: ________________________________

22. Have you been diagnosed with a malignancy?

- Yes
- No
23. Have you been diagnosed with a brain tumour or epilepsy?

☐ Yes  ☐ No

24. Have you had head injury or whiplash before?

☐ Yes  ☐ No

25. Do you have any other diseases?

☐ Yes  ☐ No

If yes, Please specify: ________________________________

26. Do you have any infectious diseases?

☐ Yes  ☐ No

If yes, Please specify: ________________________________

27. Have you had acupuncture treatment in the last 6 months?

☐ Yes  ☐ No

If yes, what was the acupuncture treatment for? ________________

28. Are you willing and able to participate in the study?

☐ Yes  ☐ No  ☐ Not sure

29. Are you currently participating in any other clinical trial research?

☐ Yes  ☐ No
Appendix 7: Consent Form

RMIT HUMAN RESEARCH ETHICS COMMITTEE

Prescribed Consent Form for Persons Participating In Research Projects Involving Interviews, Questionnaires, Disclosure of Personal Information, Tests and/or Medical Procedures

PORTFOLIO OF
SCHOOL OF Health Sciences

Name of participant:

Project Title: Evaluation of effectiveness and safety of acupuncture in the treatment of migraine: a randomised, single blind and sham controlled trial

Name(s) of investigators:
(1) Yanyi Wang
(2) Zhen Zheng
Charlie Xue
Lin Dong
Cliff Da Costa
Helme Robert

Phone: 03-99257002
03-9925 7167
03-9925 7745
03-9925 7990
03-9925 6114
03-9288 4696

1. I have received a statement explaining the interview/questionnaire and tests/procedures involved in this project.

2. I consent to participate in the above project, the particulars of which - including details of the interviews or questionnaires - have been explained to me.

3. I authorise the investigator or his or her assistant to interview me, administer a questionnaire, and to use with me the tests or procedures referred to in 1 above.

4. I acknowledge that:

   (a) Having read Plain Language Statement, I agree to the general purpose, methods and demands of the study.
   (b) The possible effects of the tests or procedures have been explained to me to my satisfaction.
   (c) I have been informed that I am free to withdraw from the project at any time and to withdraw any unprocessed data previously supplied (unless follow-up is needed for safety).
   (d) The project is for the purpose of research and/or teaching. It may not be of direct benefit to me.
   (e) The privacy of the personal information I provide will be safeguarded and only disclosed where I have consented to the disclosure or as required by law.
(f) The security of the research data is assured during and after completion of the study. The data collected during the study may be published, and a report of the project outcomes will be provided to all participants. Any information which will identify me will not be used.

Participant’s Consent

Name: ________________________________ Date: __________________

(Participant)

Name: ________________________________ Date: __________________

(Witness to signature)

Participants should be given a photocopy of this consent form after it has been signed.

Any complaints about your participation in this project may be directed to the Secretary, RMIT Human Research Ethics Committee, University Secretariat, RMIT, GPO Box 2476V, Melbourne, 3001. The telephone number is (03) 9925 1745. Details of the complaints procedure are available from the above address.
Appendix 8: Credibility of Sham Acupuncture

1. Which treatment do you believe you received?

☐ Real acupuncture
☐ Sham (placebo) acupuncture
☐ Unsure

2. If your answer is “Real acupuncture” why do you think so?

☐ The manner, attitude, or words of acupuncturist
☐ The manner, attitude, or words of the personnel in this clinic
☐ The result of my treatment (eg. Feel better, or feel worse)
☐ Other ____________________________________

3. If your answer is “Sham acupuncture” why do you think so?

☐ The manner, attitude, or words of acupuncturist
☐ The manner, attitude, or words of the personnel in this clinic
☐ The result of my treatment (eg. Feel better, or feel worse)
☐ Others ____________________________________
Appendix 9: Headache Diary

1. Do you have migraine today?

☐ Yes  ☐ No

If yes, please indicate the migraine period today.

6am  8    10   12pm 2    4     6     8   10   12am  2   4am   6am

2. What is the **lowest level** of your headache today?
(0 means “no pain”; 10 means “pain as bad as it could be”)

[ ] 0  [ ] 10

3. What is the **highest level** of your headache today
(0 means “no pain”; 10 means “pain as bad as it could be”)

[ ] 0  [ ] 10

4. What is the **average level** of your headache pain intensity today?
(0 means “no pain”; 10 means “pain as bad as it could be”)

[ ] 0  [ ] 10

5. Please tick (✓) the symptoms that you have today.

☐ Nausea  ☐ Vomiting  ☐ Light Sensitive

☐ Sound Sensitive  ☐ Pain with movement

☐ No symptoms  ☐ Other ____________________________

6. Headache Medication Taken
If you take any medication for headache, please fill in the name of the medication, how many tablets do you take at one time, how often do you take the medication and whether the medication is effective or not. Please give a score between 1 and 5 where 1 means the medication is not effective and 5 means the medication is most effective.

1 means: not effective     5 means: most effective

<table>
<thead>
<tr>
<th>Medication</th>
<th>Amount</th>
<th>Effectiveness Scale (in each box, enter the number that best reflects the effectiveness of your relief) from 1(not effective) to 5 (most effective)</th>
<th>Score</th>
</tr>
</thead>
</table>

7. Likert Scale of Headache Severity

Please tick (√) **only one** answer in the table below, which corresponds to the headache of today.

- □ 0: No headache
- □ 1: I notice the headache only when I pay attention to it
- □ 2: Mild headache that can be ignored at times
- □ 3: Headache is painful, but I can do my job or usual tasks
- □ 4: Very severe headache: I find it difficult to concentrate and can do only undemanding tasks
- □ 5: Intense, incapacitating headache
Appendix 10: McGill Pain Questionnaire

1. Categories 1-20 below describe your present pain. In any appropriate category circle ONLY word that best describes it– the one that applies best. Leave out any category that is not suitable.

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Flickering</td>
<td>5</td>
<td>Pinching</td>
<td>9</td>
<td>Dull</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Quivering</td>
<td>Pressing</td>
<td>Sore</td>
<td>Frightful</td>
<td></td>
<td>Terrifying</td>
</tr>
<tr>
<td></td>
<td>Pulsing</td>
<td>Gnawing</td>
<td>Hurting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Throbbing</td>
<td>Champing</td>
<td>Aching</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beating</td>
<td>Crushing</td>
<td>Heavy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pounding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Jumping</td>
<td>6</td>
<td>Tugging</td>
<td>10</td>
<td>Tender</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Flashing</td>
<td>Pulling</td>
<td>Taut</td>
<td>Rasping</td>
<td>Gruelling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shooting</td>
<td>Wrenching</td>
<td>Fraying</td>
<td>Splitting</td>
<td>Vicious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Killing</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pricking</td>
<td>7</td>
<td>Hot</td>
<td>11</td>
<td>Tiring</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Boring</td>
<td>Burning</td>
<td>Exhausting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drilling</td>
<td>Scalding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stabbing</td>
<td>Searing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lancinating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sharp</td>
<td>8</td>
<td>Tingling</td>
<td>12</td>
<td>Sickening</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Cutting</td>
<td>Itchy</td>
<td>Suffocating</td>
<td></td>
<td></td>
<td>Troublesome</td>
</tr>
<tr>
<td></td>
<td>Lacerating</td>
<td>Smarting</td>
<td></td>
<td></td>
<td></td>
<td>Miserable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stinging</td>
<td></td>
<td></td>
<td></td>
<td>Intense</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unbearable</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

2. Please tick (✓) the word or words, which you use to describe the pattern of your pain changing with time.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Brief</td>
<td>Rhythmic</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Momentary</td>
<td>Periodic</td>
<td>Steady</td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>Intermittent</td>
<td>Constant</td>
<td></td>
</tr>
</tbody>
</table>
3. Evaluate overall intensity of total pain experience. Please tick (✓) in the appropriate column.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Discomforting</td>
</tr>
<tr>
<td>3</td>
<td>Distressing</td>
</tr>
<tr>
<td>4</td>
<td>Horrible</td>
</tr>
<tr>
<td>5</td>
<td>Excruciating</td>
</tr>
</tbody>
</table>
Appendix 11: Migraine Specific Quality of Life Questionnaire (v. 2.1)

Dear Participants,

Please fill out this questionnaire. It will help us understand the effects of migraine headache on your daily activities.

Thank you for your time.

While answering the following questions, please think about all **migraine attacks** you may have had in the past 4 weeks.

1. In the **past 4 weeks**, how often have migraines **interfered** with how well you dealt with family, friends and others who are close to you? (Select only **one** response.)
   - 1 □ None of the time
   - 2 □ A little bit of the time
   - 3 □ Some of the time
   - 4 □ A good bit of the time
   - 5 □ Most of the time
   - 6 □ All of the time

2. In the **past 4 weeks**, how often have migraines **interfered** with your leisure time activities, such as reading or exercising? (Select only **one** response.)
   - 1 □ None of the time
   - 2 □ A little bit of the time
   - 3 □ Some of the time
   - 4 □ A good bit of the time
   - 5 □ Most of the time
   - 6 □ All of the time

3. In the **past 4 weeks**, how often have you had difficulty in performing work or daily activities because of migraine symptoms? (Select only **one** response.)
   - 1 □ None of the time
   - 2 □ A little bit of the time
   - 3 □ Some of the time
4. In the past 4 weeks, how often did migraines keep you from getting as much done at work or at home? (Select only one response.)

1 □ None of the time
2 □ A little bit of the time
3 □ Some of the time
4 □ A good bit of the time
5 □ Most of the time
6 □ All of the time

5. In the past 4 weeks, how often did migraines limit your ability to concentrate on work or daily activities? (Select only one response.)

1 □ None of the time
2 □ A little bit of the time
3 □ Some of the time
4 □ A good bit of the time
5 □ Most of the time
6 □ All of the time

6. In the past 4 weeks, how often have migraines left you too tired to do work or daily activities? (Select only one response.)

1 □ None of the time
2 □ A little bit of the time
3 □ Some of the time
4 □ A good bit of the time
5 □ Most of the time
6 □ All of the time
7. In the past 4 weeks, how often have migraines limited the number of days you have felt energetic? (Select only one response.)

1. None of the time
2. A little bit of the time
3. Some of the time
4. A good bit of the time
5. Most of the time
6. All of the time

8. In the past 4 weeks, how often have you had to cancel work or daily activities because you had a migraine? (Select only one response.)

1. None of the time
2. A little bit of the time
3. Some of the time
4. A good bit of the time
5. Most of the time
6. All of the time

9. In the past 4 weeks, how often did you need help in handling routine tasks such as every day household chores, doing necessary business, shopping, or caring for others, when you had a migraine? (Select only one response.)

1. None of the time
2. A little bit of the time
3. Some of the time
4. A good bit of the time
5. Most of the time
6. All of the time

10. In the past 4 weeks, how often did you have to stop work or daily activities to deal with migraine symptoms? (Select only one response.)

1. None of the time
2 □ A little bit of the time
3 □ Some of the time
4 □ A good bit of the time
5 □ Most of the time
6 □ All of the time

11. In the past 4 weeks, how often were you not able to go to social activities such as parties, dinner with friends, because you had a migraine? (Select only one response.)

1 □ None of the time
2 □ A little bit of the time
3 □ Some of the time
4 □ A good bit of the time
5 □ Most of the time
6 □ All of the time

12. In the past 4 weeks, how often have you felt fed up or frustrated because of your migraines? (Select only one response.)

1 □ None of the time
2 □ A little bit of the time
3 □ Some of the time
4 □ A good bit of the time
5 □ Most of the time
6 □ All of the time

13. In the past 4 weeks, how often have you felt like you were a burden on others because of your migraines? (Select only one response.)

1 □ None of the time
2 □ A little bit of the time
3 □ Some of the time

4 □ A good bit of the time

5 □ Most of the time

6 □ All of the time

14. In the past 4 weeks, how often have you been afraid of letting others down because of your migraines? (Select only one response.)

1 □ None of the time

2 □ A little bit of the time

3 □ Some of the time

4 □ A good bit of the time

5 □ Most of the time

6 □ All of the time
Appendix 12: Pressure Pain Threshold

1. Do you have migraine/headache today?  
   □ Yes  □ No  
   If yes, please give a score to describe the intensity

   The **lowest level** of your pain (0 means “no pain”; 10 means “pain as bad as it could be”) ____________________________

   The **highest level** of your pain ____________________________  
   The **average level** of your pain ____________________________

2. Do you have migraine/headache at the moment?  
   □ Yes  □ No  
   If yes, Please give a score to describe the intensity of your pain (0 means “no pain”; 10 means “pain as bad as it could be”) ________

3. Pressure pain threshold

<table>
<thead>
<tr>
<th>2 cm to the midline of 2 cm inferior to the external occipital</th>
<th>GB20</th>
<th>2cm to the midline at the vertex</th>
<th>EX-HN5</th>
<th>The masseter muscle in front of the mandibular angle</th>
<th>EX-HN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>left  right  left  right left  right left  right left  right left  right left  right left  right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 13: Pain Medication Class Detriment Weights

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical / transdermal anesthetics, capsaicin</td>
<td>1.1</td>
</tr>
<tr>
<td>Antidepressants – serotonin reuptake inhibitors</td>
<td>1.7</td>
</tr>
<tr>
<td>Antidepressants - other</td>
<td>1.9</td>
</tr>
<tr>
<td>Anticonvulsants - GABAergic</td>
<td>1.9</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>2.0</td>
</tr>
<tr>
<td>Anti – anxiety - miscellaneous</td>
<td>2.1</td>
</tr>
<tr>
<td>Muscle relaxants – non-dependency producing</td>
<td>2.2</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>2.2</td>
</tr>
<tr>
<td>Cyclooxygenase-2 inhibitors</td>
<td>2.3</td>
</tr>
<tr>
<td>Antidepressants – tricyclics / tetracyclics</td>
<td>2.3</td>
</tr>
<tr>
<td>Analgesic – miscellaneous (ie, tramadol)</td>
<td>2.3</td>
</tr>
<tr>
<td>Anticonvulsants – sodium channel blockers</td>
<td>2.8</td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>3.1</td>
</tr>
<tr>
<td>Opioids – Schedule II</td>
<td>3.4</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatories</td>
<td>3.4</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>3.6</td>
</tr>
<tr>
<td>Opioids – Schedule IV</td>
<td>3.7</td>
</tr>
<tr>
<td>Opioids – Schedule III</td>
<td>3.7</td>
</tr>
<tr>
<td>Muscle relaxants – dependency producing</td>
<td>3.8</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3.9</td>
</tr>
<tr>
<td>Steroids</td>
<td>4.4</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Appendix 14: Attitude to Acupuncture

1) Do you agree that acupuncture should be used as a complementary medicine?
   - □ Yes
   - □ No
   - □ Don't know

2) Do you agree with the statement that modern physiotherapy and drugs make acupuncture unnecessary?
   - □ Yes
   - □ No
   - □ Don't know

3) Would you feel more apprehensive about acupuncture than physiotherapy?
   - □ Yes
   - □ No
   - □ Don't know

4) Do you agree acupuncture should be used as an alternative to orthodox treatments, not merely used when all else fails?
   - □ Yes
   - □ No
   - □ Don't know

5) Would you like to recommend acupuncture treatment to your friends or relatives when necessary?
   - □ Yes
   - □ No
   - □ Don't know

6) Do you agree with the statement that acupuncture might actually cause more pain?
   - □ Yes
   - □ No
   - □ Don't know

7) Would you feel more anxiety about using acupuncture than taking medication?
   - □ Yes
   - □ No
   - □ Don't know

8) Do you agree that acupuncture is unscientific and will not produce a real benefit?
   - □ Yes
   - □ No
   - □ Don't know

9) Do you speak to your doctor about acupuncture?
   - □ Yes
   - □ No
   - □ Don't know

10) Do you believe that acupuncture should be more strictly regulated?
    - □ Yes
    - □ No
    - □ Don't know
11) Do you believe acupuncture should be regulated the same way as Western medicine?

☐ Yes  ☐ No  ☐ Don't know

12) Do you believe that acupuncture in conjunction with Western Medicine can be more effective than either form of therapy used alone?

☐ Yes  ☐ No  ☐ Don't know

13) For what kind of symptoms or illness do you think acupuncture might be helpful?
(Tick (✓) as many as you like)

☐ Cold/Flu/Sore throat  ☐ Dizziness  ☐ Eye related problems
☐ Hearing related problems  ☐ Cancer  ☐ Broken limb
☐ Stomach or internal problems  ☐ Pain
☐ Chronic condition
☐ Other ____________________________________________

14) Do you believe that acupuncture treatment for migraine headache is cheaper than other complementary therapies?

☐ Strongly agree  ☐ Agree  ☐ Unsure  ☐ Disagree  ☐ Strongly disagree

15) Do you believe that acupuncture treatment for migraine headache is more accessible than other therapies?

☐ Strongly agree  ☐ Agree  ☐ Unsure  ☐ Disagree  ☐ Strongly disagree

16) Do you believe that acupuncture treatment for migraine headache produces faster relief of symptoms than other therapies?

☐ Strongly agree  ☐ Agree  ☐ Unsure  ☐ Disagree  ☐ Strongly disagree

17) Do you believe that acupuncture treatment for migraine headache has fewer side effects than other therapies?

☐ Strongly agree  ☐ Agree  ☐ Unsure  ☐ Disagree  ☐ Strongly disagree

18) Do you believe that acupuncture treatment is better for long-term cure of disease than other therapies?

☐ Strongly agree  ☐ Agree  ☐ Unsure  ☐ Disagree  ☐ Strongly disagree
Appendix 15: Knowledge of Acupuncture

1) Have you had acupuncture treatment before?
   - □ Yes
   - □ No

2) If Yes, Was the treatment helpful?
   - □ Yes
   - □ No
   - □ Somewhat
   - □ Don't know

3) Have you seen acupuncture treatment performed?
   - □ Yes
   - □ No

4) What does Acupuncture involve?
   - □ Needles
   - □ Electricity
   - □ Warmth
   - □ Cold
   - □ Don't know

5) How would you describe the sensation involved in acupuncture?
   - □ No sensation
   - □ Some sensation
   - □ Painful sensation
   - □ Pricking
   - □ Forgot
   - □ Don't know
   - □ Other ___________________________

6) How much pain do you think is involved in acupuncture treatment?
   (0 means “no pain”; 10 means “pain as bad as it could be”)
   
   No pain at all                                worst pain imaginable

7) Have any of your friends or relatives had acupuncture before?
   - □ Yes
   - □ No
   - □ Don't know

8) Do you think acupuncture is more effective for some conditions, but not others?
   - □ Yes
   - □ No
   - □ Don't know

9) If yes, which condition?  ___________________________ ___________________
10) What is the chance of infection following acupuncture?
   □ None   □ Low   □ High   □ Don't know

11) Can acupuncture produce long-term effects?
   □ Yes   □ No   □ Don't know

12) Does acupuncture restore damaged tissue?
   □ Yes   □ No   □ Don't know

13) Do you know how acupuncture works?
   □ Yes   □ No   □ Some   □ Don't know

14) Does acupuncture have any side effect?
   □ Fainting   □ Infection   □ Bleeding   □ Others