

SOUTH BAYLO UNIVERSITY

**The Effectiveness of Acupuncture in Treating Migraine Headache;
A Literature Review**

by

Yongsub Jung

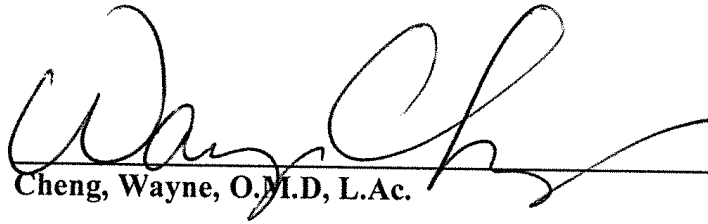
**A RESEARCH PROJECT SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE**

Doctor of Acupuncture and Oriental Medicine

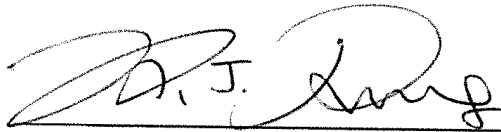
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December 2018

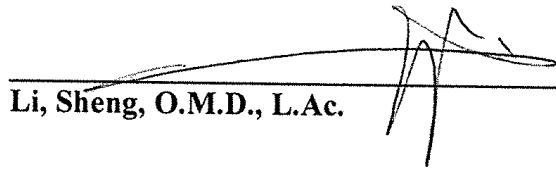
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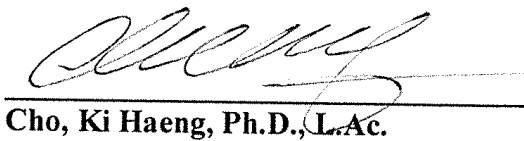
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December 5, 2018

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ACKNOWLEDGEMENTS

I have met many good teachers while studying the master and doctor degree programs of “Acupuncture and Oriental Medicine” at this wonderful school, South Baylo University. As I am now finishing my doctor degree program, I would like to share and give my gratefulness to all professors and staffs who taught me and helped me successfully finish my study at this school.

Among many others, I would like to express my sincere thanks to my research advisor Dr. Sandjaya Trikadibusana for his expertise and passion to teach, and especially for his patience.

And my special gratitude to Dr. Ki Haeng Cho, Doctoral Research Coordinator, who had sacrificed his personal time to provide me a guidance how to accomplish the research project. I have to confess that his deep knowledge and enthusiasm in helping the students impressed me in no small way that I was encouraged to go forward, otherwise having gone astray.

I also would like to take this opportunity to express my personal thanks and love to Hyesun, my wife, for her helping me finish my study. Again, I have to confess that I was not able to finish this study in my age without her supports. She did not only provide me all the comforts and amenities to study but also did her special role to be my assistant in many ways, especially as a spelling checker to pick up the typos and wrong spells when I was writing this project report.

Thank you all.

The Effectiveness of Acupuncture in Treating Migraine Headache

A Literature Review

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ABSTRACT

Migraine is a chronic neurologic disease that can severely affect the patient's quality of life. People with frequent migraine attacks report they are unlikely to return back to a normal level of biologic function. Although the pharmacotherapies provide some relief, they are associated with adverse side effects. Acupuncture is widely used, not only in some Asian cultures but also in Western countries for treating and preventing migraine attacks however, its effectiveness and the mechanism how the acupuncture treatments intervene the pathophysiology of migraine remains controversial. This Literature Review is to find the effectiveness of acupuncture in treating migraine headache, from the clinical studies which are randomized controlled trials or case studies, based on the objective and/or subjective findings. This Literature Review is conducted by using databases such as MedLINE, PubMed, Cochrane, EBSCO and the available information from the International Headache Society, through searching on Google, and books. Total 53 articles were selected by the key words “migraine” and “acupuncture” and “randomized controlled” , and among them finally 8 articles (7 randomized controlled trials and 1 case outcome report) were selected based on the inclusion and exclusion criteria. The outcome of the studies were analyzed, whether there are enough evidence-based results that explain how the effects of acupuncture on the healing mechanisms symptomatically or therapeutically. The results of this Literature Review concludes that the effectiveness of acupuncture in treating

migraine headache is likely promising, not only in the treatment but also preventing the symptoms of migraine pain, and safe with no major side effects associated with it.

However, what are the etiology, such as the root causes of the cerebrovascular constriction which is known as a pathogenesis of migraine pain, and how the acupuncture treatment intervenes the root causes of migraine headache in modern Western medicine terms are inconclusive yet, which should be pursued further in the future clinical studies through modifying the clinical study methods for validating the results based on evidence based findings.

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I. INTRODUCTION

Migraine is a common recurrent headache disorder with the characteristics of pulsating, one-sided headache, moderate or severe intensity, and the associated symptoms of photophobia, phonophobia, nausea and vomiting, etc. The prevalence of migraine was 14.7% (19.2% women and 6.6% men) in the United States, and 8-13% in Asia. (1) Over 90% of migraineurs report some level of functional impairment. In the USA, migraineurs in total spend more than 3 million days in bed each month due to pain.

People with frequent migraine attacks report they are unlikely to return back to a normal level of biologic function. (2) Migraine often begins in childhood, adolescence or early adulthood, which may be caused by any changes in the brain stem or its interactions with the trigeminal nerve, the major pain pathway. Imbalance in the brain chemicals such as serotonin, which helps subdue the pain in the nervous system also may be involved. (5) It is well known that there are some migraine-triggers, even though each migraineur may have different ones, such as hormonal changes in some women, aged or preserved foods, foods additives, alcohol or caffeine drinks, stress or changes in environment, etc. (5)

Treatments of migraine in nowadays are not complete, other than avoiding the triggers or taking pain relievers. “No cure is existing for migraine. Although the pharmacotherapies provide some relief, they are associated with adverse side effects, such as low blood pressure, nausea, depression, drowsiness and rarely renal damage. For this reason, 50% of chronic migraineurs and 27% of episodic migraineurs prefer non-pharmacotherapies and have used complementary therapies.” (2)

Acupuncture has been used for migraine sufferers as a non-pharmacotherapy, not only in Asian cultures, but also in Western countries, although the role it may play in migraine treatment remains unknown. (3)

The migraine syndromes in general fall into some patterns of symptoms in Traditional Chinese Medicine (TCM), which are like Liver-Yang-Rising, Liver-Fire, Liver-Qi-Stagnation, and Damp-Phlegm. (4, 9, 10) TCM explains acupuncture as a method to balance the imbalanced Qi flow in the meridian system of the body. Application of acupuncture needles is said to help unblock the flow and restore a balance in the force of Yin and Yang. According to TCM principles, treatment should be individualized. (3) Each acupuncturist should treat accordingly to their own experiences and feelings. In fact acupuncture can be applied in different ways.

Having said that, some questions may arise how the clinical study trials could be performed in standardized way to evaluate the effectiveness of acupuncture treatment for migraine, without having any biases involved, and what scientific approaches have been pursued to prove it.

The answers of these questions were found in pursuing the objective of this Literature Review, which is to search and investigate the clinical studies that prove the evidence based outcomes for

- Effectiveness of acupuncture treatment for migraine, without having any adverse side-effects, in terms of risks and benefits, the reality, symptomatic or curative
- The mechanisms of actions of acupuncture treatments that intervene the brain chemicals or brain vessels or brain nerves, which are the pathogenesis of migraine pain

Through the process of this Literature Review, 7 clinical studies and 1 case outcome report were selected (total 8: 2 from Germany, 3 from China, and 1 each from Australia, Turkey and USA), from searching the databases Medline, Cochrane, EBSCO. The selected trial cases were evaluated by JADAD score, which evaluates how the randomization and blinding are performed and if the drop-out subjects are properly counted during the trials, in order to make sure the

studies are performed in a manner to eliminate or minimize any unnecessary biases. Among them 5 cases were evaluated with score 4, which meant they were well designed Randomized Controlled Trial (RCT) with double or single blinding was applied. The 5 cases out of 8 were to investigate the effectiveness of acupuncture in treating migraine headache by comparing the acupuncture group to sham acupuncture control group or to non-treatment control group, or evaluate the efficacy of acupuncture as a prophylaxis for migraine symptoms. The other 3 cases were to find or evaluate or understand the mechanisms of actions of acupuncture treatments that intervene the pathogenesis of migraine. Remarkably, the principal researchers were mostly MDs or PhDs together along with MD/LAc or LAc's or in some cases with statistical analysts. In general, the study methods were to compare the baseline values which were measured before treatments, with the outcome results which were measured after treatments. The outcomes measurements were mostly number of days with migraine pain in a certain period of time, or the pain-intensity 24 hours after treatments, but on the other hand in 3 cases, the outcomes were scientific measurements such as "Cerebrovascular Valsalva Ratio" to measure the cerebrovascular response or serum Nitric Oxide level, which were influenced by acupuncture interventions differently to migraineurs and healthy control subjects. The subjects were requested to record their own diaries in the given standard formats every day during baseline period, treatment period and post treatment period, and the statistical analysis was performed in the t-test with significance level of $p < 0.05$, in most cases.

II. LITERATURE REVIEW

A) Western Medicine Viewpoints

ETIOLOGY:

Migraine may be caused by any changes in the brain stem or its interactions with the trigeminal nerve, which is a major pain pathway. Also involved may be imbalance in the brain chemicals such as serotonin, which helps subdue the pain in the nervous system. Serotonin levels drop during migraine attacks. This may cause the trigeminal nerve to release substances called neuropeptide, which travel to the meninges, the brain's outer covering. The result is migraine pain. Other neurotransmitters play a role in the pain of migraine, including calcitonin gene-related peptide (CGRP) (5)

MIGRAINE TRIGGERS:

. Hormonal changes in women: Fluctuations in estrogen may be triggering headache in some women. Women with the migraine history often repeat headache just before or during the periods, when their estrogen level drop mostly. Others may have a tendency of increasing or menopause.

Hormonal medication like oral contraceptives and a therapy of hormone replacement also may worsen the migraines. Some women, on the contrary, experience their migraines less often when taking these kinds medications.

.Foods: Aged cheeses, some processed foods or some salty foods may trigger migraines.

Skipping meals or fasting may also trigger migraine attacks.

.Food additives: The sweetener aspartame or the preservative monosodium glutamate (MSG), included in many foods, can trigger migraine.

.Drinks: Alcohol, especially wine, and caffeinated beverages can trigger migraine.

.Stress: Stress at work may cause migraine.

Sensory stimuli: Some bright lights or sun glare may induce migraines, as may loud sounds.

Strong smells such as, paint thinner, secondhand smoke, or even a strong perfume, etc may trigger migraines in some people.

.Changes in sleep pattern: Missing sleep or having too much sleep or jet lag can trigger migraines for some people.

.Physical factors: Intense physical exertion such as sexual activity can provoke migraine.

.Changes in the environment: A weather or barometric pressure change can prompt migraine.

.Medications: Oral contraceptives or vasodilators, such as nitroglycerin, may aggravate migraine.(5)

RISK FACTORS

.Family history: One of the important aspects of the migraine pathophysiology is the inherited nature. Transmission of migraine from parents to children has been reported in numerous published studies. (5)

.Age: Migraine may begin at any age, even during adolescence, though its tends to peak during 30s, and may become less severe gradually and less frequent in 40s and 50s.

.Sex: Women tend to have migraine three times more likely.

.Hormonal changes: Women may experience more headaches before or shortly after the start of menstruation. They may also experience it during pregnancy or menopause. Migraine in general improves after menopause. Some women find that migraine attacks begin or become worse in the period of pregnancy. For some women, migraine often relapse during the period of postpartum.(5)

PATHOGENESIS

Migraine is one of the most common primary headache disorders and is characterized by unilateral, throbbing headaches associated with nausea, vomiting, photophobia, and phonophobia, prior to the onset of headache. Some migraineurs experience transient focal neurologic symptoms, which may include visual disturbances, unilateral numbness, and weakness, as well as language dysfunctions. Probably because of these neurologic symptoms as well as the intensity of the headache, the research and speculation surrounding the pathophysiology of migraine has been the most intensive of all primary headache disorders. The speculation that has arisen around migraine has generally influenced the discussion of pathophysiology of other headache syndromes. Traditional theories of migraine pathogenesis fall into two categories; VASOGENIC and NEUROGENIC. (6)

.Vasogenic theory

Based on the observations, it was theorized that intracranial vasoconstriction was responsible for the aura of migraine and that the subsequent headache resulted from a rebound dilation and distention of cranial vessels and activation of inflamed perivascular sensory neurons.

.Neurogenic theory

The neurogenic theory holds that migraine is a brain disorder based on an altered cerebral susceptibility to migraine attacks and that the vascular changes occurring during a migraine are the result rather than the cause of the attack.

.Symptomology of migraine

It is the view that migraine is not a disease per se but rather a syndrome in which acute attacks occur when one or more triggering environmental events interact with a vulnerable nervous system. Why certain individuals possess this vulnerability to migraine attack is not fully understood but is likely a result of combinations of genetic and acquired factors.

There is great variability among the environmental triggers that are potentially capable of

inciting a migraine attack, as mentioned above in the etiology and triggers section.(6)

CLINICAL MANIFESTATION

Migraine often begins in childhood, adolescence or early adulthood. Migraine may progress through four stages; prodrome, aura, headache and post-drome, though some may not experience all stages.

.Prodrome: One or two days before a migraine, migraineurs may notice subtle changes that warn of an upcoming migraine, including; constipation, mood change from depression to euphoria, food cravings, neck stiffness, increased thirst and urination. (5)

.Aura: Aura may occur before or during migraine. Most migraineurs experience without aura. Auras are symptoms of the nervous system. They are usually visible disturbances such as flashes of light or wavy, zigzag vision. Sometimes auras can also be touching sensations (sensory), movement (motor), or speech (verbal) disturbances. Each of these symptoms usually gradually builds up over several minutes and lasts for 20 to 30 minutes.

Examples of aura include;

.Visual phenomena such as seeing various shapes, bright spots or flashes of light,

.Vision loss,

.Pins and needles sensation in an arm or leg

.Weakness or numbness in the face or one side of the body

.Difficulty speaking

.Hearing noises or music

.Uncontrollable jerking or other movements

.Attack: A migraine usually last from 4-72 hours in untreated. The frequency with which headache occurs varies from person to person. Migraine may be rare, or strike several times a

month. During migraine may be experienced are;

.Pain on one side or bilateral side of head

.Throbbing or pulsating pain

.Sensitivity to light, sound, and sometimes smells and touch

.Nausea and vomiting

.Blurred vision

.Lightheadedness, sometimes followed by fainting

.Post-drome: The final phase, known as post-drome, occurs after a migraine attack. Migraineurs may feel detained and washed out, while some people feel elated. For about 24 hours, experienced may be; confusion, moodiness, dizziness, weakness, or sensitivity to light and sound. (5)

DIAGNOSTIC CRITERIA

The International Headache Society Criteria for the diagnosis of migraine without aura (6)

(7)

a) At least attacks fulfilling b-d

b) Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

c) Headache has at least two of the following characteristics:

1.Unilateral location

2.Pulsating quality

3.Moderate or severe intensity that inhibits or prohibits daily activities

4.Aggravation by walking stairs or similar routine daily activities

d) During headache at least one of the following: Nausea and/or vomiting, Photophobia and

phonophobia

e) At least one of the following:

1. History, physical, and neurologic examinations do not suggest a secondary or pathologic cause for headache
2. History and/or physical, and/or neurologic examination do not suggest such disorder, but it is ruled out by appropriate investigations
3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to disorder

The International Headache Society Criteria for the Diagnosis of Migraine with Aura (6)

(7)

a) At least two migraine attacks with at least 3 of the following 4 characteristics

1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction
2. At least one aura symptom develops gradually over more than 4 minutes or
3. No aura symptom last more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionately increased.
4. Headache follows aura with aura free interval of less than 60 minutes. It may also begin before or simultaneously with aura

b) No evidence of secondary or pathologic cause of headache as defined in migraine without aura

c) Migraine with typical aura is diagnosed when in addition to the above criteria.

All four criteria under a) are met, and one or more of the following types of aura is present;

1. Homonymous visual disturbances

- 2.Unilateral paresthesias and/or numbness
- 3.Unilateral weakness
- 4.Aphasia or unclassifiable speech difficulty

TREATMENT MODALITIES

Management of migraine consists of avoidance of any precipitating factors together with prophylactic or symptomatic pharmacologic treatment if necessary.

.Elimination of Triggers: Many potential triggers have been identified; they include drinking red wine, skipping meals, excessive afferent stimuli (eg, flashing lights, strong odors), weather changes, sleep deprivation, stress, hormonal factors, particularly menstruation, and certain foods.

.Mild to moderate attacks: NSAIDs or acetaminophen is used. Analgesics containing opioid, caffeine, or butalbital are helpful for infrequent, mild attacks but are prone to being overused, sometimes leading to a type of daily headache syndrome called medication overuse headache.(8)

.Severe attacks: If mild attacks evolve into incapacitating migraine or if attacks are severe from the onset, triptans are used.

Triptans are selective serotonin 1B, 1D receptor agonists. They are not analgesic per se but specifically block the release of vasoactive neuropeptides that trigger migraine pain. Triptans are most effective when taken at the onset of attacks. They are available in oral, intranasal. When nausea is prominent, combining a triptan with an antiemetic at the onset of attacks is effective. IV dihydroergotamine with a dopamine antagonist antiemetic helps abort very severe, persistent attacks.

Triptans and dihydroergotamine can cause coronary artery contraction and are thus contraindicated in patients with coronary artery disease or uncontrolled hypertension; these drugs must be used with caution in elderly patients and in patients with vascular risk factors.

Prochlorperazine suppositories or tablets are an option for patients who cannot tolerate triptan and other vasoconstrictors.(8)

Drugs for migraine and its side-effects

Amitriptyline: weight gain (anticholinergic effects)

Beta-blocker: Avoided in patients with bradycardia, hypotension, diabetes, asthma

Divalproex: Alopecia, GI upset, hepatic dysfunction, thrombocytopenia, tremor, weight gain

Dihydroergotamine: Nausea, contraindicated in patients with hypertension or coronary artery disease

Triptans: Can cause flushing, paresthesias, and sense of pressure in chest or throat, contraindicated with coronary artery disease, uncontrolled hypertension, hemiplegic migraine, or intracranial vascular disease.

Valproate: With long term use, can cause alopecia, GI upset, hepatic dysfunction, thrombocytopenia, tremor, and weight gain

Opioid should be used as a last resort (rescue drug) for severe headache when other measures are ineffective. (9)

.Using “Natural” substances: Such as herbal or vitamin supplements. Biofeedback training can be beneficial in conjunction with or without medication. Biofeedback training teaches relaxation skills as part of overall headache management.

.Cognitive therapy: Using behavioral modification can help patients deal with the headache condition in a positive way. If patient spontaneously asks about stress or if patient recognizes anxiety or depression as significant problems, consultation with a behavioral psychologist may be very helpful.

.Physical therapy: Heat or cold applications, ultrasound myofascial releases, and massage therapy are beneficial for some patients. (6)

COMPLICATIONS

Sometimes the efforts to control migraine pain may cause other problems, as mentioned in the side effects of the drugs used, such as;

.Abdominal problems-Certain pain relievers called Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, may cause abdominal pain, bleeding, ulcer and other complications, especially if taking in large doses or for a long period of time

.Medication overuse headache- Taking over-the-counter or prescribed headache medications more than 10 days a month for three months or in high doses may trigger serious medication-overuse headache. Medication overuse headache occur when medications stop relieving pain and begin to cause headache. Then more pain medication is needed , which continues the vicious cycle

.Serotonin Syndrome: Serotonin syndrome is a rare. Potentially life threatening condition that occurs when the body has too much of the nervous system chemical called serotonin. While the risk is considered extremely low, taking migraine medications called triptans and antidepressants known as selective serotonin re-uptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) may increase the risk of serotonin syndrome. These medications naturally raise serotonin levels, and it is possible that combining them could cause levels that are too high.

Triptans and SSRIs or SNRIs may be used for possible symptoms of serotonin syndrome such as change in cognitive, behavior and muscle control (such as involuntary jerking).

Some patients experience complications from migraine such as;

.Chronic migraine: If the migraine pain lasts for 15 or more days a month for more than three months

.Status migraine: Patients with this complication have severe migraine attacks that last for longer than three days.

.Persistent aura without infarction: Usually an aura goes away after the migraine attack, but sometimes aura lasts for more than one week afterward. A persistent aura may have similar symptoms to bleeding in brain (stroke), but without sign of bleeding in the brain, tissue damage or other problems

. Migraineurs infarction: Aura symptoms that last longer than one hour can signal a loss of blood supply to an area of brain (stroke), and should be evaluated.(5)

B) Traditional Chinese Medicine Viewpoints

Even though the term “migraine” is not particularly mentioned in Traditional Chinese Medicine (TCM), the symptoms of migraine are well defined in Tou Tong (headache) disease section.

In TCM, the headaches are diagnosed in two frameworks, which are, one; channel diagnoses, according to the pain locations, two; symptom diagnoses based on external or internal factors and on the characteristics of the pain.

The four principal channels involved are Shaoyang (Temporal), Yangming (Frontal), Taiyang (Occipital), and Jueyin (Vertex).

Symptom diagnoses are based on the information from analyzing organ functions, internal, external factors, clinical symptoms and tongue diagnosis.

The symptoms are divided into excess and deficient symptoms.

The migraine syndromes in general fall into these symptoms, which are Liver-Yang-Rising, Liver-Fire, Liver-Qi-Stagnation, and Damp-Phlegm. (4, 10, 11)

Liver-Yang-Rising: The most common form symptom diagnosis of headache. It corresponds to

the classic description of migraine of Western medicine, with primary either temporal or frontal or vertex location, throbbing pain often accompanied by nausea and vomiting and dizziness.

Liver-Fire Rising: The strong and throbbing pain, which may come along with vision disorders, dizziness, tinnitus, anxiety, neck stiffness. This may cause a very strong migraine attack. The pain may be of strong intensity, pulsating, stabbing. The headache may come along with the nausea or vomiting, constipation, restlessness, insomnia, nightmares, etc.

Liver-Qi-Stagnation: This may cause a headache on the forehead or temples, which frequently occur in association with a stomach disharmony such as retention of food.

This type may resemble the pain that comes from stomach deficiency but it may be more intense. Unlike Liver-Yang-Rising, it is not throbbing.

Another characteristic of this type is that it may move from one side to the other. The headache caused by Liver-Qi-Stagnation is typically associated with anxiety, stress, or emotional disturbances in daily life.

Blood Stagnation: This type of headache may elicit a fixed, acute, localized and stabbing pain. The localization can be in a single place when it begins, but later it may extend to the entire head.

The attacks can go on for many hours, or in a bad migraine case, it may be almost continuous.

Damp-Phlegm: This type is characterized by a sense of fullness and or heaviness of the head, and mental confusion, faintness, slight vertigo especially in the morning, a sense of a full head, drowsiness, and or difficulty in concentrating. The pain location may be frontal or temporal or all over the head.

Acupuncture as an alternative treatment solution:

Acupuncture treatment has virtually no adverse side-effects. It has been used for thousands of years to treat a variety of diseases and symptoms. Recently, the mechanisms of acupuncture effects are under research, and it has been well documented that acupuncture has a powerful impact on brain chemistry as well as a variety of neurologic functions. (12)

If proven effective, it should be the solution to treat migraine patients as symptomatic therapy as well as prophylactic therapy.

C)THE CLINICAL STUDIES

Upon searching the clinical studies for effectiveness of acupuncture in treating migraine patients, following points have been taken in keen attention.

1. In TCM, differential diagnosis is to be individualized. Having said that, what acupuncture points should be used in clinical research for randomized controlled trial? How could it be standardized or semi standardized for treating migraine?
2. Are there any clinical studies performed using standardized set of acupoints for treating migraine and how effective was it?
3. The pain is subjective for each individual. If so, is relying on Visual Analog Scale (VAS)

which is the feeling of each individual, scientific enough?

4. What modern technologies could be used to measure the efficacy of acupuncture treatment based on the pathogenesis factors?

III. MATERIALS & METHODS

The research study is conducted by firstly searching and collecting the databases, such as EBSCO, MEDLINE, Cochrane, IHS-headache.org (International Headache Society), through searching Google with key words: “migraine” and “acupuncture” and the textbooks, then selecting the research articles in full text, in English language only. The selection process was based on:

Inclusion criteria: The clinical studies must have been performed in the Randomized Controlled Trial (RCT) manner. Only studies with clear hypotheses, objectives, settings, participants, assessments, interventions, results and conclusions are included. The results are analyzed statistically with significant values if $p < 0.05$ or less. Only acupuncture trials including electro-acupuncture are evaluated. Especially if there are clinical research trials to scientifically monitor or measure the factors that intervene the pathogenesis of migraine in Western Medicine, every those would be counted,

Exclusion criteria: Excluded are the clinical trials that have no indication of methods and statistics of information regarding TCM patterns.

Trials with effective acupuncture treatment on indications of animal's brain chemicals, brain bloods streams or brain nerve interventions are excluded.

Trials that compared acupuncture in different forms without a control group or non-acupuncture comparative arms are excluded.

Trials done with Ear Acupuncture, Scalp Acupuncture, or other types which were done on the points other than the points on the traditional acupuncture meridians.

From the search, there are 53 clinical studies found concerning the effectiveness of acupuncture treatment for migraine.

Among them which do not meet the inclusion criteria are excluded and the best available relevant studies are 12 human clinical studies.

Search and selection process of research articles are listed in Figure 1.

Evaluation of the selected articles:

Having selected the clinical study trial cases and the articles which have values for this Literature Review, it is required to assess the quality of the clinical trials to find how much efforts were performed by the researchers in order to eliminate or minimize any probable biases which may occur in the design stage or during the trials.

The selected articles were evaluated by the “Jadad Score”. The evaluation results are shown in table 1 below.

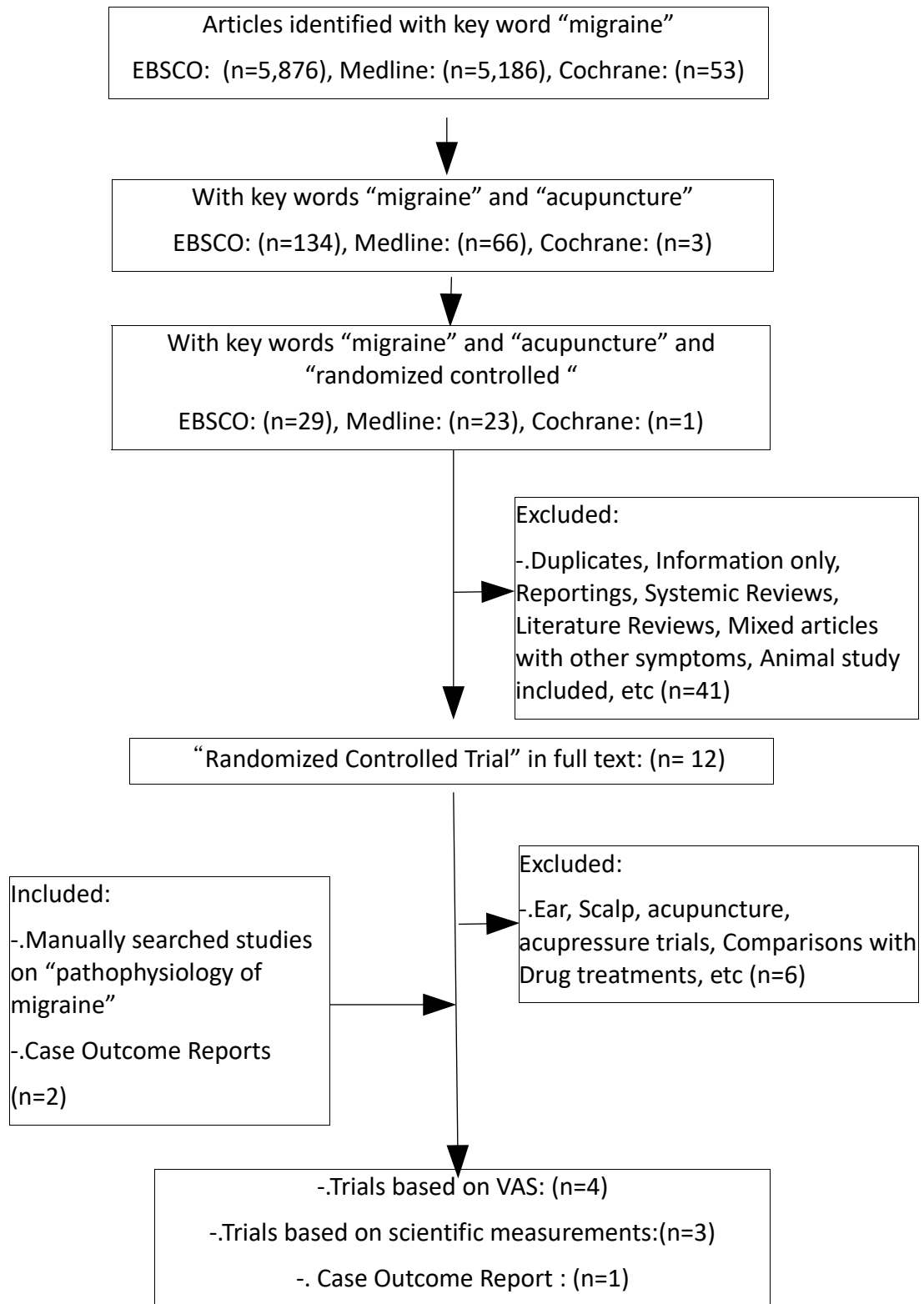


Fig.1. Exclusion and inclusion criteria of selecting research articles

Table 1: Evaluation of the selected articles in Jadad score

| Clinical Study Cases | Randomization | Blinding | Withdrawals/Dropouts | Score |
|-------------------------------|---------------|----------|----------------------|-------|
| 1. C. Linde et al (2005) | 2 | 1 | 1 | 4 |
| 2. Y. Li et al (2012) | 2 | 1 | 1 | 4 |
| 3. L. Wang et al (2012) | 2 | 1 | 1 | 4 |
| 4. Y. Wang et al (2015) | 2 | 1 | 1 | 4 |
| 5. J. Yang et al (2012) | 1 | 1 | 0 | 2 |
| 6. T. Wallasch et al (2012) | 1 | 2 | 1 | 4 |
| 7. Y. Gunduztepe et al (2014) | 0 | 0 | 1 | 1 |
| 8. S. Plank et al (2013) | 0 | 0 | 0 | 0 |

The Clinical Study Case#1, #2, #3 and #4 are the trials based on VAS, and Case#5, #6 and #7 are based on “the scientific-measurements”. Because VAS measurement is based on very individual's subjective feeling, the higher Jadad score is absolutely necessary in the clinical trials, meanwhile, the trials performed on the bases of “the scientific measurements” may elicit the very objective results that may or may not need a randomization or blinding.

Therefore, the clinical studies #5 and #7 which are performed in scientific measurements, are included in this Literature Review, instead of their low scores. The study case #8 is a “case outcome report”.

PICO analysis of the selected articles:

The selected clinical study cases are summarized in “PICO Analysis” format as shown in table 2 below, which is followed by the detail description of each article.

Table 2: PICO Analysis of the Clinical Study Cases

| Clinical Study Case | Patients/Population | Interventions | Comparisons | Outcome |
|--------------------------------|--|---|---|--|
| 1. C Linde et al (2005) | Migraine pain 302 Pts (88% women), 18 outpatients centers, Germany | Acupuncture with manual-stim/Semi- standardized pts/12 sessions in 8wks | Acupuncture Group vs Sham Acupuncture Group/ RCT | No. of days with Migraine pain in 4 weeks |
| 2. Y. Li et al (2012) | Migraine Prophylaxis/ 480 Pts/9 hospitals, China | Electro- Acupuncture/Semi- standardized pts/20 sessions over 4 wks | Shaoyang-specific vs Shaoyang non- specific vs Yangming- specific vs Sham /RCT | No. of days with migraine pain in weeks 5-8 |
| 3. L. Wang et al (2012) | Acute Migraine Attacks/ 150 Pts/ 5 hospitals, China | Acupuncture/ Obligatory pts plus supplement pts | Acupuncture Group vs Sham Acupuncture Group/ RCT | Pain in VAS Scale/ 24 hours after treatments |
| 4. Y. Wang et al (2015) | Frequent Migraine/ 50 Pts/recruited, Australia | Acupuncture Mandatory pts plus Supplement pts/ 16 sessions over 20 weeks | Real Acupuncture Group vs Sham Acupuncture Group/ RCT | No. of days with migraine pain in 4 weeks after Tx, Pain intensity in VAS |
| 5. J. Yang et al (2012) | If, Acupoints Specificity in Migraine Tx/ 30 acute Pts/ China | Electro-acu/Semi- Standardized pts/ on every migraine attack | Acupuncture (TAG) vs Control (CAG) vs No Tx (MG)/ RCT | Glucose Metabolism in pain related parts of brain by *PET-CT |
| 6. T. Wallasch et al (2012) | If, Migraine pain & Cerebrovascular response/ 35 Pts (31 female)/ Germany | Acupuncture with Standardized pts/ 8 sessions of 8 weeks | Verum Acupuncture vs Placebo group /RCT | Headache frequency/ Cerebrovascular Response by *f-TCD |

Table 2(continued)

| | | | | |
|------------------------|---|------------------------------------|--|---|
| 7. Y. Gunduztepe et al | Pathophysiology of Migraine (Nitric Oxide) | Acupuncture Standardized pts/ 5 | 22 Migraineurs vs 22 healthy subjects | Pain in VAS after tx/ Serum Nitric Oxide |
|------------------------|---|------------------------------------|--|---|

| | | | | |
|--------------------------|---|--|------------------|--|
| (2014) | 22 Pts (20 female)/ Turkey | sessions/ 2 sessions per week | | (NO) level |
| 8. S. Plank et al (2013) | If, Standardized acupuncture points reduce Migraine-pain/59 Pts/ USA | Specific Acu-pts (LR3, LI4, GB31, SJ5)/Electro-acu/2 sessions per wk over 12 weeks | No compare group | Frequency/ Intensity of migraine pain before and after |

*PET-CT: Positron Emission Tomography-Computed Tomography, TCD:Transcranial Doppler

The detail of each Clinical Study is following:

Clinical Study Case #1 ⁽¹³⁾

Klaus Linde et al, in Germany on JAMA 2005, “Acupuncture for Patients with Migraine, A Randomized Controlled Trial”

The objective of this study was to investigate the effectiveness of acupuncture compared with sham acupuncture and with no acupuncture, in patients with migraine.

Design, Setting, Patients: Three groups (Acupuncture group, Sham acupuncture group, Waiting list control group, randomly assigned on 2:1:1 ratio), involving 302 patients (80% women), with migraine headache, based on International Headache Society Criteria, patients were treated at 18 outpatients centers in Germany.

Acupuncture group: Patients were needled at predefined basic points (GB20, 40, or 41, or 42, Du20, LR3, SJ3 or 5, Taiyang) bilaterally, and additional points could be chosen individually, according to patient symptoms. Physicians were instructed to achieve “De Qi” if possible, and needles were stimulated manually at least once during each 30 minutes session. Total number of needles was limited to 25 per treatment, and 12 sessions per patients over 8 weeks, 2 sessions in each of the first 4 weeks, followed by 1 session per week in the remaining 4 weeks.

Sham acupuncture group: Number, duration, and frequency of the sessions were the same as for the acupuncture group. In each session at least 5 out of 10 predefined distant non-acupuncture points were needled bilaterally (at least 10 needles) and superficially using fine needles and “De Qi” or manual stimulation of the needles were avoided.

Waiting list control group: Patients did not receive any prophylactic treatment for a period of 12 weeks after randomization. After the period, they received 12 sessions of acupuncture treatment as like acupuncture group

Main outcome measurements: All patients completed headache diary for 4 weeks before

randomization (baseline phase), during 12 weeks after randomization. In addition patients were asked to complete a modified version of the pain questionnaire of the German Society for the Study of Pain before treatment, after 12 weeks, which includes the questionnaire on sociodemographic characteristics, numerical rating scales for pain intensity, questions on workdays lost, etc. The primary outcome measure was the difference in number of days with headache of moderate or severe intensity, (according to the questionnaire of the German Society for the Study of Pain) between the 4 weeks before and weeks 9 to 12 after randomization.

Results: Between baseline and weeks 9 to 12, the mean number of days with headache of moderate or severe intensity decreased to 2.2 days from a baseline of 5.2 days in the acupuncture group, compared with decrease to 2.2 days from the baseline 5.0 days in the sham acupuncture group, and to 0.8 days from baseline of 5.4 days in the waiting list control group, as shown in table 3 for easy comparison.

Table 3. Number of days with migraine for each trial group

| Trial Group | Base line (before treatments) | Week 9-12 (after treatments) |
|----------------------------|-------------------------------|------------------------------|
| Acupuncture group | 5.2 | 2.2 |
| Sham Acupuncture group | 5.0 | 2.2 |
| Waiting list control group | 5.4 | 0.8 |

As shown in Table 3, no difference was detected between the acupuncture and the sham acupuncture group 0.0 days, 95% confidence interval, -0.7 to 0.7 days; $p=0.96$), while there was a difference between the acupuncture group compared with the waiting list group (1.4 days: 95% confidence interval: 0.8-2.1 days: $p<0.001$)

Conclusion: Acupuncture was no more effective than sham acupuncture in reducing headaches although both interventions were more effective than the waiting list control.

Clinical Study Case #2 (14)

Ying Li, et al, on CMAJ, 2012, “Acupuncture for Migraine Prophylaxis: A Randomized Controlled Trial”

The objective of this trial was to assess the efficacy of acupuncture at migraine-specific acupuncture points and sham acupuncture.

Design, Method, Patients: Multi-center (9 hospitals in China), single-blinded randomized controlled trial. In total 480 patients with migraine were randomly assigned to one of four groups (Shaoyang specific acupuncture, Shaoyang non-specific acupuncture, Yangming specific acupuncture, or sham acupuncture control).

All groups received 20 treatments which included electrical stimulation, over a period of four weeks.

Shaoyang-specific acupuncture group: Acupuncture points for this group were SJ5, GB24, GB40, GB20, and applied unilaterally alternating between the left and right sides. “De Qi” was elicited, followed by electrostimulation for 30 minutes, and patients received 20 treatments over 4 weeks period; once per day for 5 consecutive days followed by a two-day break.

Shaoyang non-specific acupuncture group: Acupuncture points for this group were SJ18, SJ8, GB33, GB42, and other protocols were same for all acupuncture groups.

Yangming-specific acupuncture group: Acupuncture points were St8, LI6, St36, St42, and other protocols were same as other acupuncture group.

Sham acupuncture control group: Acupuncture points were a sham point at the junction of the deltoid and bicep muscles, a point at the edge of tibia (1-2 cm lateral and horizontal to St36), a point at half way between the tip of elbow and axilla, a point on the ulnar side of the arms half way between the epicondylus medialis of the humerus and the ulnar side of the wrist. All other protocols were same as the acupuncture groups including electrostimulation except that the “De Qi” was not elicited.

Measurements: The primary outcome measurement was the number of days with a migraine experienced during weeks 5-8 after randomization. Migraine-Specific-Quality -of-Life-Questionnaires were used.

Results: Compared with patients in the control group, patients in the acupuncture groups reported fewer days with a migraine during weeks 5-8, however the differences between treatments were not significant ($p>0.05$). There was a significant reduction in the number of days with a migraine during weeks 13-16 in all acupuncture groups compared with control (Shaoyang-specific acupuncture vs control: difference -1.06, $p=0.003$; shaoyang-nonspecific acupuncture vs control: difference -1.22, $p<0.001$; Yangming-specific acupuncture vs control: difference -0.91, $p=0.011$).

Table 4 below illustrates the number of days with migraine for trial groups.

Table 4. Number of days with a migraine, during the study period. Baseline data was collected during a four week period before acupuncture began

| | Baseline | 1-4 weeks | 5-8 weeks | 13-16 weeks | P value |
|--|----------|-----------|-----------|-------------|---------|
| Shaoyang-specific Acupuncture Group | 6.3 | 4.2 | 2.8 | 2.2 | <0.003 |
| Shaoyang-nonspecific Acupuncture Group | 5.6 | 3.7 | 2.7 | 2.1 | <0.001 |
| Yangming-specific Acupuncture Group | 6.1 | 4.1 | 2.9 | 2.4 | <0.011 |
| Sham Acupuncture Group | 5.5 | 4.6 | 3.4 | 3.3 | >0.66 |

Interpretation: Acupuncture treatment appeared to have a clinically more effect on migraine prophylaxis compared with sham acupuncture.

Conclusions: Acupuncture appeared to have a clinically minor prophylactic effect for migraine. However, the nonspecific effects of acupuncture may play a relevant role, and future research should provide more insight into the nature of these effects.

Clinical Study Case #3 ⁽¹⁶⁾

Lin-peng Wang et al, 2012, “Efficacy of Acupuncture for Acute Migraine Attack: A multicenter Single Blinded Randomized Controlled Trial”

The objective of this trial was to investigate the efficacy of acupuncture for acute migraine attacks comparing with sham acupuncture.

Design, Patients: Multicenter, single-blinded randomized controlled trial. 150 patients were randomly allocated to verum or sham acupuncture group in ratio of 1:1.

Practitioner training: All the physicians and assessors were required to take special training prior

to the trial to guarantee consistent practice among the five hospitals. The training program included standard operation procedure of the trial, the diagnosis and differential diagnosis of migraine without aura, the standard inclusion and exclusion criteria, the use of randomization opaque sealed envelopes. The completion of case report forms, and the location of the acupoints and correct manipulation of the needles.

Acupuncture group: The obligatory points included Du20, Du24, St8, GB8, and GB20.

Additional points could be chosen individually according to different symptoms, which were SJ5, GB34 for Shaoyang headache, LI4 and St44 for Yangming headache, UB60 and SJ3 for Taiyang headache, LR3 and GB40 for Jueyin headache, LR3 and Pc6 for nausea and vomiting, and LR3 for dysphoria and susceptibility to rage. All the needles were stimulated manually by twirling and lifting-thrusting to elicit “De Qi”.

Control group: The sham points were chosen with the following four rules; 1) acupoints unrelated to headache were selected on analysis of many Chinese acupuncture textbooks, and ancient and modern articles; 2) in order to avoid possible therapeutic effects on headache, 30 acupoints in the vicinity of elbow and knee joints were selected while the acupoints located in head, hands, feet, and trunk were excluded, and were located 3mm apart from the selected acupoints; 3) these 30 sham points were randomly assigned to five subgroups of sham acupuncture group labeled with B, C, D, E, and F, and recorded in the predetermined computer-made randomization sealed envelope. Each subgroup had two points on the arms and three points on the legs. Patients in the sham acupuncture group would be assigned to one of subgroups; 4) the number of points in sham acupuncture group was similar to that of verum acupuncture group. Sham points were all punctured perpendicularly.

Outcome measurements: The primary outcome was the between -group difference of the Visual Analog Scale (VAS) scores for pain, ranging from 0 (no pain) to 10 (the worst pain ever) for pain 24 hours after acupuncture. Short-Form of McGill Pain Questionnaire was used.

Results: The mean VAS scores 24 hours after treatment decreased from 5.7 ± 1.4 to 3.3 ± 2.5 in the verum acupuncture group, and from 5.5 ± 1.3 to 4.7 ± 2.4 in sham acupuncture group. Significant differences existed between the two groups ($p=0.001$). Comparisons are shown in table 5 below.

Table 5: Pain intensity comparison for trial groups in VAS scale

| Trial Group | Before Treatment in VAS | 24 hrs After Treatment in VAS |
|-------------------------|-------------------------|-------------------------------|
| Verum Acupuncture Group | 5.7 ± 1.4 | 3.3 ± 2.5 |
| Sham Acupuncture Group | 5.5 ± 1.3 | 4.7 ± 2.4 |

Conclusions: This trial suggested that verum acupuncture group was superior to sham acupuncture group on relieving pain and reducing the usage of acute medication.

Clinical Study Case #4 (2)

Yany Wang, et al. 2015, “Acupuncture for Frequent Migraine: A Randomized, Patient/Assessor Blinded, Controlled Trial with One-Year Follow-up”

The objective of this trial is to evaluate the efficacy and safety of manual acupuncture as a prophylaxis for frequent migraine (more than 5 attack days per month)

Method/Patients/Design: 50 frequent migraineurs were randomly allocated to receive 16 sessions of either real acupuncture (RA, n=26) or sham acupuncture (SA, n=24) during 20 weeks. Semi-standardized acupuncture points were used by the same acupuncturist for both RA and SA.

RA group: The semi-standardized acupoints used for each syndrome are shown in table 6.

Table 6: Semi-standard acupoints (2)

| Syndromes | Mandatory acupoints (unilateral) | Supplement acupoints(bilateral) |
|---------------------------------------|---|---------------------------------|
| Ascending hyperactivity of liver-yang | BG20 (bilateral), Taiyang, GB8, | DU20, LR2, LR3, Kd3, GB39, Sp6 |
| Deficiency of both Qi and blood | LI4, | DU20, DU23, St36, Sp6 |
| Wind phlegm blocking meridians | Points on the side of current migraine or points on the side of the last migraine episode, if no current migraine | St40, Rn12, Sp9 |
| Blood stasis | Same as above | Sp6, Sp10, Ashi points |

SA group: The method of sham acupuncture were as in table 7

Table 7: Method of sham acupuncture

| | Local sham points on the scalp, face, and neck | Distal sham points on the four extremities |
|-------------|--|--|
| Technique | Noninvasive, using a blunted cocktail stick | Minimal acupuncture, 2mm depth insertion |
| Sham points | 1-2cm away from the real acupoints | 1-2 cm away from the real individual distal supplementary points according to the syndrome differentiation |
| Stimulation | The stick was tapped | No needle manipulation, avoid De Qi |

Outcome measurement: The primary outcomes were days with migraine over 4 weeks, duration and intensity of migraine and the number of responders with more than 50% reduction of migraine days. The secondary outcomes were the relief medication, quality of migraine, quality of life, and the pressure pain thresholds. Six-Point Likert Scale was used to assess pain level along with VAS.

Results: The two groups were compatible at baseline (Number of days with migraine per 4 weeks, RA: 11.8 ± 5.8 , SA: 12.4 ± 6.4). At the end of the treatment, when compared with SA group, the RA group reported significant less migraine days (RA: 5.2 ± 5.0 ; SA: 10.1 ± 7.1 ;

p=0.008), less severe migraine (RA: 2.18 ± 1.05 ; SA: 2.93 ± 0.61 ; p=0.004), more responders (RA=19, SA=7), and increase pressure pain thresholds. Group differences were maintained at the end of the three-month follow-up, but not at the one-year follow-up. Comparisons of the results between RA and SA groups are shown in table 8.

Table 8: Comparisons of the results between RA and SA

| Trial Group | # of Days with Migraine | # of Days with Migraine | *Severe Headaches |
|-------------|-------------------------|-------------------------|-------------------|
| | Baseline | at end of Treatments | experienced |
| RA | 11.8 ± 5.8 | 5.2 ± 5.0 | 2.18 ± 1.05 |
| SA | 12.4 ± 6.4 | 10.1 ± 7.1 | 2.93 ± 0.61 |

*Severe Headache: Intense headache that the subject had to take rescue medications

Conclusions: Manual acupuncture was effective and safe for short-term relief of frequent migraine in adults.

Clinical Study Case #5 (17)

Jie Yang, et al. 2012, “A PET-CT Study on the Specificity of Acupoints through Acupuncture Treatment in Migraine Patients

The objective of this study was to investigate whether acupuncture points specificity exist by giving acupuncture treatment to patients with migraine.

Methods and Design: 30 patients with migraine were enrolled and randomized into three groups, which are Traditional Acupuncture Group (TAG), Control Acupuncture Group (CAG), and Migraine Group (MG).

The TAG: Patients were treated by electro-acupuncture stimulation at SJ5 (Weiguan), GB34 (Yanglingquan), and GB20 (Fengchi), on Shaoyang meridian.

The CAG: Patients were treated by electro-acupuncture stimulation at St8 (Touwei), LI6 (Pianli)

and St36 (Zusanli), on the Yangming meridian.

The MG: Patients received no treatment.

Positron Emission Tomography with Computed Tomography (PET-CT) was used to test for differences in brain activation between TAG and CAG versus MG respectively.

When the migraine attack began, each subject went through the following procedure:

1. examinations of blood sugar and Visual Analogue Scale (VAS) scores before the PET-CT scan;
2. 20 min rest in a quiet room;
3. tracer injection at the back of the right hand;
4. 40 min rest, which included at the 30 min acupuncture treatment in the TAG and CAG;
5. PET-CT scan;
6. examination of VAS scores after the PET-CT scan. Subjects were instructed to remain relaxed during the whole study, with eyes blindfolded and ears plugged.

Results:

Effect of acupuncture on pain: The VAS of pain intensity was significantly reduced in the TAG ($p=0.0005$) and CAG ($p=0.008$) groups after acupuncture stimulation (AS) compared with before. The reduction in pain intensity appeared greater in the TAG than CAG. There was no significant reduction in pain intensity in the MG ($p=0.047$)

PET results: In the TAG, metabolism increased compared with the MG in the middle temporal cortex (MTC), orbital frontal cortex (OFC), insula, middle frontal gyrus, angular gyrus, posterior cingulate cortex (PCC), middle cingulate cortex (MCC). Metabolism decreased in the parahippocampus, hippocampus etc. In the CAG, metabolism increased compared with the MG in the MTC, MCC, whereas metabolism decreased in the cerebellum.

Conclusions: Acupuncture stimulation of different points on similar body region in migraine

patients reduced pain and induced different levels of cerebral glucose metabolism in pain-related brain regions. These findings may support the functional specificity of migraine-treatment-related acupoints.

Study Case #6 (18)

Thomas Martine Wallasch, et al. 2012, “Cerebrovascular Response in Migraineurs during Prophylactic Treatment with Acupuncture: A Randomized Controlled Trial”

The objective of this clinical study was to evaluate the effect of acupuncture on cerebrovascular response in migraineurs by Transcranial Doppler Ultrasound.

Design/Patients: Randomized, quasi, double-blinded, placebo-controlled. 35 migraineurs were diagnosed according to the International Headache Society Criteria, grouped into two verum (n=18), and placebo (n=17) acupuncture groups. All patients received one session of acupuncture each week for 8 weeks.

Functional transcranial Doppler measurements: All patients underwent continuous wave-extracranial Doppler sonography to exclude a carotid stenosis. The transcranial Doppler examinations were performed in the headache-free interval at least 24 hours after the last migraine attack and within 10 days before the first and 10 days after the last acupuncture sessions. Doppler signals were obtained according to the technique described by Aaslid*. After stable baseline readings of cerebral blood flow velocities and arterial pressure had been obtained for at least 10 minutes, a standardized Valsalva Maneuver (VM) was performed, which is that the subjects blew into a mouthpiece connected to a modified sphygmomanometer and maintained a pressure of 40mm Hg for duration of 10 seconds.

A group: Acupuncture was performed in a standardized sequence during the same period of time, needling the same points bilaterally into described areas of the skin with normal needle depth.

Acupuncture points used were LI4, St36, SJ5, GB41, SJ3, UB62, Du20, GB20, Taiyang, SJ23,

LR3, Kd3, with elicitation of “De Qi”, and the needles were retained for 30 min.

PA group: Acupuncture was performed in the same way in every session, but areas of the skin that were outside a classically described acupuncture point (minimum 1-2cm beside) were chosen, and the needles were inserted superficially into the subcutaneous layer. The number of needles did not differ between groups. After insertion, the needles were remained in their location for a period of 30 min without further stimulation. The same combination of acupuncture points and mode of stimulation was used in all patients and sessions.

Outcome measurements: To evaluate the clinical effect of acupuncture treatment, headache frequency and intensity was monitored by a headache diary. Cerebral blood flow velocity data were analyzed with a validate technique based on automated stimulus-related averaging.

Vasotonus was determined by systolic and mean flow velocities and pulsatility index in right and left middle cerebral arteries during rest. Cerebrovascular response (CVR) was evaluated by detecting the cerebrovascular Valsalva Ratio by maximum end-diastolic flow velocity acceleration during the straining phase of Valsalva Maneuver.

Additionally, the centroperipheral Vasalva Ratio was determined by the quotient of the cerebrovascular ratio to the corresponding blood pressure acceleration. All these measurements were calculated automatically by the Doppler device.

Results:

VA: In the pre-acupuncture phase, CVR results for right/left middle cerebral artery measurements were $7.61 \pm 3.11 / 7.62 \pm 3.93$ cm/s². CVR decreased in the postacupuncture phase and were $5.23 \pm 2.51 / 7.62 \pm 3.93$ cm/s². There was a significant difference in pre/post acupuncture comparison ($p < 0.001$).

PA: CVR results in the pre-acupuncture phase were $10.08 \pm 7.83 / 10.13 \pm 7.67$ cm/s² for right left measurements. There was no significant difference compared to VA ($p = 0.299 / 0.300$).

Conclusions: Pre/post-acupuncture treatment comparison between verum and placebo

acupuncture groups demonstrated a significant decrease of days with migraine headache in the verum group (-52.5%, $p < 0.001$), whereas placebo acupuncture patients profited to a small extent and the duration of headache attack did not decrease significantly. Pre-post-treatment demonstrated that the cerebrovascular response patterns to Valsalva Stimulus were significantly ($p < 0.001$) diminished in verum acupuncture patients, but not in the placebo group.

Clinical Study #7 (19)

Yaemin Gunduztepe, et al. 2014 “ The Impact of Acupuncture Treatment on Nitric Oxide (NO) in Migraine Patients”

The objective of this clinical study was to contribute to efforts to understand the pathophysiology of migraine and create an alternative perspective for prophylaxis and treatment of migraine attacks.

Design/Methods/Patients: 22 migraine patients and other 22 healthy people (control group) were involved, and the acupuncture treatments were performed two sessions per week, total 5 sessions.

The practice of acupuncture was applied on standard points on LI4, Ht7, Kd3, Sp6, and LR3.

Blood samples have been collected before performing acupuncture, after the 1st session and after the 5th session for the migraine group. For the control group, blood samples were collected only once.

Measurements: Serum Nitric Oxide (NO) levels of both healthy control group and migraine group were measured in order to evaluate the difference.

For migraine group serum NO levels were measured before and after acupuncture treatments.

Results: The mean serum NO level of healthy people was 3.58 ± 0.53 , while that of migraine group was 5.55 ± 0.70 , which is 55% higher in migraine group.

The serum NO level after 5th session was decreased to 3.58 ± 0.62 , 30.63% reduction ($p < 0.05$).

Study Case #8, a Case Outcome Report (20)

Sharon Plank et al. performed a clinical study to evaluate whether a standardized set of acupuncture points, when used to deliver treatment over a predefined period of time, could reduce the frequency and intensity of migraines.

The study took place at Conemaugh Memorial Medical Center in Johnstown, PA, USA, The participants were 59 individuals with diagnosis of migraine.

Interventions: Acupuncture was administered 2 times a week for 4 weeks, followed by 1 time per week for 4 more weeks, using one set of acupoints, which are standardized (LR3, LI4, GB41, SJ5 on bilaterally), with electro-stimulation.

Outcome Measurements: Participants collected daily headache diaries and migraine quality of life measurements on the personal digital assistant for 12 weeks before starting the acupuncture intervention. Participants continued to record the frequency and intensity of their migraine during the intervention and for an additional 12 weeks beyond the intervention.

The Migraine Disability Assessment (MIDAS), Headache Impact Test (HIT6), and Beck Depression Inventory (BDI-II) were completed 4 times during the study; 12 weeks prior to the start of the intervention, immediately prior to the first acupuncture treatment, at the end of treatment, and 12 weeks after the end of treatments.

Results: When pre-intervention measurements were compared to post-intervention measurements, migraine frequency and pain intensity showed a significant decrease ($\alpha=0.05$) after acupuncture intervention. Results had not returned to the pre-intervention baseline even 12 weeks after the last acupuncture session. Acupuncture significantly influenced migraine frequency and intensity in the study's participants when pre-intervention measurements were compared to post-interventions measurements.

Conclusions: Acupuncture did not only decrease both the frequency and intensity of migraine,

but also the benefit had not subsided for 12 weeks after the final acupuncture session.

VI. RESULTS AND DISCUSSIONS

The effectiveness of acupuncture treatments could be proved by two ways of the measurements;

1. by Visual Analog Scale (VAS), which is basically the patient's subjective feelings, and
2. by “scientific measurements” which could be performed using associated tools and instruments to measure the level of intervention to the defined pathogenesis.

VAS measurements need to compare the results of acupuncture treatments with no-treatments or other treatments, based on subject's own feelings, whereas the scientific measurement would be able to show the results independently to subject's feelings.

However, the ultimate goal of treatments is to make the patients relieved from the pain, therefore, the scientific measurements should come out along with patient's subjective feelings, as well.

For patient's VAS measurements, there could be several methods to prove by comparing the results of acupuncture treatments with other treatments trials, such as that of drugs, or sham acupuncture, or other non-pharmacotherapies, or even no-treatments.

The “scientific measurements” included in this Literature Review are “Glucose metabolism in brain” (Study case#5), “cerebrovascular response” (Study case#6), “Serum Nitric Oxide (NO) level in brain vessels”(Study case#7), in order to prove how those measurements are related to the pathogenesis of migraine pain and how those factors are intervened by acupuncture treatments.

As reviewed, clinical study case #1, case #2, case #3 and case #4 (Study Group A) are to

prove the effectiveness of acupuncture treatments, and the clinical study case #5, case #6 and case #7 (Study Group B) are to prove how acupuncture treatments intervene the pathogenesis of migraine in addition to the efficacy of treating migraine headache pain.

Standardization Analysis of the Clinical Study Cases in VAS Measurements

In TCM, differential diagnosis is to be individualized in order to get more effectiveness in treating diseases. Therefore, it may be important how to standardize the acupuncture treatments in clinical study cases in order to avoid any unnecessary biases, and it may be able to reproduce the results of the studies. The cases in study group A, basically used the “semi-standardized acupoints”, which should be well compared with a “Case Outcome Report”(by Sharon Plank et al) that used a set of standardized acupoints, yet the results were significantly positive as well.

Table 9 and table 10 below are to compare the study cases and a case report one another to analyze if there were standardizations implemented properly, followed by discussions of each study case.

Table 9: The summary of clinical study cases in Study Group A and a Case Report

| Study cases | Design/Patients | Interventions | Measurements | Conclusions |
|------------------------|--|---|---|---|
| Case #1 | RCT/320 patients in 3 groups 2:1:1 ratio Acu/Sham/Waiting | Multi-centers 12 sessions each over 8 weeks | # of days with migraine pain | Acupuncture no better than Sham but much better than control group |
| Case #2 | RCT/480 patients in 4 (shaoyang/non-shaoyang/yangming/sham) groups | Multi-centers 20 sessions each over 4 weeks | # of days with migraine pain | Acupuncture appeared minor effect on migraine prophylaxis compared with Sham acupuncture |
| Case #3 | RCT/150 patients in Verum vs Sham 1:1 ratio | Multi-centers when having Mig-attacks, 30min | Pain level in VAS, 24 hours after treatments | Verum acupuncture is “superior” to Sham acupuncture |
| Case #4 | RCT/50 patients in RA vs SA | Single acupuncturist 16 sessions over 20 weeks | # of days with Migraine pain over 4 weeks | RA significantly less days with migraine pain |
| Case #8 Outcome Report | 59 migraineurs are treated at one medical center | Single acupuncturist 12 sessions over 8 wks, 2/wk for 4 wks, 1/wk for 4 wks | Frequency and intensity of pain, preintervention measurements vs postintervention | Significantly decreased ($\alpha=0.05$) after acupuncture intervention Results had not returned to preintervention baseline |

*RCT: Randomized Controlled Trial, VAS: Visual Analog Scale, RA: Real Acupuncture, SA: Sham Acupuncture

Table 10: Summary of acupuncture points used in Study Group A and a Case Report

| Study Cases | Mandatory Acupuncture points | Supplement points | Stimulation |
|------------------------|--|---|---|
| Study Case #1 | GB20, 40 or 41 or 42, Du20, LR3, SJ3 or 5 Taiyang | Additional points added individually by each acupuncturist | Manual stimulation at least during each session |
| Study Case #2 | Shaoyang specific: SJ5, GB34, GB40, GB20 Shaoyang non-specific: SJ19, SJ8, GB33, GB42 Yangming: St8, LI6, St36, St42 | | Electro-stimulation in all groups including sham group |
| Study Case #3 | Du20, Du24, St8, GB20 | Shaoyang: SJ5, G34 Yangming: LI4, St44 Taiyang: UB60, SI3 Jueyin: LR3, GB40 Nausea: Pc6 | Manual stimulations 5-10 times of twirling and lifting-thrusting of the needles |
| Study Case #4 | Liver Yang Rising: GB20, Taiyang, GB8 Qi/Blood Deficiency: LI4 Wind Phlegm Blocking the Meridian Blood Stasis | Du20, LR2, LR3, Kd3, GB39, Sp6 Du20, Du23, St36, Sp6 St40, Rn12, Sp6 Sp6, Sp10, Ashi | Manual stimulations every 10 min, |
| Case #8 Outcome Report | LR3, LI4, GB41, SJ5 | | Electro-stimulation |

Discussions of case #1:

This clinical trial was a large scale (number of patients n=302), multi-center (n=18), semi-

standardized trial, which concluded that acupuncture was no more effective than sham acupuncture in reducing migraine headache days although both intervenes were effective than a waiting list control.

To some extent, this finding contradicts with the evidences of other trials in this review, which suggest that overall acupuncture is superior to sham intervenes.

It may be necessary to collect the specific points of interest in this trial, in order to compare with other trials for later overall discussion if there are any differences, which may or may not be related to any biases. In this trial, patients were randomly stratified in a 2:1:1 ratio (acupuncture: sham acupuncture: waiting list). The 2:1:1 ratio was used to facilitate recruitment and increase the compliance of trial physicians (which is not very much convincing though).

Acupuncture treatment was semi-standardized. All patients were treated at what are called basic points; GB20, 40, or 41 or 42, Du20, LR3, SJ3 or 5, Taiyang bilaterally. Additional points could be chosen individually, according to patient's symptoms, however, the way how the additional points had to be individually selected is not clearly specified. Total number of needles was limited to 25 per treatment. Meanwhile, number, duration, and frequency of sessions in the sham acupuncture group were the same as for the acupuncture group. In each session, at least 5 out of 10 predefined distant nonacupuncture points were needled bilaterally, at least 19 needles. “De Qi” and manual simulation of the needles were avoided. The sham acupuncture intervention in this study was designed to minimize potential physiological effects by needling superficially at points distant from the segments of “true” treatment point and by using fewer needles than in acupuncture group. However, the authors of this trial could not rule out that this intervention may have had some physiological effects. The nonspecific physiological effects of needling may include local alteration in circulation and immune function as well as neurophysiological and neurochemical responses.

Another explanation for improvements that are observed with this trial could be that

acupuncture and sham acupuncture are associated with particularly potent placebo effects.

In conclusion, in this trial, acupuncture was associated with a reduction of migraine headaches compared with no treatment; however, the effects were similar to those observed with sham acupuncture and may be due to non-specific physiological effects of needling, to a powerful placebo effect, or to a combination of both. ⁽²⁴⁾ ⁽²⁵⁾ ⁽²⁶⁾ It was unknown that whether the difference in ratio of acupuncture vs sham (2:1) had influenced any biases.

Discussions of case #2:

The study design of this trial was unique in the style of acupuncture. This trial was performed with four arms, which are three acupuncture groups and one sham acupuncture (control) group.

Never the less, this trial found no difference between any of the three acupuncture groups compared with sham acupuncture (control) for number of days with a migraine during the four week period after treatment, as shown in table 4. ⁽¹⁴⁾

The results indicate that the style of acupuncture has little relevance on the outcome.

Shaoyang-specific acupuncture points did not result in better outcomes than other acupuncture points, suggesting that point-specific effects play a small role in the overall effects.

According to the results of this trial, non-specific effects may have had a more prominent role and been increased by the use of electro-stimulation in all groups.

Electro-stimulation had to be used as well for control group in order to ensure blinding.

Melzack's "gate control theory" and diffuse noxious inhibitory control might explain the stronger effect on pain inhibitory mechanisms caused by more intense local pain stimulus induced by electrostimulation. ⁽¹⁵⁾ This might explain why there were no significant differences between the acupuncture and sham acupuncture group directly following the treatment period (weeks 5-8) but the differences were found later (weeks 13-16), even though the effect was clinically minor.

The authors of this trial admitted that the trial include a short follow-up period and self-reported outcome measure in VAS, which is one of the limitations of this trial.

Discussions of case #3:

In this trial acupuncture points including obligatory and additional points were selected based on the consensus of clinical experiences of acupuncture experts in Beijing hospital of TCM, affiliated to Capital Medical University in China.

The obligatory points included Du20, Du24, St8, GB8, and GB20. According to different syndromes, additional points could be chosen individually: SJ5, and GB34 for Shaoyang headache, LI4 and St44 for Yangming headache, UB60 and SI3 for Taiyang headache, LR3 and GB40 for Jueyin headache, PC6 for nausea or vomiting; and LR3 for dysphoria and susceptibility to rage.

In order to maintain the consistency in multicenter trials, the physicians were well trained and even the sham acupuncture points were well defined.

The primary outcome measurement was the VAS score for pain 24 hours after acupuncture, which was different from other previous trials (study case #1, study case #2) that counted the number of days with migraine headache. In this trial assigned patients were not treated regularly but only when they were attacked by migraine headache, and measured pain relief by VAS scale.

Migraine recurrence is one typical problem of attack treatment. It is defined as worsening of migraine headache after free or mild pain that has been achieved with a drug within 24 hours. The incidences of recurrence were similar in comparison of verum and sham acupuncture, both of which were lower than that of taking oral triptans (between 15% and 40%).

The main limitation of this trial was failure to assess the 2 hour pain intensity, which was used for acute migraine treatment with drugs. The effect of acupuncture on pain relief should be observed at 2 hours, 24 hours, 48 hours and 72 hours.

In conclusion, verum acupuncture is superior in reducing the pain intensity, the number of patients with acute medications and the accompanying symptoms, in comparison with sham acupuncture, despite the unknown mechanism of this therapy.

Discussions of case #4:

In this trial all acupuncture treatments were performed by the same acupuncturist for both RA and SA, which is different from the previous mentioned trials that were done in multi centers.

This trial showed that acupuncture was effective in reducing migraine days, as well as effecting a reduction of medication consumption and improvement in quality of life, when compared with sham acupuncture. The effect lasted up to three months but seems to have ceased one year after the termination of treatment.

There are a couple of noticeable points with this trial.

1. Patients with more frequent migraine attacks were chosen (a minimum of five days of migraine or more during the four week baseline period).
2. The longer treatment period (20 weeks) than other trials, and the longest follow-up period at one year.
3. Sham acupuncture procedure well defined, which employed a combined shallow insertion procedure in distal area to enhance the credibility of sham intervention and non-insertion procedure on the points in the cranial area to minimize the non-specific effect of acupuncture on migraine, such as the analgesic effects produced via diffuse noxious inhibitory control (DNIC) by simply piercing the skin.⁽²⁾
4. In order to ensure the credibility of the sham acupuncture, participants with limited acupuncture experience were recruited, and it was demonstrated that they could not identify real from sham acupuncture according to past experience.
5. Because of the above mentioned noticeable points, the findings of this trial on migraine

days demonstrated that the RA was significantly better than SA, unlike the study case #1 and the study case #2 which have reported no difference between RA and SA.

Discussions of Case #8 “Case Outcome Report”

The purpose of this study was to evaluate whether a standardized set of acupuncture points delivered to migraine patients over a predefined period of time would influence the frequency and intensity of their migraine pain. The result was it did so. In TCM, individualized acupuncture treatment is the practice for any diseases, but in this case report for migraine treatment, even a standardized set of acupoints applied for eight weeks interventions produced a positive influence on the frequency and intensity of migraine occurrences as evidenced by improvements in MIDAS scores. One limitation of this study was the lack of a comparative control group. One benefit of the research methodology was that bias due to multiple practitioners did not occur.

Analysis of the Clinical Study Cases in scientific measurements:

Discussions of case #5:

This clinical study was different from other previous ones in a few points.

1. Only pain intensity was measured in VAS right after acupuncture stimulation(AS),
2. Brain activation was observed using PET-CT,
3. One experienced acupuncturist performed AS for TAG and CAG,
4. Patients received AS when the migraine attack began.

This trial showed two conclusive points;

1. On effect of acupuncture on pain: The VAS of pain intensity was significantly reduced in TAG($p=0.0005$) and CAG($p=0.008$). The reduction of pain intensity appeared greater in TAG than CAG. There was no significant reduction in pain intensity in MG ($p=0.047$).

2.PET results: In TAG, metabolism increased compared with MG, in some parts of brain such as MTC, mid-cingular cortex (MCC), OFC, etc., while metabolism decreased in other part of brain, such as cerebellum, hippocampus, etc.

The VAS score of pain intensity was significant in TAG as compared to CAG and MG, however the result of CAG was also no small ($p=0.008$). In this regard, the authors did not mention about this significance.

About the PET results, authors suggested that MTC may be related to the reaction of body to the external AS. The MCC is a part of the limbic system, which is an important region in acute pain and anxiety. Brown et al. found that the MCC could play a role in interrupting attention during the anticipation of pain. Authors hypothesized that acupuncture-specific or non-specific might modulate certain components of pain matrix.

Table11: The summary of clinical study cases in Study Group B

| Cases | Objective | Method/Design /Intervention | Acu-points used | Measurements | Conclusions |
|---------|---|---|---|---|---|
| Case #5 | To investigate if acu-points specificity exist by giving acupuncture-treatment to migraineurs | 30 pts/ RCT in TAG/CAG/MG Single acupuncturist on every migraine attack | TAG:SJ5, GB34, GB20 CAG:St8, LI6, St.36 with Electro-stimulation MG: no treatment | Pain intensity in VAS, Brain activation by PET-CT | Acupuncture tx: more effective for pain reduction in TAG, induces different level of glucose metabolism in pain related brain regions |
| Case #6 | To evaluate the effect of acupuncture treatments on cerebrovascular response in migraineurs | 35 pts/ RCT in Verum vs Placebo Single acupuncturist performed One session per week, over 8 weeks | LI4, St36, SJ5, GB41, SI3, UB62, Du20, GB20 Taiyang, SJ23, LR3, Kd3 | Headache frequency Cerebrovascular response by f-TCD | Headache frequency & intensity significantly decreased in VA, Acupuncture treatment positively influenced cerebrovascular response to autonomic stimuli |
| Case #7 | To understand pathophysiology of migraine & effects | 22 patients & 22 healthy people | Ht7, LI4, Sp6, Kd3, LR3 | Serum Nitric Oxide (NO) level which is higher | Serum NO level reduced 30.6% in migraine group and |

| | | | |
|---------------------------------------|--|----------------------|--------------------------------|
| of acupuncture treatment for migraine | Total 5 sessions each, 2 sessions/week | in migraine patients | pain level reduced accordingly |
|---------------------------------------|--|----------------------|--------------------------------|

*RCT: Randomly Controlled Trial, TAG: Traditional Acupuncture Group, CAG: Control Acupuncture Group, MG: Migraine Group, VAS: Visual Analog Scale, PET-CT: Positron Emission Tomography with Computed Tomography, f-TCD: functional Transcranial Doppler sonography

Authors also speculated that cerebellar metabolism might be related to nociceptive processing or motor preparation. The hippocampus is a major component of the human brain that links affective states with memory processing, and that has a role in pain processing.

The authors of this clinical study concluded that AS of different points on similar body regions in migraine patients reduced pain and induced different patterns of cerebral glucose metabolism in brain.

Discussions of Case #6:

Migraine is considered to be a neurovascular headache disorder. The authors of this clinical study were interested in investigating whether repetitive sessions of acupuncture would modulate cerebrovascular response measured by functional Transcranial Doppler Sonography (f-TCD), in addition to the clinical effect of prophylactic migraine treatment with acupuncture.

Treatment was performed by one licensed acupuncturist with a standard set of acupuncture point such as LI4 (Hegu), St36 (Zusanli), SJ5 (Waiguan), GB41 (Zulinqi), SI3 (Houxi), UB62 (Shenmai), Du20 (Baihui), GB20 (Fengchi), Taiyang, SJ23 (Sizhukong), LR3 (Taichong), Kd3 (Taixi).

The difference between verum acupuncture (VA) and placebo acupuncture (PA) was that VA was performed in a standardized sequence with the manually achieved “de qi” sensation, while the PA was performed on the area of skin that were outside a classically described acupuncture

point (minimum 1-2 cm beside).

When compared the clinical response of VA to PA, there was a significant improvement in headache frequency and intensity in VA while there was a minor improvement in PA group.

Table 12: Days with migraine headache (17)

| | Pre-Acupuncture | Acu-Phase (%) | Post-Acupuncture (%) | Significance |
|----|-----------------|---------------------|----------------------|--------------|
| VA | 7.86 ± 3.32 | 4.13 ± 2.55 (-47.5) | 3.76 ± 3.03 (-52.2) | P<0.001 |
| PA | 6.05 ± 2.88 | 4.82 ± 1.98 (-20.4) | 4.34 ± 2.63 (-28.2) | P=0.028 |

Table 13: Duration of headache attacks (h/month) (17)

| | pre-acupuncture | Acu-phase (%) | Post-acupuncture (%) |
|----|-----------------|---------------------|----------------------|
| VA | 89.2 ± 42.2 | 49.3 ± 33.0 (-46.8) | 43.9 ± 34.3 (-50.8) |
| PA | 68.5 ± 39.5 | 52.9 ± 33.9 (-22.9) | 51.8 ± 36.4 (-24.5) |

In evaluation of cerebrovascular resonance, this clinical study used the Valsalva Maneuver (VM), in which the subjects take action of attempting to exhale with the nostrils and mouth or the glottis closed in order to increase the blood pressure, and evaluated the Cerebrovascular Valsalva Ratio (CVR), which was defined as maximum end-diastolic flow velocity acceleration during the straining phase in cm/s^2 , and finally the Cerebroperipheral Valsalva Ratio (CPVR) was calculated (CPVR=dv/dt divided by dp/dt $cm/mmHg \times S$).

While migraineurs have the higher ratio, meaning higher velocity of blood flow in brain vessels, which could have been caused by the intracranial vasoconstriction, which was responsible for the aura of migraine and that the subsequent headache resulted from rebound dilation and distention of cranial vessels and activation of inflamed perivascular sensory neurons.

For VA group, in the pre-acupuncture phase, CVR results for right mid cerebral artery measurements were $7.61 \pm 3.11 cm/s^2$, and it was decreased to $5.23 \pm 2.51 cm/s^2$.

There was a significant difference in pre/post acupuncture comparison (p<0.001).

For PA group, CVR results in the pre-acupuncture phase was $7.29 cm/s^2$, and $6.9 \pm 3.6 cm/s^2$ in the post acupuncture phase and reached in pre/post acupuncture comparison no significance

(p=0.094).

In conclusion, this clinical study indicates that prophylactic treatment of migraineurs by standardized acupuncture might positively influence the dysfunction of the cerebrovascular response to autonomic stimuli.

Discussions of case #7:

Nitric Oxide (NO) is an endogenous molecule with powerful antiplatelet muscle relaxant properties, which is secreted by endothelial membrane of arterial wall mainly and plays an important role in regulating vascular tonus and systemic blood pressure. NO has a role in neurotransmission and neuronal circulation. It's thought that NO is important in transmission of sensory stimulant from the peripheral nerve endings.^{(18) (34)} It is considered that NO has a role in the pathogenesis of migraine and studies have been performed for it. The relationship between migraine and NO has been revealed first time by Olesen and D'Andra in 1993.^{(33) (34)} Lassen et al. had proposed the NO hypothesis in the H1 receptor-induced migraine in 1995, and Fabricius had explained the importance of cerebrovascular regulation in pervasive cortical depression through arginine and NO in migraine. In 1997 Griffiths has revealed the genetic connections in the relationship between migraine and NO.⁽³⁵⁾

Other studies have been performed also to better understand the role of NO in migraine attacks.

Attack development is observed in migraine patients about 4-5 hours after intravenous infusion of nitroglycerin as a source of exogenous NO. Significant vasodilation development in the middle cerebral artery has been found in these attacks. In another study, it has been observed that there is a relationship between the severity of headaches and the administered dosage of nitroglycerin, that the severity of headache is increased until the dosage is increased up to 0.5

g/min, and the pain severity does not change in proportion to the dose after that level. (36) (37)

In conclusions, this clinical study revealed that NO is likely to trigger migraine attacks by causing vasodilation. This possibility has been supported by demonstrating the enlargement in cerebral arteries with the start of the attack in patients administered with glyceryl-trinitrate, which is a NO precursor, and that acupuncture therapy significantly lowered the serum NO level in migraine patients, (30% decreased by 5 times of treatment, $p < 0.05$).

Overall Discussions

The objective of this Literature Review is to find the clinical studies that prove;

1. The effectiveness of acupuncture treatment for migraine patients, and
2. The mechanisms of actions of acupuncture treatments that intervene the pathogenesis of migraine pain.

As reviewed, clinical study case #1, case #2, case #3 and case #4 (Study Group A), and a Case Outcome Report are to prove the effectiveness of acupuncture treatments, and the clinical study case #5, case #6 and case #7 (Study Group B) are to prove how acupuncture treatments intervene the pathogenesis of migraine in addition to the efficacy of treating migraine headache pain.

All study cases have proved that acupuncture treatment is effective in healing migraine pain, as well as a method of prophylaxis.

However, in “Study Group A”, the case #1 and case #2 concluded that acupuncture was no more effective than sham acupuncture, while the conclusions of case #3 and case #4 were “Verum Acupuncture (VA) or Real Acupuncture (RA) is superior or significantly better than SA

in reducing the pain intensity and/or the number of days of migraine pain.”

The major differences between the cases that concluded the inconsistent results were reviewed.

The major differences of the cases in Study Group A were whether the acupuncture trials were performed in multi-center by different acupuncturists, and what outcomes were measured to induce the conclusions.

The case #1 and case #2 were performed in multi-center by multiple acupuncturists, and the measured outcome was the number of days with migraine pain, whether mild or severe pain which were logged by the patients in their diaries.

Meanwhile, case #3 was performed in multi-centers though, acupuncture treatment was given only when the assigned patients had pain, and the pain level (VAS) was evaluated 24 hours after each treatment.

Case #4 measurement outcome was also the number of days with migraine pain, same as that of case #1 and case #2, but each trial was performed by the same acupuncturist.

Acupuncture points used for interventions were all different for each case, even though there were some common points. The supplement points were defined for each case except the case #1, in which the multiple acupuncturists had their own freedom to select. Manual stimulations were applied in all cases except in case#2, which applied electro-stimulation even in sham acupuncture group.

As mentioned in Western Medicine Viewpoints, the traditional theories of migraine pathogenesis fall into two categories; Vasogenic and Neurogenic.

In Vasogenic theory, intracranial vasoconstriction was responsible for aura of migraine and the subsequent headache resulted from a rebound dilation and distention of cranial vessels and activism of inflamed perivascular sensory neurons. (6)

In Neurogenic theory, migraine is a brain disorder based on altered cerebral susceptibility to migraine attacks and that the vascular changes occurring during a migraine are the result rather than the cause of attack. (6)

Having these in mind, let us take a look at what the cases in “Study Group B” have tried to prove.

The summary is in table 11.

The objective of study case #5 was to investigate whether acupoints specificity exist by giving acupuncture treatment to migraine patients, using PET-CT, and proved AS reduced the pain level significantly, and induced different levels of cerebral glucose metabolism in pain-related brain regions.

The study case #6 was to evaluate the effects of acupuncture on cerebrovascular response in migraineurs by transcranial Doppler Ultrasound, and it proved that acupuncture treatment might positively influence the dysfunction of the cerebrovascular response to autonomic stimuli.

The study case #7 proved that acupuncture treatment significantly lowers the serum Nitric Oxide level in migraine patients.

Upon searching the clinical studies for effectiveness of acupuncture in treating migraine patients, this author had a couple of basic questions on following points.

1. In TCM, differential diagnosis are to be individualized. Having said that, what acupuncture points should be used in clinical research for randomized controlled trial? How could it be standardized or semi standardized for treating migraine?
2. Are there any clinical studies performed by using standardized set of acupoints for treating migraine and how effective was it?

3. The pain is subjective for each individual. If so, is relying on VAS which is the feeling of each individual, scientific enough?
4. What modern technologies could be used to measure the efficacy of acupuncture treatment based on the pathogenesis factors?

The answers found through this Literature Review are;

1. Mostly semi-standardized points (mandatory plus supplementary points) were used, selected by either TCM theory and/or experienced practitioner's opinions, which were very reasonably acceptable.
2. There was a clinical study that adapted a standardized set of acupuncture points, as in Case #6, Case #7 and Case #8, and the results were very effective as well.
3. The answer should be “yes”, as there were standard questionnaires used, such as the Modified version of the Pain Questionnaires of the German Society of the Pain in the Case#1, Migraine-Specific-Quality-of-Life Questionnaires in the Case#2, Short-Form of McGill Pain Questionnaire (SF-MPQ) in the Case#3, Six-Point Likert Scale along with VAS in the Case#4, and finally the Case Report used Migraine Disability Assessment (MIDAS) and Headache Impact Test (HIT-6). And in each case, the proper statistical analysis had been performed.
4. As reviewed in the Case#5, Case#6 and Case#7, the modern medical technologies were used to find the pathophysiology and how acupuncture treatment had intervened the pathogenesis.

Author's Interpretation of the combined conclusions of case#5, case#6 and case#7

The combined conclusion of above mentioned three study cases may be summarized as

follows.

“Acupuncture treatment to migraine patients may induce cerebral glucose metabolism differently in the pain related regions of brain, and positively influence the dysfunction of the cerebrovascular response to autonomic stimuli, and lower the serum NO level.”

It could hardly conclude and explain how and what mechanism of actions of acupuncture treatment resulted to intervene or removed the pathogenesis of migraine attacks.

It was not enough to grasp “the causes and the effects” relationship of migraine and its curing effects.

However, what have been proven by these great works of study cases, in terms of “pathophysiology and the results”, may be summarized as follows;

“Migraine headache is caused by cerebrovascular dilation which is caused by the increased serum NO level in intracranial vessels as an autonomic rebounding action from cerebrovascular constriction to adjust the blood pressure autonomically in brain vessels, and during these series of process, some parts of the brain consumed more glucose, and while what had caused the cerebrovascular constriction was not yet known, acupuncture treatment resulted that NO serum level lowered, and that the dysfunction of the cerebrovascular response to autonomic stimuli was positively influenced, and that induced was the different levels of cerebral glucose metabolism in pain-related brain regions.” This suggests highly that migraine pain is very much associated with “Vasogenic theory”.

Even with these great works of studies, the basic root questions have not been answered, “what caused the cerebrovascular constriction in the first place, and what mechanism of actions of acupuncture treatments intervened the causes of it?”

It is this reviewer's conjecture that all the conclusions induced by the “Study Group B” might be the results of acupuncture stimulation which intervened the root causes of cerebrovascular

constriction, which could be the true etiology of migraine. It might have been caused by imbalance in the brain chemicals, such as dropped serotonin level that causes trigeminal nerve to release neuropeptide or other neurotransmitters including calcitonin gene related peptide (CGRP). (5)

In TCM terms, it had been already defined and proven.

The causes of migraine pain are one or combination of those; Liver-Yang Rising, Liver-Fire-Rising, Liver-Qi-Stagnation, Blood-Stagnation, or Damp-Phlegm, which are caused by various triggers in living or genetic environments.

It is this reviewer's wish that these TCM terms should be able to be explained in modern Western Medicine terms, and be proven with the “scientific-measurements” in the near future.

V. CONCLUSIONS

This Literature Review concludes that acupuncture treatment is effective in treating and preventing the symptoms of migraine headache pain, as shown below in the Conclusions Summary, Table 14, where 3 cases concluded as effective, 4 cases significantly or superiorly effective and 1 case minor effective.

However, the effectiveness is only good for reducing or temporarily removing the symptoms of migraine pain and /or providing the prophylactic measures for migraine symptoms, which may last up to 3 months. Then, the symptoms may relapse. None of the clinical trials in this Literature Review rendered any curative results. “No cure is existing for migraine” is yet a true statement as of today. Migraineurs need to have continuous treatments regularly or irregularly in order to maintain a quality of life with less or without migraine pain. Nevertheless, the effectiveness of acupuncture treatments is much more beneficial for migraineurs, because there are no major side-effects involved with it, unlike in pharmacotherapies, and because there are less chances of using the rescue medications such as opioids.

From the very beginning of this Literature Review, one of the concerns encountered was how to standardize the acupuncture points to apply to each subject in RCT, which according to TCM theory, should be individualized for better treatments, and when individualized, would it induce any unnecessary biases. All cases in this Review had used the semi-standardized or standardized acupuncture points to produce the significant results, without having any biases involved, so to believe. The most commonly used acupuncture points were GB20, LR3, LI4, GB41, SJ5, GB40, Sp6, Du20, no matter what individual subject's differential diagnoses were.

Stimulation is another concern that may induce different results in conjunction with the different skill level of the individual practitioner. Electrical stimulation seemed to be a solution in

order to maintain the “consistency”. Three cases applied electro-stimulation, which were case#2, case#5 and case#8. The study case#2 used electro-stimulation for both acupuncture group and sham acupuncture control group, and that the results showed even the sham acupuncture was effective in reducing migraine symptoms for some noticeable degree, which on the other hand, generated another kind of “a bias”, whereas case#5 and case#8 showed the significant results as shown in table 14.

In order to avoid or minimize the biases, “consistency” is the key word, on top of randomization and blinding. Consistency could be achieved by well-training of the involved acupuncturists in case of the trials performed by multi-centers, otherwise it would be better to be performed by a single acupuncturist. And also the “sham” or “placebo” points must be well defined and well understood by the practitioners to keep consistency.

Having analyzed the strengths and weaknesses of each clinical study in this Review, recommended is to design a future clinical study for migraine as following summary, which may produce the better, bias free outcome results.

1.Subjects: 60 migraineurs with frequent migraine attacks, 2-3 times/week, based on International Headache Society criteria

2.Randomization/Blinding: Computer-made randomization opaque sealed envelop allocation unknown to practitioner, 30 Real-Acu group (RA), 30 Sham-Acu (SA) control group

3.Single-center/single acupuncturist with standardized acupoints and well-defined sham points

4.Interventions: Standardized acupoints GB20, LR3, LI4, GB41, SJ5 bilaterally 2 times in first 4 weeks, followed by 1 time a week in next 4 weeks. Electro-stimulation is to be applied only to RA group on the points LR3-GB41, LI4-SJ5

5.Outcome measurements: Pain-intensity of the first attack after treatments, number of days with migraine pain

6. Statistics: Compare the baseline values of 4 weeks before treatments with the outcome results for both RA group and SA control group, in t-test with significant level of $p < 0.05$

7. Long term follow-up: 3 months, 6 months, 1 year

The scientific measurements of the results of acupuncture treatment, such as “Brain Activation or different glucose metabolism in pain related parts of brain” in the Case#5, “Cerebrovascular Response” in the Case#6, and “Serum Nitric Oxide level” in the Case#7, had supported how the positive conclusions derived along with VAS measurements, and how it might be related to the pathogenesis of migraine. Having reviewed above mentioned cases performed in modern scientific measurements, this author interpreted that the pathogenesis of migraine is more “Vasogenic” rather than “Neurogenic”.

However, inconclusive yet is the etiology of migraine, such as the root causes of cerebrovascular constriction in the first place and how this could be intervened by the acupuncture treatments.

And further studies should be pursued to explain in modern scientific terms how these pathogenesis of Western Medicine terms are related to the TCM terms, such as Liver-Yang Rising, Liver-Fire Rising, Liver Qi Stagnation, Blood Stagnation and Damp-Phlegm etc.

In this author's opinion, first of all, the research to explain how and what the “Liver-Yang Rising” is related to any neuro-transmitters or brain chemicals such as serotonin, that may cause the cerebrovascular constriction, which has been so far identified as the pathogenesis of migraine.

That being said, this author has a strong recommendation for a future clinical research design, which should compare the outcome results from the trials performed with the “standardized acupoints” as mentioned above vs that from the trials performed with the “genuinely customized acupoints” according to the differential diagnosis of the individual subject, and that are practiced

by a single acupuncturist. This kind clinical study, if being tried along with the scientific measurements that are related to the cerebrovascular constriction or dilation, should help a step closer to understand the pathogenesis of migraine pain.

Table 14: Conclusions Summary

| Clinical Study Case | Conclusions |
|-----------------------------|---|
| Study Case#1 | Acupuncture no better than Sham but much better than control group. Acupuncture treatments decreased days of migraine pain ($p < 0.001$) |
| Study Case#2 | Acupuncture appeared minor effect on migraine prophylaxis, but treatments reduced the days of migraine in 13th-16th week |
| Study Case#3 | Verum acupuncture is “superior” to Sham acupuncture. Pain intensity reduced significantly ($p = 0.001$) |
| Study Case#4 | Real acupuncture significantly less days with migraine pain. Days of migraine reduced ($p = 0.008$), pain intensity ($p = 0.004$) |
| Study Case#5 | Acupuncture tx: more effective for pain reduction in TAG ($p = 0.0005$) induces different level of glucose metabolism in pain related brain regions |
| Study Case#6 | Headache frequency & intensity significantly decreased in Verum acupuncture. ($p < 0.001$) Acupuncture Treatment positively influenced cerebrovascular |
| Study Case#7 | Serum Nitric Oxide level reduced 30.6% in migraine group and pain level reduced accordingly ($p < 0.05$) |
| Case #8 Case Outcome Report | Significant decrease in pain intensity and frequency ($\alpha = 0.05$) after acupuncture intervention. Results had not returned to preintervention baseline |

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