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Comparison of the Prophylactic Effect Between Acupuncture and Acupressure on Menstrual Migraine: Results of a Pilot Study

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Graduate Program in Kinesiology
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Arts
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Abstract

Background: Menstrual migraine (MM) is one kind of migraine associated with females' menses. It is often associated with increased menstrual distress and disability, leading to decreased daily activity and quality of life. **Purpose:** To make comparisons between acupuncture and acupressure for preventing MM. **Design:** A randomized and controlled pilot study with three groups: verum acupuncture (VA) group, acupressure (AP) group, and control acupuncture (CA) group. The study lasted for seven cycle-months, with a 1-cycle-month baseline observation (T1), a 3-cycle-month intervention (three times per cycle-month) (T2-T4), and a 3-cycle-month follow-up (T5-T7). **Outcome measures:** number of migraine days, average and peak pain, total duration period of MM, and percentage of patients with $\geq 50\%$ reduction in the number of MM days. **Results:** A total of 18 participants were included in the analysis (VA, n = 7; AP, n = 6; CA, n = 5). Both VA and AP were significantly more effective than CA for reducing MM days during intervention period. Both VA and AP tended to be more effective than CA for reducing peak pain of MM during intervention period. No significant differences for the outcomes were observed among VA, AP, and CA during follow-up period. No serious adverse events were reported. **Conclusion:** Results of the pilot study suggests that both VA and AP could be considered as alternative and safe prophylactic interventions for MM. Register ClinicalTrials.gov Identifier: NCT02592681.

Keywords

menstrual migraine, acupuncture, acupressure, prophylactic effect

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Chapter 1

1 Introduction

Migraines are a type of primary headache of moderate to severe intensity that can lead to disability, decreased quality of life, and workplace absenteeism (“WHO | Headache disorders,” n.d.). The estimated financial burden associated with migraines has been slightly over \$4.2 billion annually in health care services in the USA (Insinga, Ng-Mak, & Hanson, 2011). In Canada, migraines affect approximately 15% of the population (Worthington et al., 2013). The overall prevalence of migraines in women is 11.8% compared with 4.7% among men, with the highest prevalence between ages 30 and 49 years in both sexes (Ramage-Morin & Gilmour, 2014). It has been reported that women suffering from migraines experience reduced performance at work or in school, decreased participation in social activities, and less time spent with family (Dueland, Leira, Burke, Hillyer, & Bolge, 2004; MacGregor, Brandes, Eikermann, & Giammarco, 2004). The predominant ages for migraines in women are between the ages of 18 and 49 years (Lipton et al., 2007).

Women who report their migraine associated with their menses are referred as having a menstrual migraine (MM) (Pavlović et al., 2015). MM is defined by the International Classification of Headache Disorders III beta version (ICHD-III beta) with the criteria for two subcategories. One is pure menstrual migraine (PMM), which is defined as migraine attacks without aura that occur exclusively between two days before and three days after menstruation for at least two out of three consecutive menstrual cycles. The other is menstrual related migraine, which is similar to PMM, but also involves additional migraine episodes outside the menstrual cycle. In this study, the term MM encompasses both subcategories (Headache Classification Committee of the International Headache Society (IHS), 2013).

According to epidemiologic studies, from 20% to 60% of women with migraines report an association between migraines and menses (Couturier, Bomhof, Neven, & Van Duijn, 2003; Dzoljic et al., 2002; Mannix & Calhoun, 2004; Pavlović et al., 2015; Vetvik,

MacGregor, Lundqvist, & Russell, 2010). MM is often associated with increased menstrual distress and disability, leading to decreased daily activity and quality of life (Beckham et al., 1992; Kibler et al., 2005). Quite a few prospective studies have confirmed that the MM attacks tend to be more severe, lead to more functional disability, last longer, are more susceptible to relapse, and are more resistant to symptomatic treatment than attacks off the cycle (Dowson, Massiou, & Aurora, 2005; Granella et al., 2004; MacGregor et al., 2004; MacGregor et al., 2010; MacGregor & Hackshaw, 2004; Pavlović et al., 2015).

The primary mechanism of MM appears to be related to the withdrawal of estrogen (S. Silberstein & Patel, 2014). According to a series of studies, it is suggested that the fluctuation of estrogen levels could modulate the production and the pathways of endogenous opioids, which play a role in the pathogenesis of migraines (Colson, Lea, Quinlan, MacMillan, & Griffiths, 2005; De Créé, 1989; Kvisvik, Stovner, Helde, Bovim, & Linde, 2011; MacGregor, Frith, Ellis, Aspinall, & Hackshaw, 2006; V. T. Martin & Behbehani, 2006; Murray & Muse, 1997; Nappi & Martignoni, 1988).

Since the 1970s there have been quite a few studies about pharmacologic treatments for both acute onset and prevention of MM (Dalton, 1976; Kornstein & Parker, 1997; MacGregor et al., 2006; Nierenburg, Ailani, Malloy, Siavoshi, Hu, & Yusuf, 2015; Pradalier, Clapin, & Dry, 1988; S. Silberstein & Patel, 2014). Nevertheless, the results from recent clinical trials have pointed out that menstrual-related attacks do not always respond as well as non-menstrual attacks to acute pharmacological treatments (Dowson et al., 2005; MacGregor et al., 2010; Mathew, Dun, & Luo, 2013). Quite a few prophylactic drugs are contraindicated when women have other comorbidities, such as cardiac disease, uncontrolled hypertension, peptic ulcer disease, previous gastrointestinal bleeding, or breast cancer (MacGregor et al., 2010; Pringsheim, Davenport, & Dodick, 2008).

For the past two decades, several non-pharmacologic approaches, including life style changes, maintaining routines for eating, regular exercise, repetitive cathodal direct current stimulation, and short-term non-invasive vagus nerve stimulation, have been suggested (Campbell, Penzien, & Wall, 2008; Grazzi, Egeo, Padovan, Liebler, &

Barbanti, 2016; Mannix & Calhoun, 2004; V. Martin & Brandes, 2005; Wickmann et al., 2015). However, to date the research for many of these non-pharmacologic treatments, including acupuncture is inconclusive and/or sparse. This is unfortunate since some of these alternatives, if effective, may be preferable to pharmacologic treatment.

Acupuncture is an ancient therapeutic intervention grounded in the theory of traditional Chinese medicine (TCM). It is defined as the practice of inserting fine needles into precisely defined points (also known as acupoints) on the human body surface to keep the body healthy or to recover the body from illness (Kaptchuk, 2002). According to TCM, the mechanism of acupuncture lies in its effect on balancing “yin” and “yang” (two opposing yet complementary forces inside the human body supporting health) and harmonizing the flow of “qi” (described as quantitative energy in the Western sense) (Ernst, 2006; Kaptchuk, 2002). From the modern scientific perspective, the effect of acupuncture comes from regulating the nervous system, thus stimulating the release of neurochemicals such as endogenous opioids or serotonin from immune system cells at specific sites in the body providing the rationale for the analgesic effect (Moffet, 2006).

There are a few studies from China suggesting that acupuncture is a promising treatment for MM (C. Li, 2008; C.-H. Li, Liu, Yang, Shi, & Wang, 2011; Tian & Li, 2014; Tong, Dong, & Zhao, 2011; C.-G. Wang & Xu, 2007; H. Wang & Wang, 1996; Z.-X. Wang, 1994; Wei, 2003; Zhang & Fu, 2001; J.-Y. Zheng & J.-Z. Zheng, 2001), which coincides with a study carried out in Germany (Hu, 1998). However, all of those studies had low methodological quality due to a lack of randomization or blinding. A study carried out in Sweden also supported the potential effectiveness of acupuncture for preventing MM (M. Linde, Fjell, Carlsson, & Dahlöf, 2005). One significant flaw of this study was lack of a true control since the placebo method was similar to acupressure (AP). This could create a definite therapeutic effect by stimulating the acupoints, as it was regarded as having the same treatment mechanism as acupuncture (Selfridge, 2012).

Although acupuncture is not a cure for everyone, it does help a certain number of females with MM. As a naturopathic method, it has fewer side effects compared with medicines. Since medication has been used to treat MM for a relatively long period and has showed

some effects though with many side effects and certain contraindications, it could be used as the last resort, rather than primary strategy. Acupuncture might be worthy of being considered as a front-line method for dealing with MM. AP has been used recently in one study to treat migraine headaches (Bhati & Kumar, 2013), and in three others to treat general headaches (Hendrich, Kahanov, & Eberman, 2011; Hsieh, Liou, Lee, Chen, & Yen, 2010; Rossi et al., 2005). All of these studies suggested AP's potential effectiveness for controlling headaches.

None of the studies discussed above have compared the therapeutic effect of acupuncture and AP on MM. If there is no significant difference between the two methods, it would offer the patients the possibility of them applying AP at home (or by a family member) to prevent or control MM. Therefore, it is worth exploring the true effect of acupuncture and AP on MM by planning a controlled clinical study. This study was designed as a pilot study to test the procedures and potential efficacy of acupuncture and AP compared to a true control group.

Although quite a few studies have focused on preventing migraines including MM, there was still a lack of consensus on standard measurements to determine the efficacy of the treatment. Migraine days, migraine attack frequency, the percentage of patients with $\geq 50\%$ reduction in the number of migraine days or migraine attacks, were the measurements that have been used most often among the studies over the last decade (Alecrim-Andrade, Maciel-Júnior, Carnè, Vasconcelos, & Correa-Filho, 2008; Buettner et al., 2015; Burke, Olson, & Cusack, 2002; Diener et al., 2006; Dodick et al., 2014; Ho et al., 2016; M. Linde et al., 2005; E. A. MacGregor et al., 2006; S. Silberstein, Goode-Sellers, Twomey, Saiers, & Ascher, 2013; L.-P. Wang et al., 2011; Y. Wang, Xue, Helme, Da Costa, & Zheng, 2015). Total duration period of migraine and the amount of analgesic medication usage have also been used (Alecrim-Andrade et al., 2008; Buettner et al., 2015; Burke, Olson, & Cusack, 2002; E. A. MacGregor et al., 2006; Y. Wang et al., 2015). Pain scales such as a visual analogue scale and a Likert scale were also used in a few studies (Y. Li et al., 2009; M. Linde et al., 2005; L.-P. Wang et al., 2011; Y. Wang et al., 2015). Based on these studies, all of the above measurements seemed to be useful

and potentially valid. Thus, the present study was also designed to observe which measurement worked best for evaluating the intervention effect on MM.

Chapter 2

2 Methods

2.1 Participants and Design

This was a randomized and controlled pilot study. The study was approved by the Western University Research Ethics Board (Appendix 1). Informed, written consent was obtained from each participant. Register ClinicalTrials.gov Identifier: NCT02592681.

In total, 33 female participants were recruited between the ages of 22 and 52 years. This age group was targeted as migraines decline through menopause, which could affect the therapeutic effect (V. T. Martin & Lipton, 2008; Neri et al., 1993; S. D. Silberstein et al., 1999). Participants were recruited through posters on bulletin boards on the main campus of Western University and e-posters through the online health service system.

The inclusion criteria were: (1) females aged from 18 to 49, exceptions could be made as long as the female presented without any manifestation of menopausal syndromes; (2) a diagnosis of MM according to the criteria of the ICHD-III beta; (3) regular menstrual cycles, as reported by potential participants themselves; (4) repeated self-reported MM attacks of at least half a year; and (5) no plan to become pregnant or change hormonal treatment during the study.

Participants were excluded if they had: (1) difficulties in differentiating migraines from other types of headaches; (2) other primary headaches such as tension headaches and cluster headaches, and secondary headaches which are activated by another disorder that is known to cause headaches (Ihclassification, n.d.); (3) starting the use of any new kind of migraine prophylactic drugs in the past three cycle-months; (4) serious cardiovascular, neurological, or psychiatric diseases according to their self-reported medical history; (5) severe bleeding disorder or anticoagulation according to the medical history; (6) a cardiac pacemaker; (7) metal allergy; (8) a severe needle phobia; or (9) if they were pregnant or lactating.

Block randomization was used and the participants had an equal chance of being allocated into one of the three groups: a verum acupuncture (VA) group, an acupressure (AP) group, or a control acupuncture (CA) group. To minimize bias, participants were not told the exact name of each group. Instead, they were told that because the aim of this study was to compare different intervention methods, they were allocated to different intervention groups. In addition, due to the obvious intervention differences between the AP group and the other two acupuncture groups, it was difficult to blind all participants.

2.2 Procedure

All females interested in this study had an appointment with the researcher to decide their eligibility according to the inclusion and exclusion criteria. Once eligible, participants then signed the consent form. Then, all participants who met the inclusion criteria were asked to keep a migraine diary (Appendix 2) prior to treatment for one cycle-month as baseline data. A cycle-month could range from 25—35 days in most women in the middle reproductive years, and it is entirely based on these participants' own cycle (Riley III, Robinson, Wise, & Price, 1999). The term cycle-month was used rather than the calendar month designation as the timing of the interventions was connected to the woman's cycle not the calendar month. The diaries were collected by the researcher at the end of the first cycle-month and the TCM patterns of MM were diagnosed using a few symptom-related questions (Appendix 3). In addition, times/dates for treatments were scheduled. All participants received their corresponding interventions on the eighth, fifth and third days before the estimated first day of menstruation (determined individually from the diaries) in each cycle-month for three cycle-months, making a total of nine treatment sessions in each condition. In case of an acute migraine attack, participants were not restricted from using "normal" medications (Tfelt-Hansen et al., 2012). After completion of treatment, there was a 3-cycle-month follow-up period. All participants were asked to complete the migraine diaries every cycle-month from baseline to the end of the study, after which they were collected. The timeline for the treatment protocol can be seen in Table 1.

Table 1: Protocol of the study

Time	Visit	Procedures
Cycle-month 0	Screening	Use inclusion and exclusion criteria to test eligibility
Cycle-month 1	Base line, TCM pattern diagnosis	Keep diaries of MM attacks for 1 cycle-month; hand in at the end of the 1 st cycle-month and get the TCM pattern diagnosis
Cycle-month 2	Treatment Visit 1 (30 min)	VA/ or AP/ or CA
	Treatment Visit 2 (30 min)	VA/ or AP/ or CA
	Treatment Visit 3 (30 min)	VA/ or AP/ or CA, and keep diaries
Cycle-month 3	Treatment Visit 4 (30 min)	VA/ or AP/ or CA
	Treatment Visit 5 (30 min)	VA/ or AP/ or CA
	Treatment Visit 6 (30 min)	VA/ or AP/ or CA, and keep diaries
Cycle-month 4	Treatment Visit 7 (30 min)	VA/ or AP/ or CA
	Treatment Visit 8 (30 min)	VA/ or AP/ or CA
	Treatment Visit 9 (30 min)	VA/ or AP/ or CA, and keep diaries
Cycle-month 5-7	Follow-ups	Keep diaries of MM attacks for 3 cycle-months, and hand in the diary at the end of the 7 th cycle-month

The study was carried out in a lab located on Western University main campus and equipped with a comfortable massage table together with sterile facilities (i.e., 70% medical alcohol, sterile cotton balls and sanitizer). Upon arrival on a treatment day, participants were asked to sit and relax for 1—2 min. They were then asked to lie down in a prone position to receive their corresponding interventions by the certified acupuncturist (XY).

In the VA group, participants received needle insertions at designated, valid acupoints (see description of points below). Sterile needles (0.18 mm in diameter and 30 mm in length, DONGBANG Needle, Korea) were used for all acupoints. The depth of insertion varied from 15 mm to 20 mm depending on location. An initial manual stimulation was given at insertion by rotating the needle to produce a specific sensation described as “de-qi” in TCM (a sensation perceived by the acupuncture receiver as numbness, fullness,

and sometimes soreness around the point (Kong et al., 2007)). Then the needles were left in the acupoint for 20 min, with a manual rotation at 4—8 Hz and an amplitude of approximately 0.5—2 rotations at a 10-min interval to maintain the sensation of “de-qi” (Bäcker et al., 2002).

Primary acupoints used in the VA group were: LR3 (Taichong), LI4 (Hegu), SP6 (Sanyinjiao), GB20 (Fengchi). They were selected according to several previous relevant clinical studies (Hu, 1998; K. Linde et al., 2005; M. Linde et al., 2005; L. Sun et al., 2015; Y. Wang et al., 2015; H. Wang & Wang, 1996; Wei, 2003; J.-Y. Zheng & J.-Z. Zheng, 2001). Extra acupoints were selected based on the TCM pattern (Maciocia, 2011). If the pattern was due to *qi* and blood deficiency, ST36 (Zusanli) was added (Z.-H. Sun, 2008; Wei, 2003). If it was due to *qi* stagnation and blood stasis, SP10 (Xuehai) was added (Y.-Y. Li, 2010). If it was due to Liver and Kidney *yin* deficiency, KI3 (Taixi) was added (Y.-Y. Li, 2010; Wei, 2003). If it was due to Liver fire, LR2 (Xingjian) was added (Huang & Yue, 2011). The exact locations of these acupoints are described in a textbook (Deadman, Al-Khafaji, & Baker, 2000). They can be seen in Figure 1 and Figure 2 below (Deadman et al. , 2000).

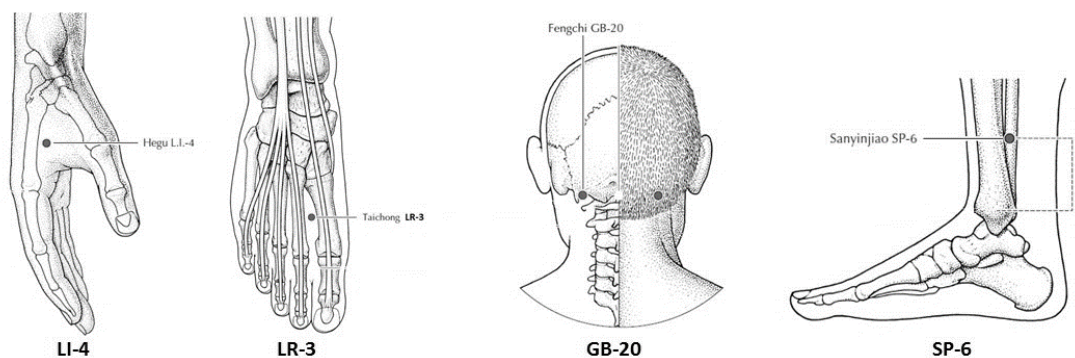


Figure 1: Primary acupoints selection for VA and AP groups (bilaterally)

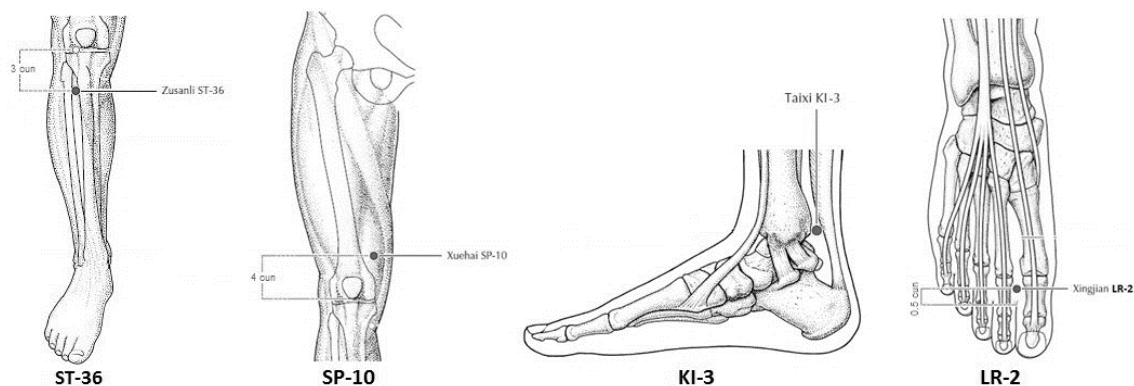


Figure 2: Additional acupoints according to TCM pattern (bilaterally)

In the AP group the acupoints and the number of sessions were exactly the same as for the VA group. AP was applied on all the corresponding acupoints described in the VA group. Finger pressure was applied to each acupoint for eight seconds followed by a 2-s rest, repeating this sequence for 3 min (Jun, Chang, Kang, & Kim, 2007; Lin et al., 2010). The strength of the AP was applied in a flexible manner depending on the individual participant's feedback. It was set at a point where the participant had an obvious sensation of “de-qi”, and just before they would experience unpleasant and intolerable feelings (Dibble et al., 2007; Yip & Tse, 2004). Duration of each session was 15 min.

In the CA group, the number, duration, and frequency of the sessions were the same as for the VA group. Sterile needles (0.18 mm in diameter and 15 mm in length, DONGBANG Needle, Korea) were used on acupoints that should have had no therapeutic effect on either menstruation or migraines, based on the acupuncture text books and acupuncture research literature (Deadman et al., 2000; Maciocia, 2008). The points chosen were: LR7 (Xiguan), GB35 (Yangjiao), LI12 (Zhouliao), M-BW-1 (Dingchuan). They can be seen in Figure 3 (Deadman et al., 2000). The depth of needle insertion was as superficial as 3 mm, and without manual rotation, in order to minimize stimulation of the needle (Diener et al., 2006).

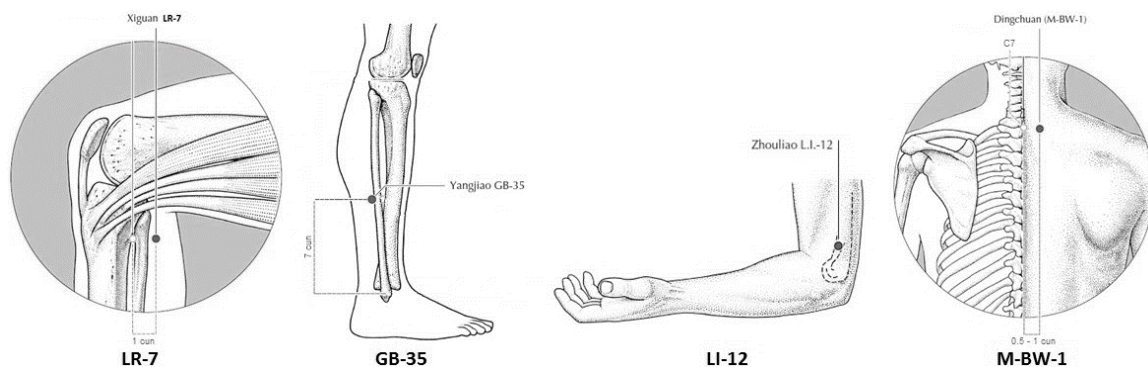


Figure 3: Acupoints for CA group (bilaterally)

All interventions were performed by the same acupuncturist (XY) licensed by the College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario (CTCMPAO). Before the acupuncture treatment, appropriate infection control measures were employed, and different sizes of single use, sterile, disposable needles in appropriate packages were available. Participants were advised to wear shorts and T-shirts to the lab for their treatments. During treatment, they assumed a prone position on a massage table. To lessen the risk of infection the skin over the acupoints were swabbed with 70% ethyl alcohol, using an outward rotary motion from the center of the point to the surrounding area. No treatment was administered until the alcohol dried (“Safety_Program_Handbook(December-04-2015).pdf,” 2012). The acupuncturist washed his hands immediately before both insertion and removal of needles. On withdrawing a needle, a sterile cotton ball was used to press the skin at the insertion site. If blood was drawn, light pressure was applied with a clean swab (“Safety_Program_Handbook(December-04-2015).pdf,” 2012).

2.3 Analysis

It is important to note that the literature does not suggest a gold standard outcome measure for migraine research. As a result, several measures were chosen. The outcome measures included: the number of MM days per cycle-month, an average pain scale (i.e., a Likert scale using a 10-point scale, with anchors at 0 and 10 where 0 means no pain and 10 means worst pain) represented as an average score of all attacks in a cycle-month, a peak pain scale per cycle-month which was the maximum score among all attacks

(indexed on the Likert scale), total duration period of MM (hours per cycle-month), the percentage of participants with a $\geq 50\%$ reduction in the number of MM days per cycle-month compared with the baseline period, the amount of analgesic medication used for MM per cycle-month, change of accompanied symptoms, and the absence from work days or school days and/or classes missed due to MM per cycle-month.

The outcome measures were assessed at baseline and each cycle-month following until the end of data collection (T1 to T7).

All the adverse events (AEs) that the participants encountered were reported to the researcher, such as dizziness, nausea, palpitations, excessive sweating, faint, hematoma, and any other discomfort due to the treatment. Any dropout or withdrawal was documented in detail during the entire study period.

For statistical analyses the significance level was set at $p \leq .05$ (2-tailed). The following dependent variables (i.e., the number of migraine days per cycle-month, pain scale including average pain and peak pain, and total duration period of MM) were statistically analyzed, except the percentage of participants with a $\geq 50\%$ reduction in the number of MM days per cycle-month due to insufficient data in several cells. One-way ANOVA was used to test the dependent variables at baseline. Factorial analyses of variance (ANOVA) were then used to investigate group by time relationships (3 x 3) during the intervention period (T2-T4). If there were significant main effects of time and/or group, and/or interaction between time and group, Tukey's post hoc tests were used to analyze between-group intervention difference during intervention period (T2-T4), and/or for time to analyze between-group time difference from T2 to T4 regardless of group, and/or for group on each level of time point (T2-T4) to analyze between-group intervention difference. If required, paired t-tests with Holm-Bonferroni correction for time were used within-group comparisons during intervention period (T2-T4). Linear regressions were used to predict the relationship between time and the above dependent variables respectively to test the existence of cumulative effects for each intervention method (i.e., VA, AP, and CA) (T2-T4). A mean cycle-month score of each dependent variable for the follow-up period (T5-T7) was used to analyze pre- (T1) and post-intervention differences

by applying 3 x 2 factorial analyses of variance (ANOVA). If required, Tukey's post hoc tests were used to analyze between-group difference. If required, paired t-tests with Holm-Bonferroni correction were used to analyze within-group difference.

All the analyses were performed using R software Version 0.96.122 (RStudio, Boston, MA) (RStudio, 2012).

Chapter 3

3 Results

3.1 Demographic characteristics of the participants

There were 33 out of 42 who expressed an interest to participate who were eligible to enroll, and they were randomly assigned to different groups (Figure 4). Eighteen out of 33 participants completed the whole study and had their data analyzed, while 12 dropped out and three were removed. Among the 12 dropouts, six participants (one in the VA group, three in the AP group and two in the CA group) were due to a conflict between their work/school schedule and the study schedule; four participants (one in the AP group and three in the CA group) never responded to the researcher's email or phone calls again after they signed the consent forms; one participant in the VA group quit after the first session due to uncomfortable sensations; one participant in the VA group left Canada due to emergent family issues. Among the three removed, two participants (one in the VA group and one in the AP group) showed irregular periods during their baseline data collection period, while one participant in the CA group received a hormonal intra uterine device one week after signing the consent form.

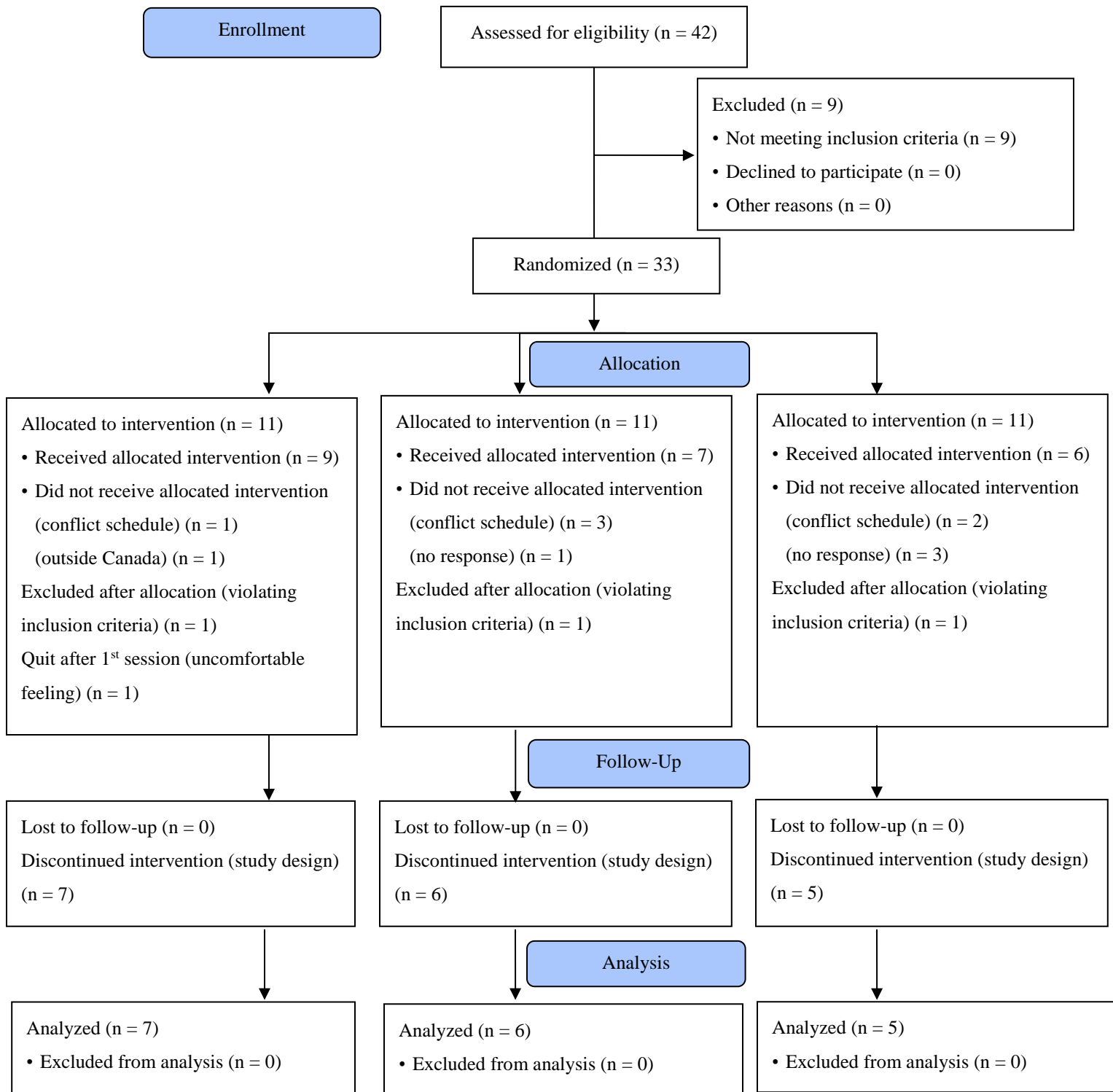


Figure 4: Trial flow diagram

Three out of 18 participants with one in each group received eight interventions. Each had missed one treatment session during the 3-cycle-month intervention period, owing to the fact that the day of their third session overlapped with the first day of their cycle. Within the 18 participants, eight were diagnosed as *qi* stagnation and blood stasis pattern, six as liver fire pattern, and four as liver and kidney *yin* deficiency pattern according to TCM theory. The history of MM varied among these participants from 16 months to over 30 years. All but one of the participants were within the set age range from 22—49 years. One participant was 52 years old, but still had a regular period and therefore was included in the study.

3.2 The efficacy of the intervention conditions

Data collected from the amount of analgesic medication used for MM per cycle-month, change of accompanied symptoms, and the absence from work days or school days and/or classes missed due to MM per cycle-month were not usable, so they were not analyzed and reported.

3.2.1 The number of MM days per cycle-month

One-way ANOVA indicated that there were no significant differences among the three groups at baseline, $F(2, 15) = .20, p = .82$ (Table 2). Factorial ANOVA indicated that there was significant main effect of intervention $F(2, 15) = 6.41, p = .01$, but no significant main effect of time $F(2, 30) = 3.21, p = .054$, and no significant interaction between intervention and time $F(4, 30) = .25, p = .91$. Tukey's post hoc test indicated both VA ($M = 1.43, SD = 1.08$) and AP ($M = 1.39, SD = 1.20$) resulted in significant decreased MM days compared with CA ($M = 2.80, SD = 1.47$), $p = .005$, respectively, during the intervention period. Linear regression results showed that MM days had a significant negative relationship with time in the VA group, $R^2 = .20, p = .043$ (Figure 5).

Table 2: The number of MM days per cycle-month (Mean \pm SD)

	Cycle-month 1	Cycle-month 2	Cycle-month 3	Cycle-month 4	Cycle-month 5-7 (average)
VA group	2.57 \pm 0.79	2.00 \pm 1.29	1.43 \pm 1.13	0.86 \pm 0.38	1.40 \pm 0.41
AP group	2.50 \pm 0.84	1.67 \pm 0.52	1.83 \pm 1.60	0.67 \pm 1.03	1.28 \pm 0.63
CA group	2.80 \pm 0.84	3.00 \pm 1.00	3.00 \pm 2.24	2.40 \pm 1.14	2.06 \pm 0.64

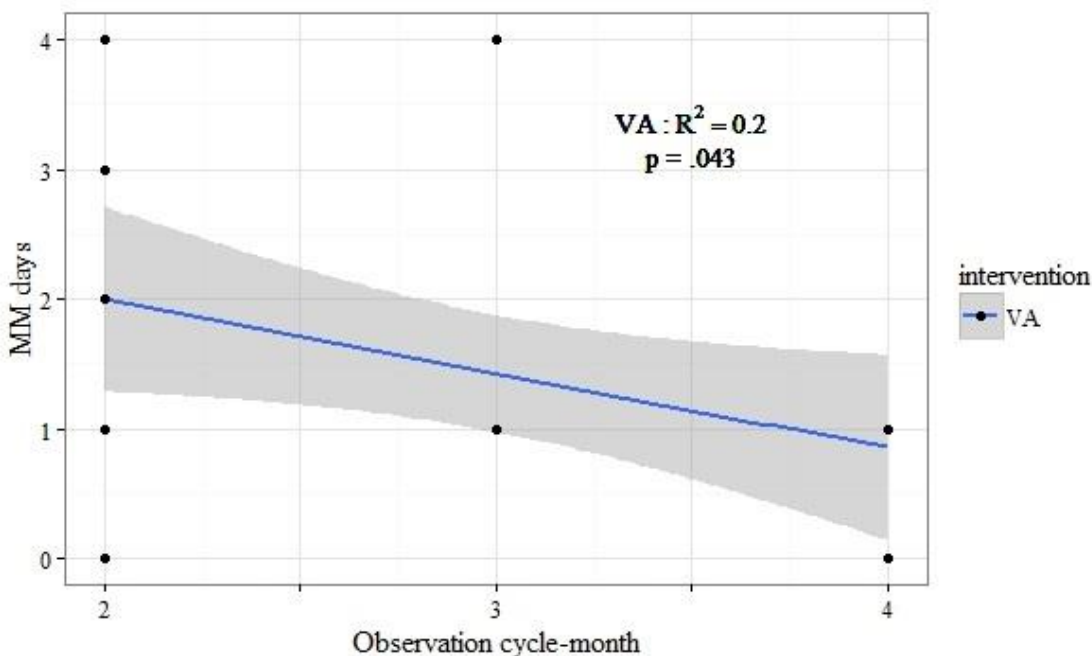


Figure 5: Cumulative effect of VA on MM days

In the pre/post analysis the factorial ANOVA indicated that there was a significant main effect of time $F(1, 15) = 18.45, p < .001$, but no significant main effect of intervention $F(2, 15) = 2.10, p = .16$, and no significant interaction between intervention and time $F(2, 15) = .34, p = .72$ (Table 2). Tukey's post hoc test indicated that MM days in the post-intervention period ($M = 1.54, SD = .62$) were significantly less than in the pre-intervention period ($M = 2.61, SD = .78$), regardless of intervention methods, $p < .001$.

Individually, there were huge variations among participants from all the three groups throughout the entire study period (Figure 6). For example, one participant had gradually reduced MM days during the intervention period and had no MM attacks in the fourth cycle-month, but had MM recurrence in the follow-up period. Another participant had steadily reduced MM days to no MM attacks during the study period. A third participant had no change after six sessions but was free from MM attacks after nine sessions, and had then fluctuated MM days in the follow-up period. In general, seven out of 13 participants (three in the VA group and four in the AP group) had at least one cycle-

month free from MM attacks during the whole study period, whereas one participant in the CA group also had one MM-free cycle-month.

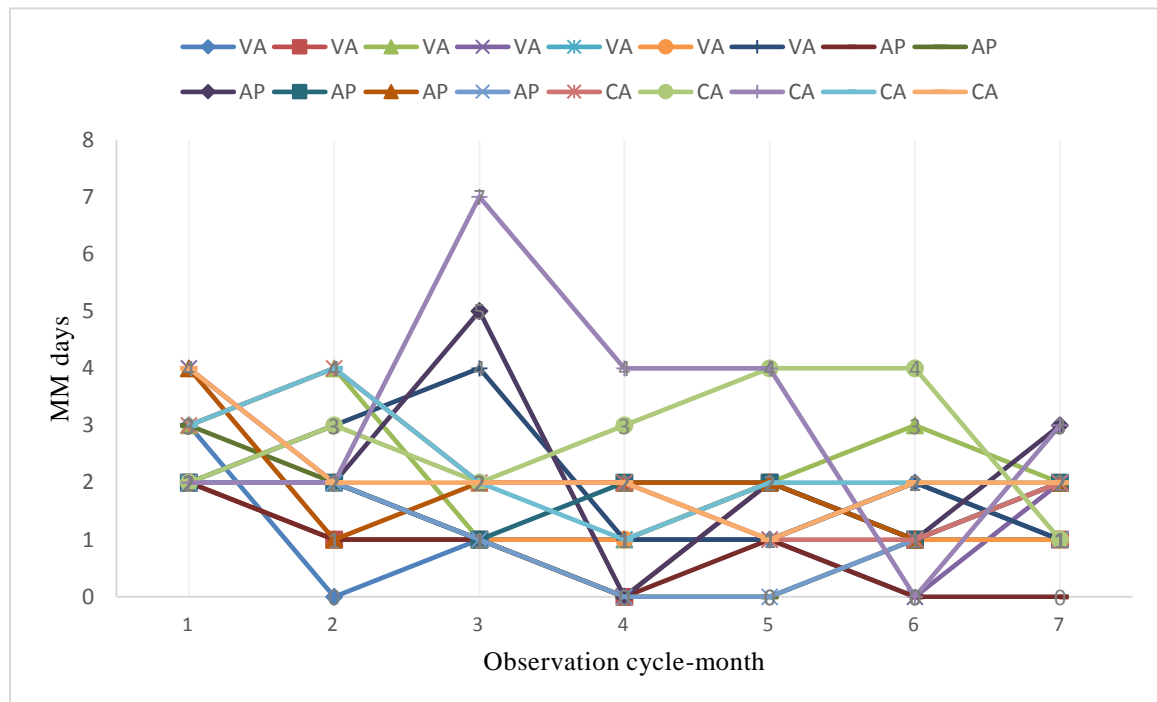


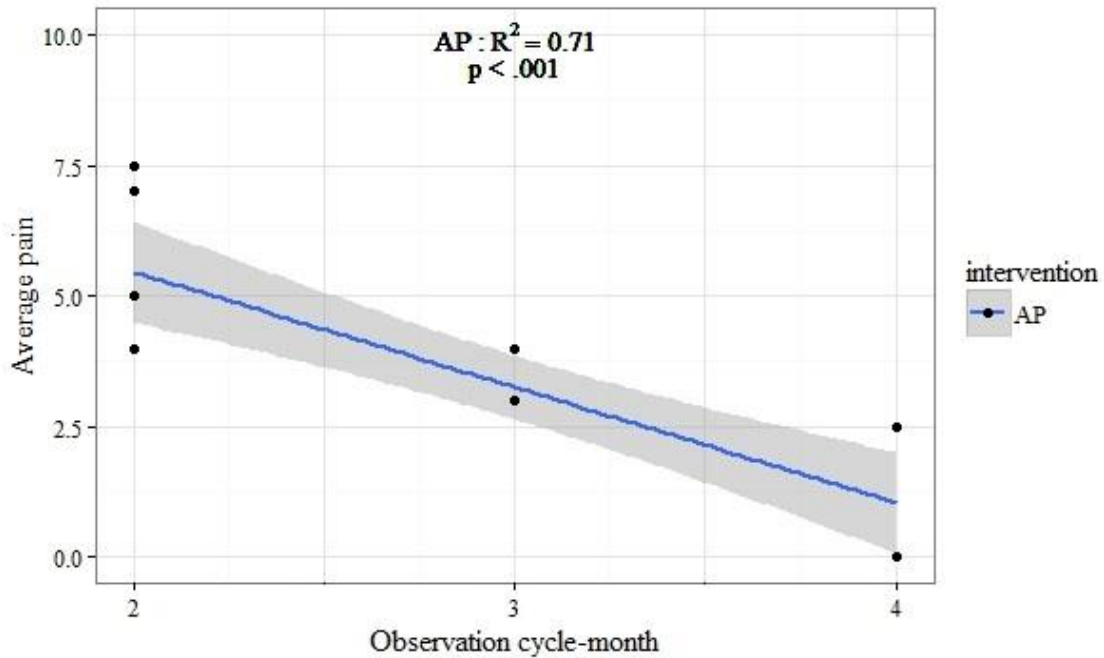
Figure 6: Individual MM days per cycle-month for seven cycle-months

3.2.2 Average pain per cycle-month

One-way ANOVA indicated that there were no significant differences among the three groups at baseline, $F(2, 15) = .08, p = .93$ (Table 3). Factorial ANOVA indicated that there was a significant main effect of time $F(2, 30) = 7.98, p = .002$, but no significant main effect of intervention, $F(2, 15) = 2.42, p = .12$, and no significant interaction between intervention and time $F(4, 30) = 2.58, p = .057$. Tukey's post hoc test indicated that average pain reduced significantly in the fourth cycle-month ($M = 2.28, SD = 1.87$) than in the second ($M = 4.57, SD = 2.42$), $p < .001$, and third cycle-months ($M = 4.14, SD = 1.61$), $p = .003$, respectively, regardless of intervention. Linear regression results showed that the average pain had a significant negative relationship with time in the AP group, $R^2 = .71, p < .001$ (Figure 7).

Table 3: Average pain per cycle-month (Mean \pm SD)

	Cycle-month 1	Cycle-month 2	Cycle-month 3	Cycle-month 4	Cycle-month 5-7 (average)
VA group	5.07 \pm 1.74	3.00 \pm 2.84	4.36 \pm 2.30	2.79 \pm 2.23	4.27 \pm 1.96
AP group	5.33 \pm 0.88	5.25 \pm 1.60	3.67 \pm 0.52	0.83 \pm 1.29	2.67 \pm 2.36
CA group	6.10 \pm 1.85	5.96 \pm 1.48	4.40 \pm 1.47	3.30 \pm 0.67	3.65 \pm 1.70

**Figure 7: Cumulative effect of AP on average pain**

In the pre/post analysis the factorial ANOVA indicated that there was significant main effect of time $F(1, 15) = 12.62, p = .003$, but no significant main effect of intervention, $F(2, 15) = .10, p = .91$, and no significant interaction between the intervention and time $F(2, 15) = 1.24, p = .32$. Tukey's post hoc test indicated that average pain in the post-intervention period ($M = 3.87, SD = 1.60$) was significantly less than in the pre-intervention period ($M = 5.44, SD = 1.51$) regardless of intervention, $p = .005$.

3.2.3 Peak pain per cycle-month

The one-way ANOVA indicated there were no significant differences among the three groups at baseline, $F(2, 15) = .01, p = .98$ (Table 4). The factorial ANOVA indicated that there were significant main effects of both intervention, $F(2, 15) = 4.13, p = .037$, and

time $F(2, 30) = 7.72, p = .002$, but no significant interaction between intervention and time $F(4, 30) = 1.89, p = .13$. However, Tukey's post hoc test only indicated that both VA and AP had the tendency to result in a significant lower peak pain than CA, $p = .08$ and $p = .09$ respectively. Tukey's post hoc test also indicated that peak pain reduced significantly in the fourth cycle-month ($M = 2.72, SD = 2.14$) compared to the second ($M = 5.47, SD = 2.92$), $p = .003$, and third cycle-months ($M = 4.75, SD = 1.91$), $p = .03$, respectively regardless of intervention methods. Linear regression results showed that peak pain had a significant negative relationship with time in the AP group, $R^2 = .60, p < .001$ (Figure 8).

Table 4: Peak pain per cycle-month (Mean \pm SD)

	Cycle-month 1	Cycle-month 2	Cycle-month 3	Cycle-month 4	Cycle-month 5-7 (average)
VA group	6.29 \pm 2.29	3.64 \pm 3.57	5.00 \pm 2.08	3.00 \pm 2.16	4.66 \pm 2.23
AP group	6.17 \pm 1.17	6.00 \pm 2.10	4.17 \pm 1.17	1.17 \pm 1.83	3.93 \pm 1.84
CA group	7.00 \pm 2.00	7.40 \pm 0.89	5.40 \pm 2.07	4.30 \pm 1.30	4.44 \pm 1.58

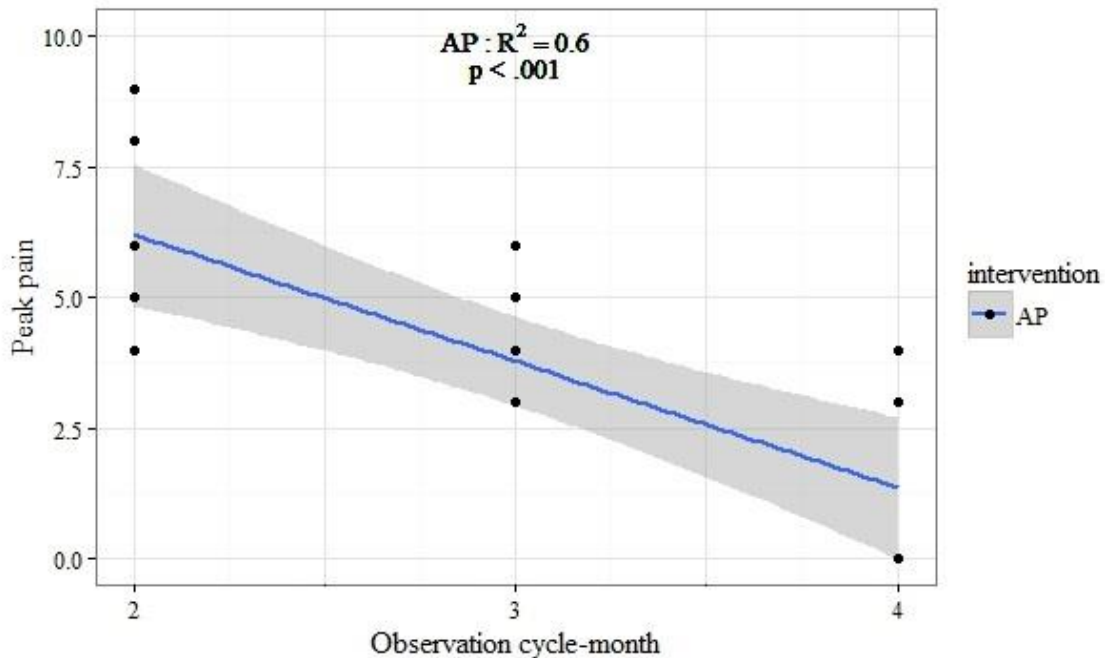


Figure 8: Cumulative effect of AP on peak pain

In the pre/post analysis the factorial ANOVA indicated that there was a significant main effect of time $F(1, 15) = 16.36, p = .001$, but no significant main effect of intervention, $F(2, 15) = .26, p = .78$, and no significant interaction between intervention and time $F(2, 15) = .28, p = .76$. Tukey's post hoc test indicated that peak pain in the post-intervention period ($M = 4.36, SD = 1.85$) was significantly less than in the pre-intervention period ($M = 6.44, SD = 1.82$), regardless of intervention, $p = .002$.

Individually, huge variations in peak pain were observed among these participants (Figure 9).

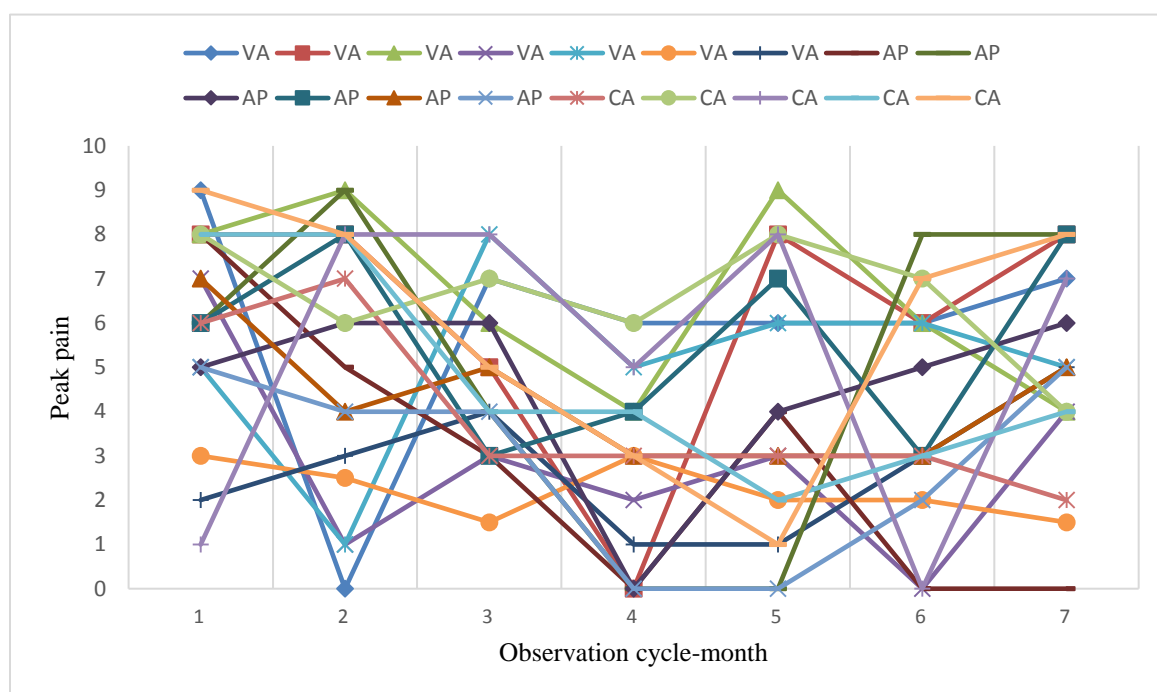


Figure 9: Individual peak pain per cycle-month for seven cycle-months

3.2.4 Total duration period of MM (hours per cycle-month)

The one-way ANOVA indicated there were no significant differences among the three groups at baseline, $F(2, 15) = 2.18, p = .15$ (Table 5). The factorial ANOVA indicated that there was significant main effect of time $F(2, 30) = 4.45, p = .02$, but no significant main effect of intervention, $F(2, 15) = .94, p = .41$, and no significant interaction between intervention and time $F(4, 30) = 1.13, p = .36$. Tukey's post hoc test indicated MM

duration during the intervention period was significantly less in the fourth cycle-month ($M = 10.08$, $SD = 9.63$) than in the second cycle-month ($M = 22.22$, $SD = 15.53$), regardless of intervention, $p = .029$. Linear regression results showed that duration of MM had a significant negative relationship with time in both the VA group, $R^2 = .22$, $p = .031$, and the AP group, $R^2 = .24$, $p = .04$ (Figure 10).

Table 5: Total duration period of MM (hours per cycle-month) (Mean \pm SD)

	Cycle-month 1	Cycle-month 2	Cycle-month 3	Cycle-month 4	Cycle-month 5-7 (average)
VA group	40.93 \pm 26.66	25.14 \pm 18.96	15.50 \pm 11.29†	8.57 \pm 8.43	14.34 \pm 4.47
AP group	20.25 \pm 7.47	21.67 \pm 16.56	14.17 \pm 17.60	3.67 \pm 5.99	10.28 \pm 5.14
CA group	25.20 \pm 13.17	18.80 \pm 10.63	24.20 \pm 18.59	19.90 \pm 7.54	23.58 \pm 19.06

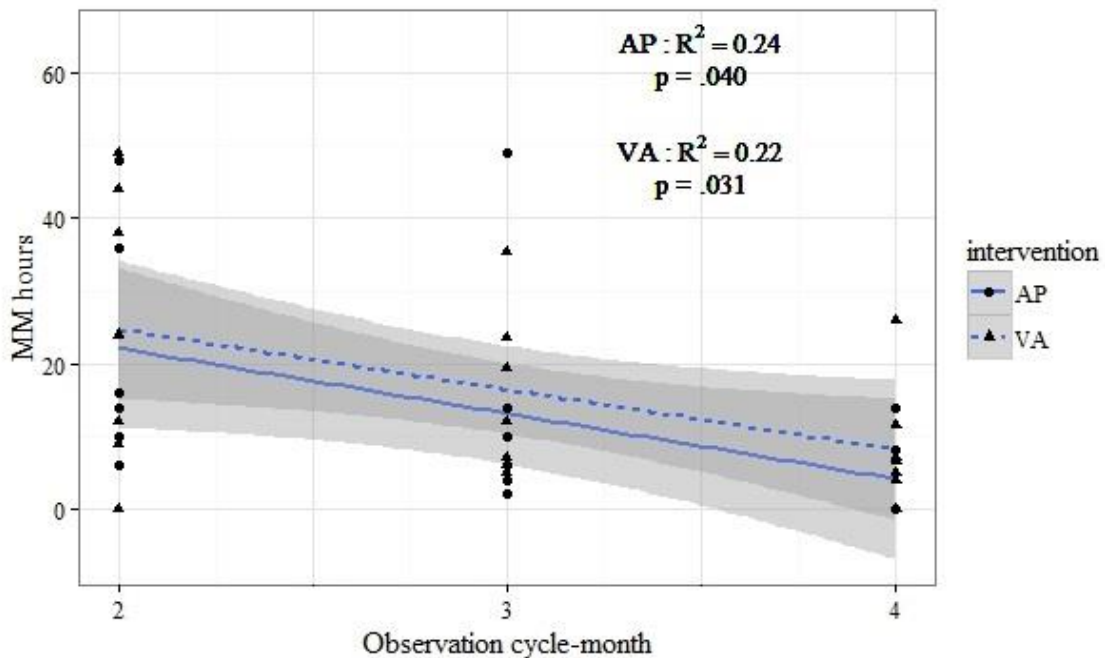


Figure 10: Cumulative effect of VA and AP on MM duration

In the pre/post analysis the factorial ANOVA indicated that there was a significant main effect of time $F(1, 15) = 8.66$, $p = .01$, but no significant main effect of intervention, $F(2, 15) = 2.02$, $p = .17$, and no significant interaction between intervention and time $F(2, 15) = 2.38$, $p = .13$. Tukey's post hoc test indicated that MM duration in the post-intervention

period ($M = 15.56$, $SD = 11.39$) was significantly less than in the pre-intervention period ($M = 29.67$, $SD = 19.64$) regardless of intervention, $p = .01$.

Individually, the total duration period of MM varied greatly among the participants (Figure 11). Five out of 13 participants in both the VA and AP groups had no MM attacks in the fourth cycle-month, whereas five other participants (three in the VA group and two in the AP group) reported only 25% of baseline MM hours or even less. Meanwhile, two out of five participants in the CA group also had approximately 25% of baseline MM hours.

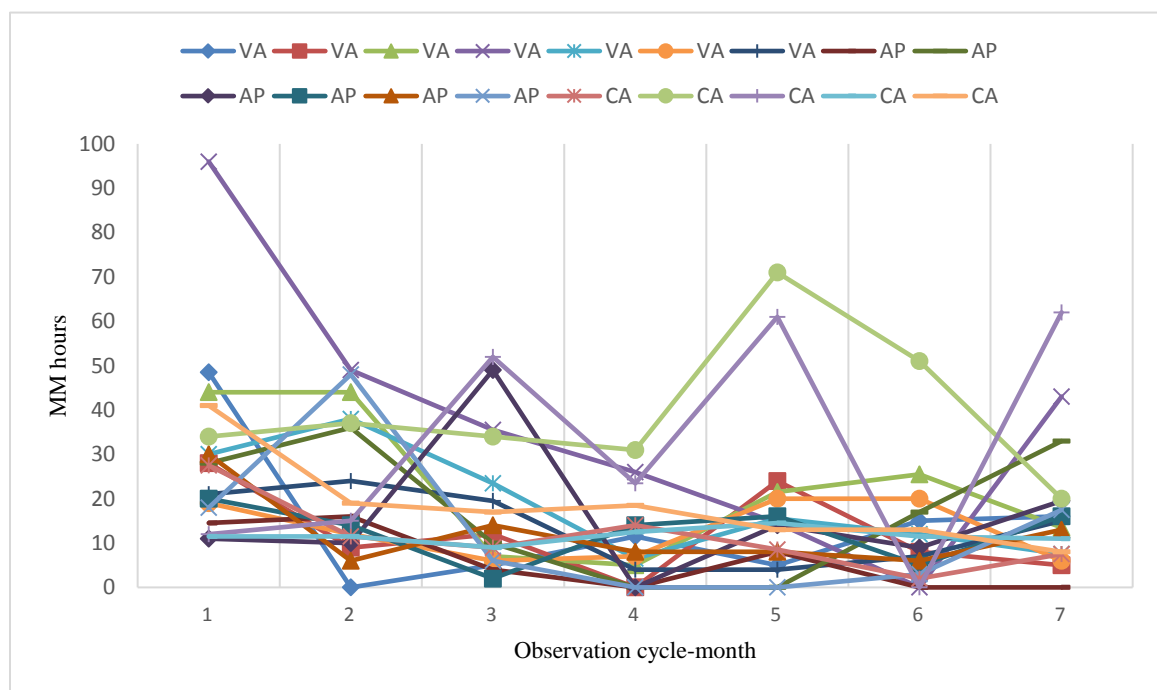


Figure 11: Individual MM duration per cycle-month for seven cycle-months

3.2.5 The percentage of patients with a $\geq 50\%$ reduction in the number of MM days per cycle-month

The proportion of responders (participants having over 50% reduction in the number of MM days) each cycle-month was greater in both the VA and AP group than in the CA group during the intervention period (Table 6). VA displayed a marginally better result than AP.

Table 6: The percentage of patients with a $\geq 50\%$ reduction in the number of MM days per cycle-month

	Cycle-month 2	Cycle-month 3	Cycle-month 4	Cycle-month 5-7 (average)
VA group	42.86%	85.71%	100%	61.90%
AP group	33.33%	83.33%	83.33%	66.67%
CA group	0	0	40%	46.67%

During the follow-up period, there was little difference between the VA and AP groups, while the proportion of responders in these two groups were greater than that in the CA group.

3.3 Adverse events (AEs)

No serious AEs were reported. Only one participant in the VA group reported uncomfortable feelings around the acupuncture site on the right thumb which she believed to have affected bending and moving function of the finger for a few hours, and thus she withdrew from the study. Most AEs were mild to moderate localized soreness and tiny Subcutaneous hemorrhage around acupoints after sessions which disappeared within the next 24 hrs. This was reported in nine participants (three in the VA group and six in the AP group). Small hematomas and tiny bruises were found in six participants (two in the VA group, three in the AP group, and one in the CA group).

Chapter 4

4 Discussion

4.1 Treatment Efficacy

4.1.1 The number of MM days per cycle-month

Both VA and AP showed a significantly better result than CA during the intervention period. This finding was consistent with two relevant studies (L.-P. Wang et al., 2011; Y. Wang et al., 2015) which indicated that VA was significantly better than CA, and partially consistent with one study which showed the same result in the first two intervention months (Alecrim-Andrade et al., 2008). But it was inconsistent with three other studies which indicated no significant differences between VA and CA (Diener et al., 2006; K. Linde et al., 2005; M. Linde et al., 2005). The possible explanation might be the choice of irrelevant acupoints (control) used in their studies lying on the meridian pathway which is related to migraine. This may have led to some treatment effect. During the follow-up period, the prophylactic effect of both VA and AP persisted, but were not superior to CA, which was inconsistent with the above two studies as they found VA was significantly more effective than CA during the post treatment period (Diener et al., 2006; L.-P. Wang et al., 2011). This was also inconsistent with M. Linde et al.'s study as they did not find any significant differences between VA and CA at any time point throughout the study. The follow-up effect in Y. Wang et al.'s study was more complicated as they found VA significantly better than CA at the end of a 3-month follow-up, but no significant difference between VA and CA at 1-year follow-up. As the present study designed a 3-cycle-month follow-up period, the result was regarded as inconsistent with Y. Wang et al.'s study. One possible explanation might be the different intervention frequency design. However, this result was consistent with Alecrim-Andrade et al.'s and K. Linde et al.'s studies as they found a persistent effect of VA, but no significant differences between VA and CA during this period. In the present study, VA showed time cumulative effects, which was not analyzed in any of the above studies. The difference between this study and the other five studies could be mainly due to the study

focus. This study focused exclusively on MM, whereas the other studies targeted generalized migraines.

4.1.2 Average pain per cycle-month

Neither VA nor AP showed significantly superior effects to CA during the intervention period. However, average pain reduced significantly during the intervention period regardless of intervention method. This was consistent with three relevant studies, which showed that both VA and CA led to decreased pain compared to pre-intervention, and no significant differences were found between VA and CA (K. Linde et al., 2005; L.-P. Wang et al., 2011; Y. Wang et al., 2015). During the follow-up period, the intervention effect persisted without significant differences between VA, AP and CA, which was again consistent with the above three studies. AP also demonstrated a time cumulative effect in the intervention period.

4.1.3 Peak pain per cycle-month

Both VA and AP tended to have a significantly better result than CA during the intervention period, which was inconsistent with Y. Wang et al.'s study as they did not reveal any significant differences between VA and CA. Peak pain reduced significantly in the intervention period regardless of intervention method, and AP showed a time cumulative effect in this period. During the follow-up period, the intervention effect persisted without significant differences between VA, AP and CA, which was consistent with Y. Wang et al.'s study. Since K. Linde et al.'s and L.-P. Wang et al.'s studies did not elaborate whether it was a peak pain or an average pain, it is difficult to make direct comparisons.

4.1.4 Total duration period of MM (hours per cycle-month)

Neither VA nor AP showed significantly superior effects to CA during the intervention period. However, MM duration reduced significantly in the intervention period regardless of intervention method. This was consistent with one relevant study which showed no significant differences between VA and CA (Y. Wang et al., 2015), and partially inconsistent with another study which showed a significantly better result of VA than CA

in the first two intervention months but no significant differences between VA and CA from the third intervention month to the follow-up period (Alecrim-Andrade et al., 2008). In the present study, both VA and AP showed a time cumulative effect. Since neither of the two related studies has analyzed this effect, it was impossible to make comparisons here. During the follow-up period, the intervention effect persisted without significant differences between VA, AP and CA, which was consistent with the above two studies (Alecrim-Andrade et al., 2008; Y. Wang et al., 2015).

4.1.5 The percentage of patients with a $\geq 50\%$ reduction in the number of MM days per cycle-month

Both VA and AP showed a better result than CA during both the intervention period and follow-up period. Since no statistical analysis could be carried out for this outcome, it was difficult to make comparisons with other studies. A similar result was found in two related studies which showed that VA led to a significantly greater proportion of responders than CA in both intervention and follow-up period (L.-P. Wang et al., 2011; Y. Wang et al., 2015). However, two other studies demonstrated different results than this study as they found no significant difference between VA and CA (Diener et al., 2006; M. Linde et al., 2005). One study had a partially consistent result with this study as they found a significantly better result of VA than CA in the first two intervention months but no significant differences between VA and CA from the third intervention month to the follow-up period (Alecrim-Andrade et al., 2008).

4.1.6 Overall effects

Based on the overall results, both VA and AP showed some prophylactic effect on MM, and indicated time cumulative effects on some measures, although the effects were not consistent. AP could be regarded to be as effective as VA for its prophylactic effect, since the statistical analyses did not reveal any significant differences between the two methods. It seems the treatment locations (i.e., acupoints) played a more important role than the manipulation technique, as the primary acupoints were the same in both VA and AP groups. Furthermore, with regard to the AP treatment used in the present research, a few studies using AP for pain management have applied a standard strength for every participant by mechanically measuring the pressure applied (Chen, Chang, & Hsu, 2005;

U.-L. Chung, Hung, Kuo, & Huang, 2003; Jun et al., 2007; Lee, Chang, & Kang, 2004; Wong, Lai, & Tse, 2010). The present study used a more flexible way in order to keep the pressure within each participant's tolerance threshold while not compromising the therapeutic effect. There is no study to date that would permit a conclusion about which kind of AP method may have better clinical effects. However, based on the results of this study, AP with a flexible pressure application appears to be a promising intervention method.

4.2 Adverse events (AEs)

AEs are an important consideration in migraine management. With respect to pharmacologic treatments, fatigue, somnolence or insomnia, depression, vomiting, nausea, dizziness, glaucoma, concentration difficulties, rash, weight gain or loss, paresthesia, abdominal pain, gastrointestinal symptoms (i.e., nausea, vomiting, gastritis, and blood in the stool), musculoskeletal system symptoms (i.e., tremor, restless leg syndrome, and leg pain), mastitis, abnormal menstrual cycles (i.e., frequent periods, infrequent or absent periods, and irregular cycles), are mild to severe AEs that have been reported in the existing literature (Estemalik & Tepper, 2013; Ramadan, Silberstein, Freitag, Gilbert, & Frishberg, 2000; S. D. Silberstein et al., 2012). Regarding relevant studies using acupuncture to treat or prevent migraines, mild to moderate AEs such as tingling sensation, local paraesthesia, hematoma, subcutaneous hemorrhage, subcutaneous ecchymosis, leg weakness, fatigue, and triggering of a migraine attack, have been reported in the past decade (K. Linde et al., 2005; Y. Wang et al., 2015; Streng et al., 2006; Alecrim-Andrade et al., 2008; Y. Li et al., 2012).

AEs found in this study were all mild to moderate and were consistent with these relevant studies, and were relatively less severe than many pharmacologic treatments. In addition, those with AEs in this study fully recovered without disabilities, which is consistent with other studies (MacPherson, Scullion, Thomas, & Walters, 2004; White, Hayhoe, Hart, & Ernst, 2001; Witt, Lao, & MacPherson, 2011). The dropout rate due to AEs was also very low in the present study with only one participant withdrawing from the study. Thus, acupuncture is considered to be a generally safe procedure (Lao, Hamilton, Fu, & Berman, 2003) and may be preferable as an initial headache treatment. Also, since AEs

for acupuncture are comparably minor, this should facilitate future research study recruitment.

4.3 Participant feedback

One participant in the VA group had fluctuating symptoms during her treatment period. This might be due to manipulations on the needles. She was treated by the acupuncturist following the standard procedure strictly for three sessions. However, starting from the fourth session, she insisted no more twisting needles or she would rather withdraw from the study, and the acupuncturist compromised. Thus, the effect after six and nine sessions appeared not to be as promising as that after three sessions. It was reasonable to deduce that the rotation of the needles might also affect the acupuncture effect. Using fMRI, previous studies have found that twisting the needles on specific acupoints could increase activation in certain cortical areas, which suggested a strengthened effect of for the acupuncture (Fang, Krings, Weidemann, Meister, & Thron, 2004; Jeun, J. S. Kim, B. S. Kim, Park, Lim, Choi, & Choe, 2005). It was suggested that the researcher should try to educate the participant to allow to the original treatment plan instead of being compromised in future studies, in order to preserve the prophylactic effect.

Three participants in the VA group reported greatly decreased peak pain after three sessions, while four in the same group reported accentuated peak pain after six sessions of treatments compared with the three sessions, but the pain was less than baseline. This phenomenon, which indicated some fluctuation of the acupuncture effect, has not been reported by any other relevant studies. Thus, it was suggested that more participants were recruited to further look into this issue.

Four participants (three from the VA group and one from the CA group) had their MM one to three days ahead of their normal schedule in the last intervention cycle-month (fourth cycle-month), while this phenomenon was not observed in the AP group. This might be due to the stimulation of the needle causing a change to the female's endocrine status (Aso et al., 1976). Thus, the session dates should perhaps be more flexible for participants who receive acupuncture in future studies (i.e., the last three sessions could be set at eight, six, and four days before the projected onset day of their next cycle).

One participant reported aggravated MM (i.e., increased MM days, prolonged MM duration, and increased peak pain) in the AP group after six sessions, but then noted improvement after nine sessions in the fourth cycle-month. The participant had taken birth control pills for more than one year. Birth control pills may impact the efficacy of AP (Aegidius, Zwart, Hagen, Schei, & Stovner, 2006). However, the deterioration of the migraine might be more attributed to over mental stress and strain which was confirmed by the participant during that specific 2-cycle-month period. The AP effect may be compromised by other factors, but may eventually produce an anticipated effect. Another participant in the AP group had fluctuating symptoms during the 3-cycle-month intervention period. A possible explanation would be her exhausted physical status which might compromise the therapeutic effect (Loder, 2006), as she had two long-distance trips across 12-hr time zones three days after the third session and two weeks before the start of the fourth session respectively.

Three participants in the CA group reported no improvement (i.e., same or increased MM days, same or prolonged MM duration, and same or increased average and peak pain) after three sessions, but showed some improvement after six sessions. Another two participants in the same group reported some improvement (i.e., decreased MM duration) after three sessions, with further improvement after nine sessions. It appeared that the sham acupuncture in this study showed some positive effects, which is consistent with the finding of a previous systematic review that sham acupuncture could be associated with a more prominent reduction of migraine frequency than oral pharmacological placebos (Meissner et al., 2013).

4.4 The clinical trial control condition

In this study, all but one participant claimed that they were not sure about the intervention condition since only one participant in the VA group had had previous acupuncture experience. Those who were assigned to the AP group reported a different kind of experience compared with massage, so they were not sure what kind of effect they were expecting. The only participant who held a strong belief of a potential acupuncture effect was in the CA group. In addition, all the participants were told that they would be assigned into different intervention groups including two different acupuncture methods

instead of VA and CA, and one AP method. Thus, a potential placebo effect, as indicated by a study that patients with higher expectations about the intervention could get better improvement for chronic pain (K. Linde et al., 2007), had already been minimized.

In retrospect, the acupoints selected for the CA group were not as ineffective as expected. One possible explanation might be the meridians on which these points were located. Although these points (i.e., GB35, LI12) were not reported to have efficacy when dealing with migraines according to previous studies or documents, the meridians they belonged to, do cover the frontal and temporal area of the head. As documented in a book named *Huangdi's Classic*, the therapeutic function of a meridian could reach wherever it covers. Another possible explanation might be the effect of the needle stimulations on twelve cutaneous regions covering the whole human body, which were also intimately related to twelve primary meridians (Ellis, Wiseman, & Boss, 1991). It is not clear whether an invasive sham acupuncture method (i.e., penetrating the skin) would be a better control condition than a non-invasive sham acupuncture method (i.e., not penetrating the skin) since there were no studies that have compared the two different methods. Based on the results of the present study, an invasive sham acupuncture on irrelevant acupoint locations avoiding headache-related meridians, is recommended for future studies.

4.5 Advantages and disadvantages of the measurements

Among the measurements used in this study, number of MM days, pain scale, the percentage of patients with $\geq 50\%$ reduction in the number of MM days, and total duration period of MM provided a positive result of VA and/or AP. However, these measurements also have weaknesses.

Pain scale is a useful measurement tool, as it indicated how each participant felt during this study. This offered the researcher a direct view on how well the intervention might be. Nevertheless, the most obvious drawback of this scale is its subjectivity. Participants' attitude could be affected by many unpredictable factors on the given day, as three participants confessed that they were not in a good mood or they were in extreme mental stress and strain on that day, so they could be biased when documenting the pain. In addition, they recorded their pain after each attack rather than during MM attacks, which

made this outcome not as accurate as expected. Thus, it is sometimes hard to use pain scale alone to determine the real effect of an intervention.

In this study, the researcher analyzed both average and peak pain change before and after interventions among the three groups. According to the relevant literature, only one study used both peak and average pain but did not into further discuss about the best choice (Y. Wang et al., 2015), while the remaining studies either used average pain or did not elaborate this point at all (K. Linde et al., 2005; M. Linde et al., 2005; L.-P. Wang et al., 2011). The present researcher suggests that reduction of peak pain may be more meaningful to this specific population based on the feedback from participants in this study, as they argued that the reduced peak pain made it easier for them to cope with the MM attacks.

The literature calculating the percentage of responders varied mainly on three outcomes (i.e., MM days, attack frequencies and MM duration) (Nierenburg et al., 2015), but no studies have made comparisons between the MM days and MM duration with regard to the percentage of responders. In this study, the number of MM days per cycle-month was used to calculate the percentage of patients with 50% or more reduction in number of MM days. However, it might not be as sensitive as MM duration. Based on the participants' diary, MM days decreased from two days to one day in three females, while their MM duration decreased from 15.5 hrs to 12 hrs, increased from 15 hrs to 16 hrs, and remained 20 hrs respectively. Ideally, the trend of change would be the same or at least similar in the two outcomes. However, in this study, the result would change if MM duration was chosen instead of MM days. In addition, several participants were asked to give feedback on the documenting process at the conclusion of the study, and they agreed unanimously that it was much easier to record MM days than duration of each headache. Thus, it was impossible to decide which measure was more sensitive to detect a treatment effect.

Total duration period of MM (hours per cycle-month) was one of the essential outcomes used to indicate any alleviation of the migraine, but it might not be as accurate as it was expected to be. As one participant documented, "The pain was gone when I woke up the

next morning at 7am” under “time attack ends” column in the MM diary, the researcher had to contact the participant again for more accurate information. The result turned out to be that the participant could not recall accurately when the migraine ended and she assumed that the time she woke up was approximately the “end” time. Thus, the duration of MM was not as reliable as expected. Since no literature to date has discussed this issue, it is felt that it requires further attention. Another point worth mentioning was the diversity of duration hours, as four participants had continuous migraine attacks for one to two days, while the others had several intervals between attacks during one menstrual cycle. The extreme case showed up in the VA group. A participant had her MM duration much longer than the rest of the participants in both pre- and post-intervention periods. Thus, it seemed that keeping both MM days and duration may be necessary to capture the diversity of experiences and therefore potential effects. Only much larger sample sizes could possibly tease out these differences.

Finally, the records kept in the dairies were not always accurate and reliable. To improve this there may need to be a more thorough training protocol and more frequent feedback during early days of keeping the dairies to fine tune record keeping.

In conclusion, it is difficult to establish which measurements are most effective in capturing the prophylactic effects of VA or AP. It is recommended that a diversity of dependent measures be used in future research until a gold standard measure of MM relief can be established.

4.6 Limitation of this study

Although the most significant issue in this study was the small number of participants, it offered the researcher a good chance to observe all subjects in depth, and to get useful feedback which may be helpful for future study design. It took a period of seven cycle-months to finish this study, and the drop-out rate was higher than the researcher had expected. In addition, the recommended design would be nine cycle-months for the whole study, which required two additional cycle-months for baseline data collection as per ICHD-III beta definition on MM.

4.7 Suggestion for future studies

The dates of sessions were completely based on the participants' own menstrual cycle. However, were not always able to attend the exact days due to conflicts with work schedules or emergent business and/or family issues. This happened frequently for four participants in this study. Even though the practitioner was quite flexible with his own schedule to adapt to the participants, one third of all the participants changed their original session dates one day ahead or behind the schedule at least once. Since this study showed either a positive result or a promising trend in both the VA and AP groups, it might be reasonable to deduce that small adjustments to intervention dates may not affect the results significantly. The participants' compliance would be better if the treatment dates are more flexible, which might be taken into consideration in future study designs.

All the participants claimed to have a regular period, but it was still impossible for them to predict an accurate onset date of their upcoming menstrual cycle. Thus, the third session which was expected to be three days before the onset of the period day, always turned out to be only one or two days ahead, or even overlapping with the onset day. It might be beneficial to reconsider the intervention date for the last session before each period. It would also be interesting to explore the optimum intervention period to achieve the maximum therapeutic effect in future studies.

Despite the fact that all the participants were given clear instructions to use a number to represent the pain during each attack while documenting their diaries, there were still three participants reporting a range of scores for each attack (e.g., 4—8), as they claimed that the pain varied from low to high scores during each attack. Thus, a midpoint of score range was used to represent the average pain in this study (e.g., if pain range was 4—8, then the average pain was 6). The peak pain was set arbitrarily as the maximum score among all attacks by the researcher in this study, which might not represent the real peak. As it appeared to be essential and meaningful in clinical evaluation, it is suggested that all participants be required to record both average and peak pain for each attack in future studies.

As AP was effective in preventing MM in this study, it would be essential to determine a suitable method of application which is convenient to follow in clinical practice, and easy to copy in a scientific study. Thus, comparisons between standardized AP pressure and flexible AP pressure is suggested to be compared in future studies. In addition, it may be advantageous to test whether combining VA and AP together compared with VA and AP alone might improve treatment results. For example, after a participant receives VA clinically, they could apply AP themselves at home during intervening days.

From a clinical perspective, acupoint selection could be individualized (rather than standardized) based on a client's body pattern per TCM theory. Since this was a randomized controlled study, the freedom of acupoints selection was limited and thus the potential effect of either VA or AP might be underestimated here. Nevertheless, the results of this study could be used as a reference for future studies in comparison to an individualized acupoints approach.

The study design included a 3-cycle-month follow-up observation period without any further interventions. It appeared that the effect of either VA or AP had faded away in the follow-up period compared with that in the intervention period, although this effect still appeared to be better than pre-intervention on some aspects (i.e., MM days and peak pain). This was inconsistent with five relevant studies dealing with migraines (Alecrim-Andrade et al., 2008; Diener et al., 2006; Y. Li et al., 2012; K. Linde et al., 2005; Vincent, 1989). However, these studies focused on general migraine instead of this specific MM, which had a more intimate relationship with estrogen level fluctuations. Thus, it might be worth considering to keep interventions at a relatively lower frequency (e.g., once every third cycle-month) during the follow-up period in order to maintain the treatment effect, as indicated by a previous study using acupuncture to treat chronic low back pain (Carlsson & Sjölund, 2001).

4.8 Clinical significance vs statistical significance

Statistical significance is essential in the research world to decide whether the effect of VA and AP are good enough to be popularized for this targeted population. However, from clinical perspective, even if VA and AP work well only on a very limited number of

clients, it would be still worth trying as they are natural and safe intervention methods with little to no AEs compared with medication which may have multiple significant side effects. Based on the individual results in this study, three participants did benefit greatly from VA or AP from a clinical perspective. Thus, either VA or AP could be recommended as a front-line method for the prevention of MM.

Chapter 5

5 Conclusion

Both VA and AP could be considered as alternative and safe prophylactic interventions for MM, even though the group effects were inconclusive in the present research. Nine sessions within a 3-cycle-month period seems to be efficient enough as the effect is time-cumulative. As AP is more convenient for clients to apply by themselves at home, it could also be considered as a first line approach. Future large scale RCTs are necessary before conclusive statements about treatment efficacy can be made.

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Appendix



Research Ethics

Western University Health Science Research Ethics Board HSREB Full Board Initial Approval Notice

Principal Investigator: Dr. Alan Salmoni
Department & Institution: Health Sciences\Kinesiology, Western University

Review Type: Full Board
HSREB File Number: 107223
Study Title: Comparison of the prophylactic effect between acupuncture and acupressure on menstrual migraine

HSREB Initial Approval Date: November 05, 2015
HSREB Expiry Date: November 05, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Other	cover	2015/09/20
Recruitment Items	e-mail script for contacting potential participants	2015/09/21
Advertisement	Poster for advertisement	2015/09/20
Data Collection Form/Case Report Form	Received Oct 13, 2015	
Western University Protocol		2015/10/13
Letter of Information & Consent		2015/10/13

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.



Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information: Erika Basile, Nicole Kaniki, Grace Kelly, Mina Mekhail, Vikki Tran

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Appendix 1: Research Ethics approval letter

Appendix 3: Questions for pattern diagnosis according to TCM

Name:	Visit date:
<p>Q1: Do you often feel cool or cold or warm or hot?</p> <p>Q2: Do you sweat a lot? If the answer is yes, which areas on your body are easily getting wet?</p> <p>Q3: Do you often feel thirsty or not? If the answer is yes, do you prefer cold or warm drinks?</p> <p>Q4: How is your appetite? And what is your favorite flavor? Do you prefer warm food or not?</p> <p>Q5: How is your night sleep? Do you dream a lot? If the answer is yes, can you remember your dream when you wake up?</p> <p>Q6: Do you often feel and easily get tired? If yes, do you think you can be refreshed after a whole night sleep?</p> <p>Q7: Is your bowel movement regular? How many times a day?</p> <p>Q8: How is your temper? Do you easily get irritated?</p> <p>Q9: Could you describe the color of your period? With or without clots?</p> <p>Q10: Is your vaginal discharge normal? Will you describe it as transparent or turbid? Is it yellow or white?</p> <p>Q11: Could you please show me your tongue?</p> <p>Q12: Could you please let me take your pulse?</p>	

Curriculum Vitae

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