CHAPTER 3

METHODOLOGY

3.1 Research design

A pilot study with randomization, open–label, cross over and placebo-controlled trial was designed to investigate the effect of mobile phone use with hands-free equipment on migraine headache. It was a two period comparative study and two groups of patients received similar intervention in different periods. Group A received hands-free equipment use for 4-8 weeks followed by non hands-free equipment use for 8-12 weeks. Group B received non hands-free equipment use for 4-8 weeks followed by hands-free equipment use for 8-12 weeks.

3.2 Research area

The study was conducted at the outpatient department of 4 central hospitals including Mahosot Hospital, Sethathilat Hospital, 103 Hospital and Mitthapap Hospital in Vientiane Municipality, Lao PDR. All adult patients (aged between 18-55 years old) diagnosed with migraine headache according the International Headache Society (IHS) criteria, who visited at the hospital during the study period, were enrolled into this study. The study protocol was approved by the research ethics committee, Faculty of Medical Sciences, National University of Laos as use for

human data. Informed consent was obtained from all the subjects (in the patient's native language).

3.3 Study population

3.3.1 Inclusion criteria

- All prevalence and incidence cases (aged between 18-55 years old).
- All subjects who fulfilled the International Headache Society criteria for migraine with or without aura and visited the outpatient department of 4 central hospitals in Vientiane Municipality, Lao PDR during the study period.
- Patients who had between 1-10 migraine attacks per month.
- Patients with normal physical and neurological examinations.
- Patients who had submitted a written informed consent form (personally signed and dated).

3.3.2 Exclusion criteria

- Subjects who had types of headache other than migraine, secondary headache or types of migraine other than that with or without aura.
- Patients who had a migraine attack for more than 3 continuous days or a migraine attack for more than 15 days in one month.

- Patients who had migraine with co-morbidities such as cardiac disease, chronic liver disease, e.g. cirrhosis, hypertension, and chronic renal disease including renal insufficiency.
- Patients who had other neurological conditions.
- Subjects who were currently using hands-free equipment for their cellular telephone or stopped using it less than 1 month before.

3.4 Method

After subjects were diagnosed with migraine headache according to the IHS criteria, they were firstly interviewed with structural questionnaires by an investigator before receiving a headache diary for noting their headache attacks. Secondly, patients who matched the inclusion criteria of this study were enrolled into it with an open-label by the investigator. A computer-generated sequence of random numbers was used to allocate intervention in blocks of 4 to form group A and group B. Finally, eligible subjects were evaluated for primary outcomes comprising number of migraine attacks, number of days with migraine attack, total headache intensity, total headache severity, total headache duration, amount of acute medication and number of days with acute medication. Also, secondary outcomes such as patient's global assessment, investigator's global assessment and number of responders with treatment at the baseline visit on D0 of the second visit. After 1 month from the second visit, subjects were crossed over for intervention between groups and evaluated again for primary and secondary outcomes on D30 and D60. All participants received standard

treatment for migraine according to an appropriate regimen for each patient during a study period of 3 months (see Table 3.1).

Table 3.1 Medication for acute attack and preventive treatment for migraine patients

No.	Acute attack	No.	Prevention
1.	Prednisolone (5mg)	1.	Propranolol (10mg)
2.	Naproxen (250mg)	2.	Amitryptiline (10mg)
3.	Propranolol (10mg)	3.	Flunarizine (5mg)
4.	Amitryptiline (10mg)	4.	Valproate acid (500mg)
5.	Flunarizine (5mg)	5.	Topiramate (25mg)

3.5 Research instrument

3.5.1 Questionnaire design

The tools of this study were developed by the investigator under the supervision of an advisor and co-advisors. The structure of the questionnaire was synthesized and adapted from the Suandok questionnaire [108] and a reliability coefficient was tested with the target population in Vientiane (Cronbach's alpha = 0.702). The questionnaire structure consisted of demographic characteristics, history of headache, clinical manifestations, trigger factors, aggravating factors and information on mobile phone use.

3.5.2 Outcomes assessment

This test evaluated the clinical improvement of patients after receiving intervention and treatment for migraine [109] on D0, D30 and D60, including:

3.5.2.1 Primary outcomes

Frequency of headache attacks, total severity scores, total intensity scores, total duration of headache attacks, number of days with migraine attack, amount of acute medication and number of days with acute medication use per month were calculated by the investigator from the headache diary of the patients.

3.5.2.2 Secondary outcomes

This study used the investigator's global assessment, patient's global assessment, and the number of responders (a patient was considered a responder if there was an improvement in the self rating).

3.5.3 Headache diary form in two parts as follows

⇒ Part 1: The level of headache severity was graded into 3 levels as follows:

- Mild headache (can cope with the pain without medication)

- Moderate headache (has to take medication to relieve pain)

▪ Severe headache (requires medication to relieve pain and needs to rest or has to visit a hospital)

⇒ Part 2: An intensity score of headache was divided into 5 levels from 0 - 10. A 0 score equaled no pain and increased in scale according to the severity of pain, as follows:

- No headache if the score is 0
- Mild headache if the scale is from 1-3
- Moderate headache if the scale is from 4-6
- Severe headache if the scale is from 7-9
- Very severe headache if the score is 10

Then, the number of migraine attacks, number of days with migraine attack, intensity score, severity score, duration score of headache attacks, amount of acute medication, and number of days with acute medication were calculated by the investigator at D0 and re evaluated on D30 and D60. This form provided the scale and the notes of primary outcomes from the patients.

3.5.4 The Hospital Anxiety and Depression Scale [110] was used to evaluate the mental status of patients on D0, D30 and D60.

- Anxiety Scores = scoring of question number 1+3+5+7+9+11+13
- Depression Scores = scoring of question number 2+4+6+8+10+12+14

The norms below gave an idea of the Anxiety and Depression level.

⇒ 0-7 = Normal

⇒ 8-10 = Borderline abnormal

⇒ 11-21 = Abnormal

(Source of data: Zigmond AS and Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361-70)

3.6 Data collection

Subjects were informed regarding the purpose of this study and they gave their signed informed consent before being enrolled. After giving informed consent, eligible patients were interviewed by the investigator based on the structural questionnaire, and other outcomes were evaluated with global assessment of change and the headache diary form. Each eligible patient remained in the study for about 12 weeks. The time for screening patients in the study was about 1 month and that for follow up was about 2 months. Data collecting was conducted from August 2007 through January 2008.

3.7 Data analysis

- Descriptive statistics were used for demographic characteristic, where continuous variables were described by mean and standard deviation (S.D) and categorical variables by percentages, proportions, rates and ratio.

- To test the carry over effect, treatment effect and period effect between baseline to sequence 1, and sequence 1 to sequence 2, the independent t-test or McNemar test was used when data provided category variables.
- Inferential statistics were used to compare variables of primary outcomes such as number of migraine attacks, number of days with migraine attack, total intensity scores, total severity scores, total duration scores, amount of acute medication for migraine attack and number of days with acute medication use per month. Also, secondary outcomes of Migraineurs between the baseline and hands-free use group, baseline and non hands-free use group, and hands-free use and non hands-free use group were performed by repeated ANOVA or Friedman test when data was available. The rate of responders with treatment, when patients were considered clinically improved if presenting an improvement score of +3 to +1, was shown on the investigator's and patient's global assessment of change. Comparisons of these clinical outcomes were performed between groups with the McNemar test.
- The association of other trigger factors and migraine headache were determined by the paired t-test or Wilcoxon Signed Rank test when data was available between baseline and sequence 1, and sequence 1 and sequence 2. Category variables were performed by the McNemar test. As a result, variables that had a significant association with

migraine headache in each phase comparison were included as adjustment variables in the subsequent multiple regression models.

The level of significance was set at 95% confidence ($P<0.05$) with a two way analysis. The analysis was performed with SPSS (version 11.5; SPSS).