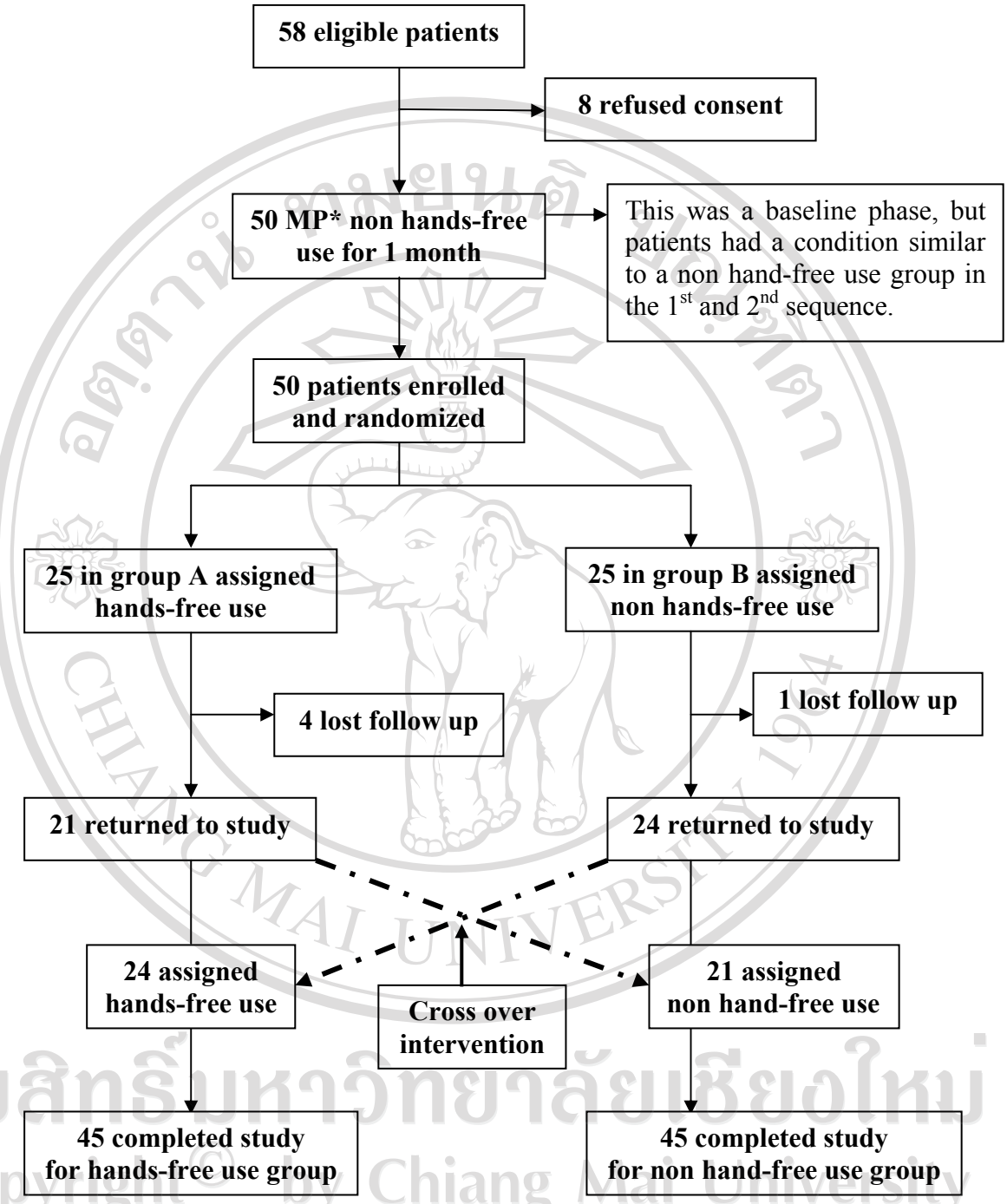
CHAPTER 4

RESULTS

4.1 The information of patients' illness at baseline

4.1.1 Patients

A total of 58 subjects aged between 18-52 years were screened at four central hospitals in Vientiane Municipality, Lao PDR, and 50 of them were randomized into this study. Eight subjects refused to participate in the study. Five subjects terminated the study prematurely because of personal reasons and some had no more headache attacks after the first visit. One of them disappeared from the study (could not be contacted). Two subjects felt uncomfortable and another had no more headache attacks. The numbers of patients exposed to hands-free use and non exposed to hands-free use between 2 sequences were 21, 24 and 24, 21; respectively (see Figure 4.1).



*MP: Mobile phone

Figure 4.1 Participant flow and follow-up.

4.1.2 Demographic characteristics of eligible subjects

Of 45 patients, 15.6% and 84.4% were male and female, respectively. Among them, the frequency of age grouped at 18 – 24, 25 – 31, 32 – 38, 39 – 45 and 46 – 52 years was 37.8 %, 33.3 %, 11.1 %, 11.1 % and 6.7 %, respectively; with an average age of 28 years. The education levels in nearly half of the subjects comprised mainly secondary and high school (48.9%), then university (28.9%), primary school and college (8.9% and 8.9%), and post graduate (4.4%). The main occupations were government officer and private company employee (35.6%), student (26.7%), vendor and tailor (15.5%), housewife (8.9%), soldier or policeman (6.7%) and worker (6.7%). The proportion of married to single people was nearly equal at 48.9% and 51.1%, respectively. Only 20% of subjects had migraine with aura (see Table 4.1).

Table 4.1 Demographic characteristics of study population at baseline

Characteristics	**Group A (%)** (n=21)	**Group B (%)** (n=24)	**Total (%)** (n=45)
Sex			
Male	28.6	4.2	15.6
Female	71.4	95.8	84.4
Age group (years)			
18 – 24	28.6	45.8	37.8
25 – 31	52.4	16.7	33.3
32 – 38	4.8	16.7	11.1
39 – 45	9.5	12.5	11.1
46 – 52	4.8	8.3	6.7

Table 4.1 (Continued)

Characteristics	Group A (%) (n=21)	Group B (%) (n=24)	Total (%) (n=45)
Education			
Primary school	14.3	4.2	8.9
Secondary and high school	23.8	70.8	48.9
College	14.3	4.2	8.9
University	38.1	20.8	28.9
Post graduate	9.5	0	4.4
Occupation			
Housewife	9.5	8.3	8.9
Soldier or police	4.8	8.3	6.7
Worker	9.5	4.2	6.7
Officer	42.9	29.2	35.6
Student	19	33.3	26.7
Other (vendor)	14.3	16.7	15.5
Status			
Single	52.4	50	51.1
Married	47.6	50	48.9
Diagnosis			
Migraine with aura	19	20.8	20
Migraine without aura	81	79.2	80
Mean age (range, years)	28(18-52)	25(18-49)	28.20(18-52)

4.1.3 Past history of headache

All patients had a previous history of headache (100%). While the average age at starting to have headaches was about 20 years, only 31.1% of them had a family history of headache. Regarding underlying disease, 13.3% of them had allergy, 15.6% had a history of head injury and 8.9% had had fever convulsion (see Table 4.2).

Table 4.2 Previous headache and past history of illness in the study population at baseline

Variables	**Group A (%)** (n=21)	**Group B (%)** (n=24)	**Total (%)** (n=45)
Previous history of headache	100	100	100
Family history of headache	28.6	33.3	31.1
Underlying disease	19	8.3	13.3
History of head injury	14.3	16.7	15.6
History of fever convulsion	19	0	8.9
	Mean (range, year)		
Age at starting to have headache	20(12-42)	18(13-38)	20.47(12-42)

4.1.4 Clinical manifestations in current history of headache

Aura symptoms included scotoma (11.1%), paraesthesia (4.4%), paresis (8.9%), and other symptoms (4.4%). Non aura symptoms were about 80%, with more than half of the patients feeling dizziness (80%), tenderness of the muscles and stiff neck (73.3%), nausea/vomiting (71.1%), blurred vision (68.9%), sleep disturbance (57.8%) and photophobia (51.1%). Phonophobia (37.8%) and other symptoms (20%) including tinnitus, diarrhea, dyspnea, anxiety, and abdominal discomfort were less commonly seen and only 2.2% of patients suffered vertigo (see Table 4.3).

The type of pain was mostly throbbing (62.2%), dull/tight (13.3%) and mixed (13.3%), and to a lesser extent stabbing (6.7%), burning (2.2%) and sharp shooting (2.2%). The most frequent headache attacks from the questionnaire interview were 1-3 times/week (51.1%), everyday (35.6%), less for 3-5 times/week (8.9%) and > 5 times/week (4.4%). However, the frequency of headache attacks from the patients' headache diary was 1-3 times/week (53.3%), 3-5 times/week (28.9%) and 5-7 times/week (17.8%). Duration distribution of attacks from the questionnaire interview showed little difference between each other such as: 15 min - 3 hr (28.9%), 4 - 72 hr (37.8%), and > 72 hr (33.3%). Even so, durations of attack from the headache diary had some difference: 15 min – 3 hr (28.9%) and 4 - 72 hr (71.1%). Most patients had pain radiation (93.3%) (see Table 4.3).

The most common location of headache was the temporal area and central head (40% and 33.3%, respectively) following by the orbital and occipital area (20% and 6.7%, respectively). Pain areas almost always presented with change side and both sides (46.7% and 40%, respectively). Pain distribution was located less at the

unilateral left and right side (8.9% and 4.4%, respectively). However, headache mainly began at the temporal area (44.4%) and then occipital area (24.4%), orbital area (17.8%) and central head (13.3%). Furthermore, the median of headache days was about 4 days (see Table 4.3).

Table 4.3 Clinical manifestations in current history of headache at baseline

Clinical manifestations	**Group A (%)** (n=21)	**Group B (%)** (n=24)	**Total (%)** (n=45)
Aura			
Scotoma	9.5	12.5	11.1
Paraesthesia	4.8	4.2	4.4
Paresis	14.3	4.2	8.9
Other aura	0	8.3	4.4
No aura	81	79.2	80
Symptoms			
Nausea/vomiting	76.2	66.7	71.1
Photophobia	38.1	62.5	51.1
Phonophobia	23.8	50	37.8
Blurred vision	66.7	70.8	68.9
Dizziness	81	79.2	80
Vertigo	0	4.2	2.2
Sleep disturbance	61.9	54.2	57.8
Tenderness of muscle	76.2	70.8	73.3
Other symptoms	19	20.8	20

Table 4.3 (Continued)

Clinical manifestations	Group A (%) (n=21)	Group B (%) (n=24)	Total (%) (n=45)
Type of pain			
Throbbing pain	47.6	75	62.2
Sharp shooting pain	4.8	0	2.2
Dull/tight pain	23.8	4.2	13.3
Stabbing pain	4.8	8.3	6.7
Burning pain	4.8	0	2.2
Mixed pain	14.3	12.5	13.3
Frequency of headache interview			
1-3 times/week	42.9	58.3	51.1
3-5 times/week	9.5	8.3	8.9
5-7 times/week	4.8	4.2	4.4
Everyday	42.9	29.2	35.6
Frequency of headache diary			
1-3 times/week	52.4	54.2	53.3
3-5 times/week	23.8	33.3	28.9
5-7 times/week	23.8	12.5	17.8
Time of attack from interview			
15 min - 3 hr	19	37.5	28.9
4 - 72 hr	42.9	33.3	37.8
> 72 hr	38.1	29.2	33.3
Time of attack from diary			
15 min - 3 hr	23.8	33.3	28.9
4 - 72 hr	76.2	66.7	71.1
		Mean ± SD*	
Severity	1.9 ± 0.62	2.1 ± 0.64	2 ± 0.63

Table 4.3 (Continued)

Clinical manifestations	Group A (%) (n=21)	Group B (%) (n=24)	Total (%) (n=45)
Headache radiation	85.7	100	93.3
Location of headache			
Occipital area	14.3	0	6.7
Orbital area	9.5	29.2	20
Temporal area	47.6	33.3	40
Central head	28.6	37.5	33.3
Side of headache			
Right side	9.5	0	4.4
Left side	14.3	4.2	8.9
Bilateral sides	42.9	37.5	40
Change side	33.3	58.5	46.7
Location at the beginning of headache			
Occipital area	19	29.2	24.4
Orbital area	9.5	25	17.8
Temporal area	46.7	41.7	44.4
Central head	23.8	4.2	13.3
		Median ± IQR$^{\theta}$	
Headache day(s)	5±7	3.5±7	4 ± 6.5

*SD: standard deviation
$^{\theta}$ IQR**:** interquartile range

4.1.5 Factors associated with migraine headache

Headache severity was aggravated by head movement (77.8%) and waking or going up stairs (60%) (see Table 4.5). For female patients, 33.3% suffered migraine through menstruation (see Table 4.4). Migraine attack was precipitated by varied stimulators such as stress, lack of sleep, weather, travel, smell, food, cheese, seasoning powder, fruits, cool water, coffee/tea and alcohol. The most common factors were weather and alcohol (51.1% and 51.1%, respectively), stress (48.9%), lack of sleep (42.2%), smell (22.2%) and travel (17.8%) (see Table 4.5).

The patient's choice for releasing pain was most commonly medication including nonsteroidal anti-inflammatory drugs (NSAIDS) (46.7%) and 15.4% of the patients taking NSAIDS took about 15 tablets per week. Paracetamol (68.9%) was also taken and other drugs (6.7%) such as amitryptiline and flunarizine. Apart from drugs, relaxation or sleep (64.4%) and massage (17.8%) were practiced. Some patients were taking other drugs daily such as oral contraceptives among female patients (13.3%) (see Table 4.4) and antihistamine (6.7%) (see Table 4.5). Among female patients, 33.3% had been using oral contraceptives for more than 6 years (see Table 4.4).

Table 4.4 Stimulated factors for migraine among the female group at baseline

Aggravated factors	Group A (%) (n=15)	Group B (%) (n=23)	Total (%) (n=38)
Menstruation	46.6	53.3	39.4
Oral contraceptive	33.3	66.6	15.78
Oral contraceptive > 6 years	50	25	33.3

Table 4.5 Stimulated factors for migraine in the study population at baseline

Stimulated factors	Group A (%) (n=21)	Group B (%) (n=24)	Total (%) (n=45)
Aggravated factors			
Walking or going up stairs	81	87.5	60
Head down or movement	61.9	58.3	77.8
Trigger factors			
Stress	61.9	37.5	48.9
Lack of sleep	52.4	33.3	42.2
Hot weather	52.4	50	51.1
Travel	19	16.7	17.8
Smell	28.6	16.7	22.2
Food	9.5	12.5	11.1
Cheese	4.8	4.2	4.4
Seasoning powder	0	4.2	2.2
Fruits	4.8	0	2.2
Cool water	9.5	12.5	11.1
Coffee/tea	9.5	4.2	6.7
Alcohol	57.1	45.8	51.1

Table 4.5 (Continued)

Stimulated factors	Group A (%) (n=21)	Group B (%) (n=24)	Total (%) (n=45)
Pain release conditions			
Relaxation or sleep	57.1	70.8	64.4
Massage	19	16.7	17.8
Medication	95.2	91.7	93.3
▪ NSAIDS	47.6	45.8	46.7
▪ Paracetamol	57.1	79.2	68.9
▪ Other drugs	9.5	4.2	6.7
Antihistamine	14.3	0	6.7

4.1.6 Information on mobile phone use

The most common use of a mobile phone among patients was 1-5 times/day (82.2%), less commonly 6-10 times/day (15.6%) and for a few patients 16-20 times/day (2.2%). Among all of the patients, the shortest period of cellular telephone use was 1-5 minutes/day (55.6%), then 6-10 minutes/day (22.2%), 11-15 minutes/day (8.9%) and 26-30 minutes/day (13.3%). More than half of them used Nokia (73.3%) and some used Motorola (2.2%), Sonny Ericson (4.4%), Samsung (4.4%), I-mobile (11.1%), and others (4.4%) such as LG. There were 4 types of telephone communication systems in Laos including GSM, ETL, Star phone, and Tigo. However, the frequency of those systems was similar (900 MHz and 1,800 MHz). Of these, the GSM system (46.7%) was mainly used. Only 20% of subjects had a previous history of sometimes using hands-free equipment for their cellular phone.

About 15.6% of them discontinued using this equipment after more than 1 month and 4.4% after more than 1 year. Most of them held the phone on the right side of the head (66.7%), and some on the left side (28.9%) and on both sides (4.4%) (see Table 4.6).

Table 4.6 Information on mobile phone use in the study population at baseline

Information	**Group A (%)** (n=21)	**Group B (%)** (n=24)	**Total (%)** (n=45)
Frequency of mobile phone use			
1-5 times/day	71.4	91.7	82.2
6-10 times/day	23.8	8.3	15.6
16-20 times/day	4.8	0	2.2
Duration of mobile use/day			
1-5 minutes	52.4	58.3	55.6
6-10 minutes	28.6	16.7	22.2
11-15 minutes	9.5	8.3	8.9
26-30 minutes	9.5	16.7	13.3
Brand name of mobile			
Nokia	61.9	83.3	73.3
Motorola	0	4.2	2.2
Sonny Ericson	4.8	4.2	4.4
Samsung	9.5	0	4.4
I-mobile	14.3	8.3	11.1
Other	9.5	0	4.4
System of mobile use			
GSM	47.6	45.8	46.7
ETL	19	29.2	4.4
Star phone	14.3	4.2	8.9
Tigo	19	20.8	20

Table 4.6 (Continued)

Information	Group A (%) (n=21)	Group B (%) (n=24)	Total (%) (n=45)
Previous hands-free equipment use	28.6	12.5	20
Discontinued using hands-free equipment			
> 1 month	23.8	8.3	15.6
> 1 year	4.8	4.2	4.4
Side of head used when talking on phone			
Left side	23.8	33.3	28.9
Right side	76.2	58.3	66.7
Both sides	0	8.3	4.4

4.2 Test of carry over effect, treatment effect and period effect

Before testing the inferential statistics for comparison of mean difference between baseline, the hand-free use and non hand-free use in the study population by repeated ANOVA or paired t-test, tests were carried out on carry over effect, treatment effect and period effect between baseline and sequence 1, and sequence 1 and sequence 2 for all primary and secondary outcomes by independent t-test. Primary outcomes included the number of attacks, number of days with migraine attack, total intensity scores, total severity scores, total duration scores, amount of acute medication and number of days with acute medication per month. Secondary

outcomes comprised patient's global assessment, investigator's global assessment and number of responders having treatment per month (see Figures 4.2 - 4.10).

- B_A, B_B: group A and group B at baseline with normal mobile phone use.
- E_A, E_B: group A and group B in the experimental phase (using hands-free equipment with their mobile phone).
- C_A, C_B: group A and group B in the controlled phase (not using hands-free equipment with their mobile phone, but using a normal mobile phone).

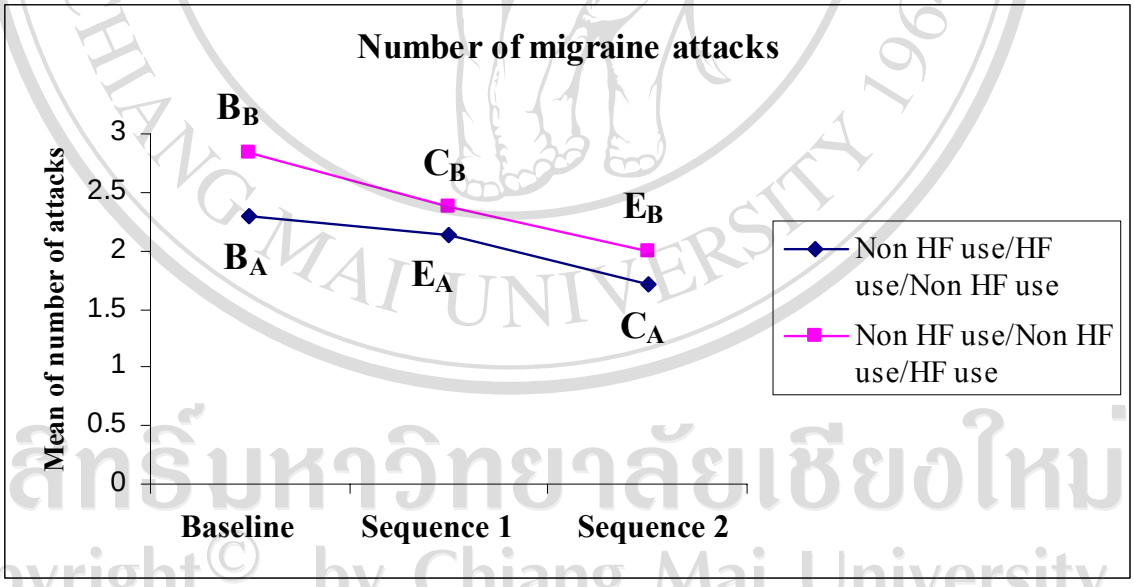


Figure 4.2 Number of migraine attacks per month. This figure shows no carry over effect, no treatment effect and no period effect between baseline to sequence 1 and sequence 1 to sequence 2 after testing the statistics with the p-value as follows: 0.2, 0.4 and 0.4; and 0.4, 0.9 and 0.9.

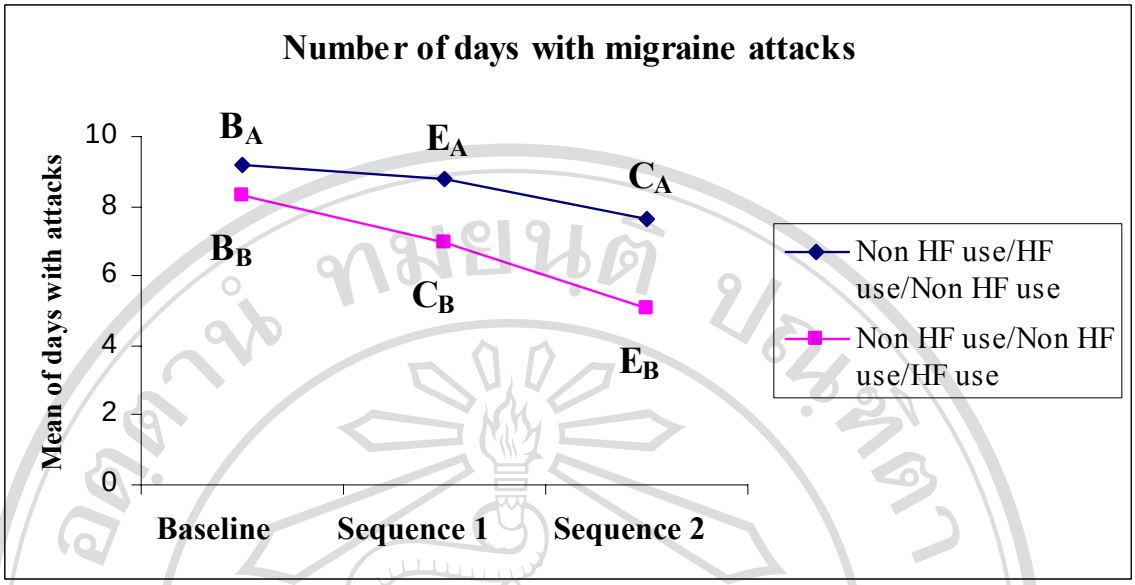


Figure 4.3 Number of days with migraine attacks per month. This figure shows no carry over effect, no treatment effect and no period effect between baseline to sequence 1 and sequence 1 to sequence 2 after testing the statistics with the p-value as follows: 0.3, 0.4 and 0.4; and 0.1, 0.4 and 0.4.

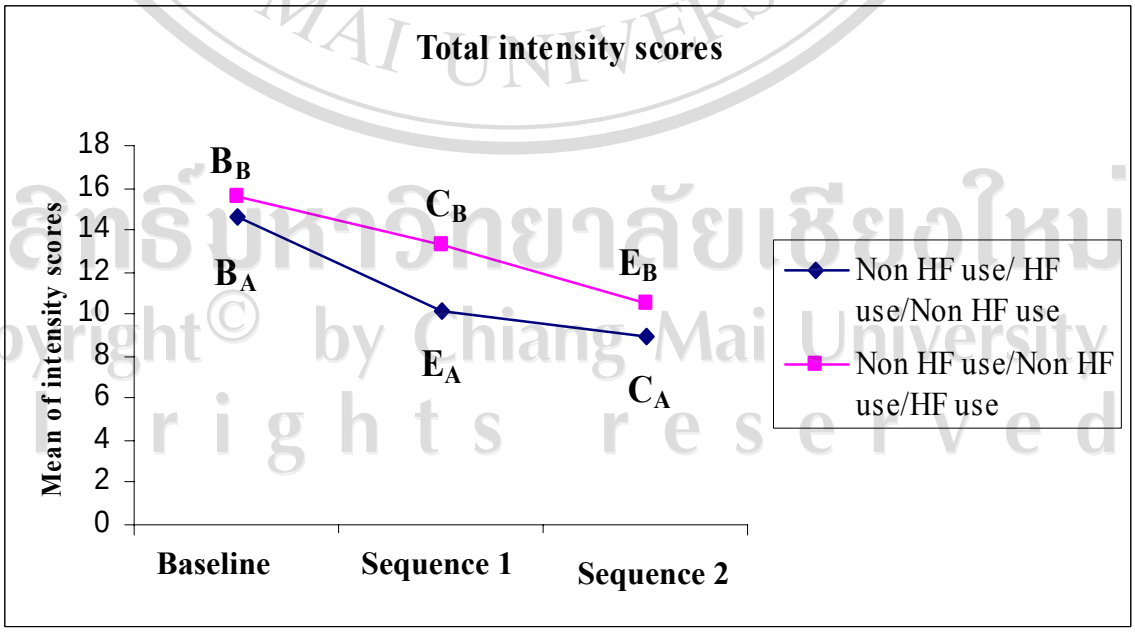


Figure 4.4 Total intensity scores per month. Again, figure 4.4 shows no carry over effect, no treatment effect and no period effect between baseline to sequence 1 and sequence 1 to sequence 2 after testing the statistics with the p-value as follows: 0.2, 0.4 and 0.4; and 0.2, 0.5 and 0.5.

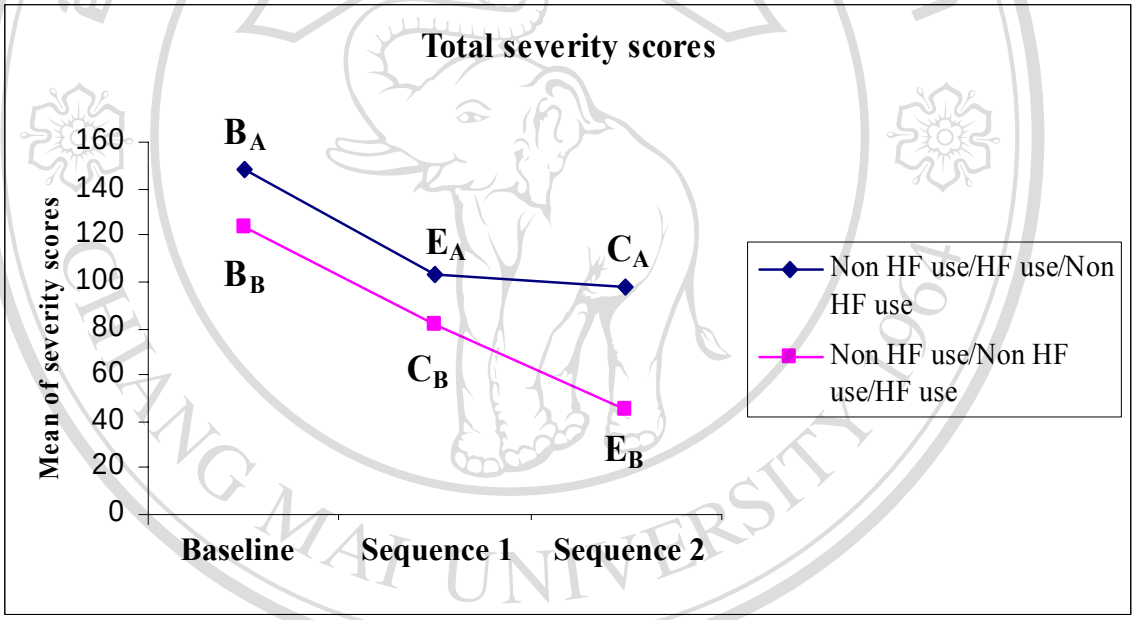


Figure 4.5 Total severity scores per month. This figure also shows no carry over effect, no treatment effect and no period effect between baseline to sequence 1 and sequence 1 to sequence 2 after testing the statistics with the p-value as follows: 0.5, 0.9 and 0.9; and 0.2, 0.1 and 0.1.

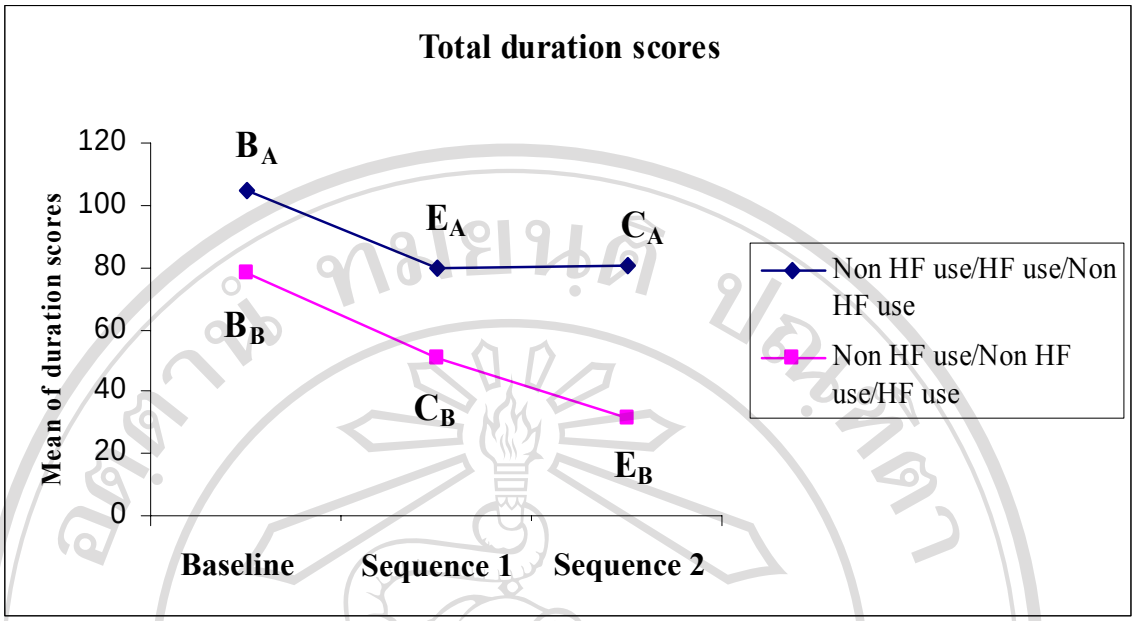


Figure 4.6 Total duration scores per month. This figure similarly shows no carry over effect, no treatment effect and no period effect between baseline to sequence 1 and sequence 1 to sequence 2 after testing the statistics with the p-value as follows: 0.2, 0.9 and 0.9; and 0.1, 0.1 and 0.1.

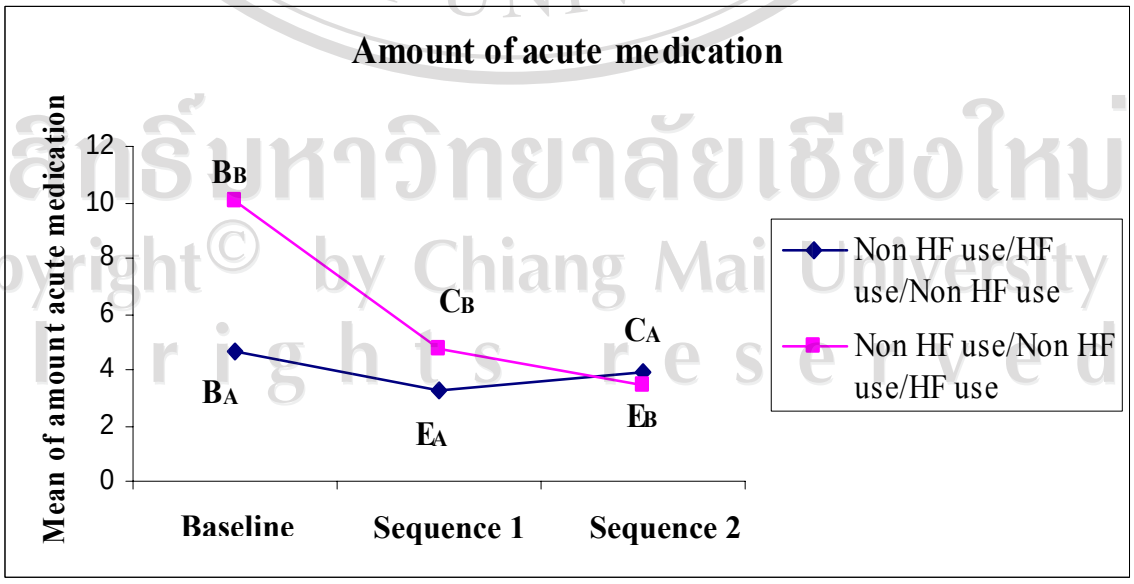


Figure 4.7 Amount of acute medication per month. This figure shows a carry over effect, treatment effect and period effect between baseline to sequence 1 after testing the statistics with the p-value as follows: 0.007, 0.04 and 0.04; however, there was no effect between sequence 1 to sequence 2 with the p-value of 0.6, 0.2 and 0.2.

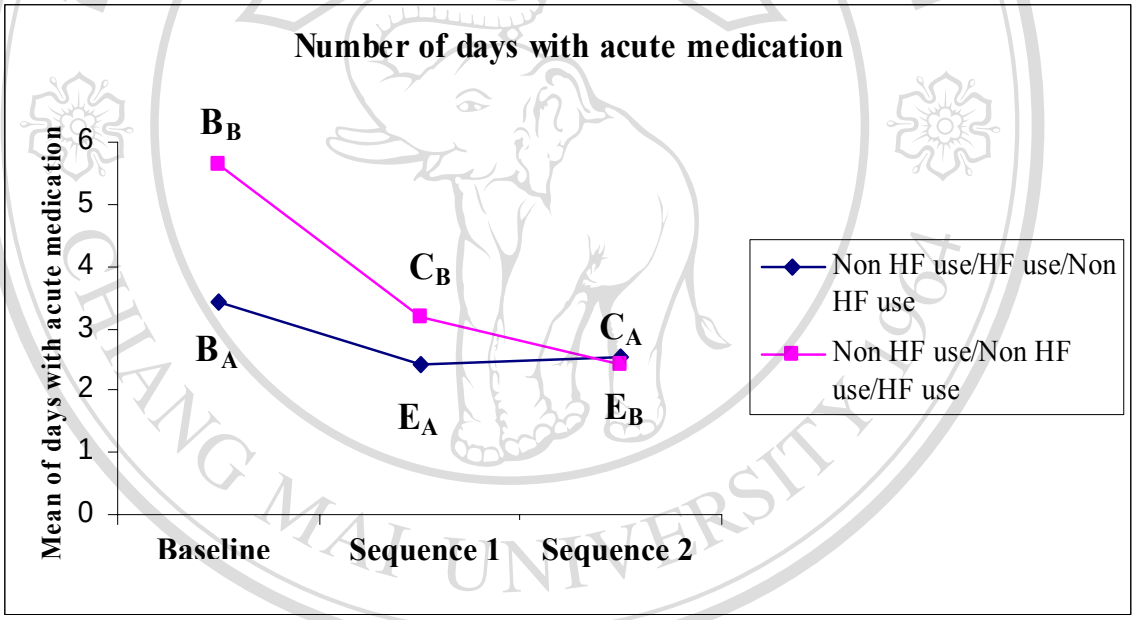


Figure 4.8 Number of days with acute medication per month. This figure shows a carry over effect with the p-value of 0.02, but there was no treatment effect and no period effect between baseline to sequence 1 with the p-value of 0.1 and 0.1; and there was also no effect between sequence 1 to sequence 2 with the p-value of 0.6, 0.3 and 0.3.

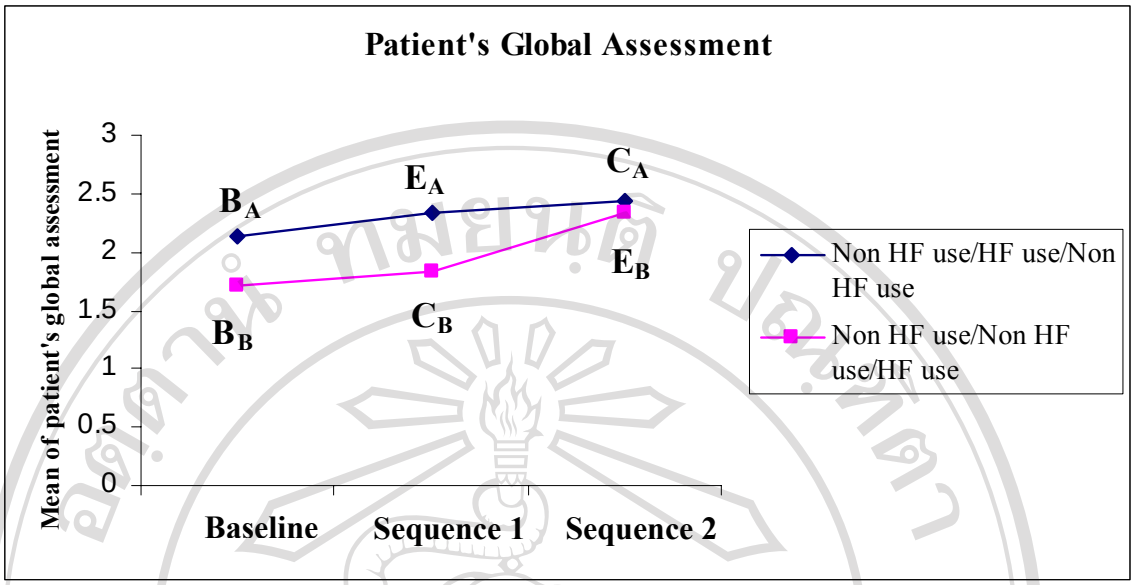


Figure 4.9 Patient's Global Assessment. This figure shows a carry over effect with the p-value of 0.04, but there was no treatment effect and no period effect between baseline to sequence 1 with the p-value of 0.7 and 0.7. Even so, there was no effect between sequence 1 to sequence 2 with the p-value of 0.1, 0.1 and 0.1.

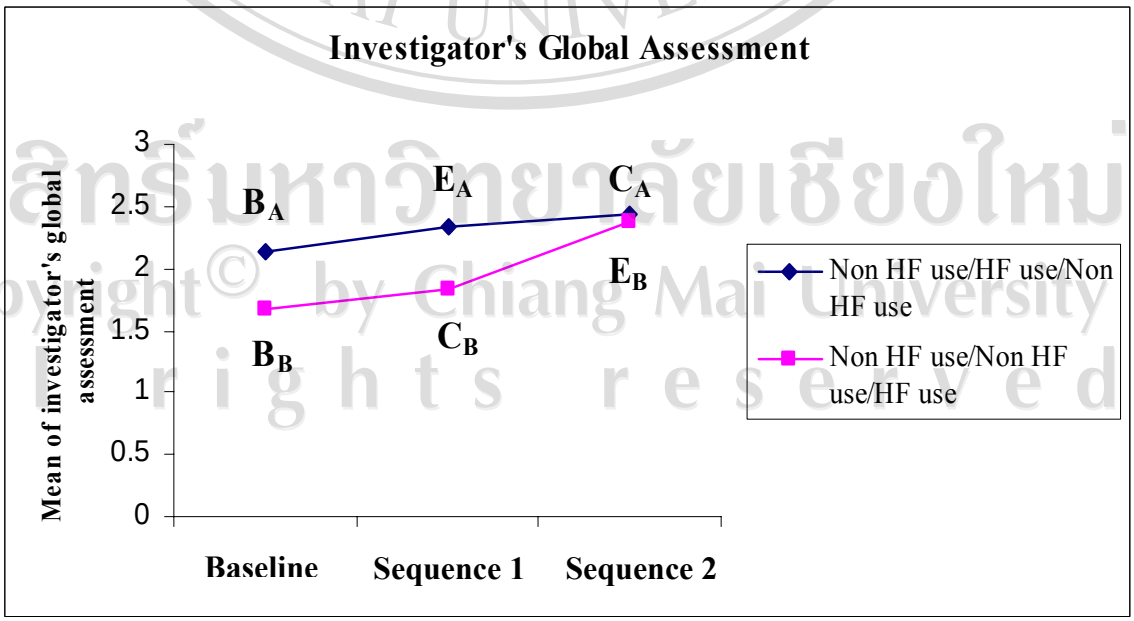


Figure 4.10 Investigator's Global Assessment. This figure shows a carry over effect with the p-value of 0.03, but there was no treatment effect and no period effect between baseline to sequence 1 with the p-value of 0.9 and 0.9. There was also no effect between sequence 1 to sequence 2 with the p-value of 0.1, 0.1 and 0.1.

- Another secondary outcome, number of responders having treatment, showed an effect between baseline to sequence 1 with the p-value of 0.001. On the contrary, there was no effect between sequence 1 to sequence 2 with the p-value of 0.7 by the McNemar test (data not shown).

In summary, there were only some primary outcomes that had no carry over effect, no treatment effect and no period effect between baseline phase to sequence 1, and sequence 1 to sequence 2, including number of migraine attacks, number of days with migraine attack, total intensity scores, total severity scores, and total duration scores per month. All of these were taken to perform the mean difference in the repeated ANOVA model. Other primary outcomes such as amount of acute medication and number of days with acute medication, and secondary outcomes consisting of patient's global assessment, investigator's global assessment and number of responders having treatment could not be tested for mean difference by repeated ANOVA, due to the carry over effect between baseline phase to sequence 1. Therefore, these outcomes were performed for the mean difference only in sequence 2 between the hands-free use group and non hands-free use group by independent t-test. The mean difference of primary and secondary outcomes for carry over effect,

treatment effect and period effect tests are showed in Table 4.7, 4.8 and 4.9 at Appendix M.

4.3 Comparison of mean difference of outcomes

4.3.1 Comparison of primary outcomes between each group

Only a number of migraine attacks per month showed no significant mean difference between baseline, and the hands-free use and non hands-free use group (P= 0.06). Other primary outcomes such as number of days with migraine attacks, total intensity scores, total severity scores, and total duration scores per month showed a significant mean difference between each group comparison with the p-value as follows: 0.01, 0.001, < 0.001, and 0.002 (see Table 4.10).

Table 4.10 Mean difference of primary outcomes between baseline, and the hands-free use and non hands-free use group by comparison (n=45 in each group)

	Mean (95% confidence interval)			
Primary outcomes	**Baseline**	**HF†**	**Non HF‡**	**P-value**
1. Number of migraine attacks/month*	2.57 (2.16, 2.99)	2.06 (1.61, 2.52)	2.06 (1.71, 2.41)	0.06
2. Number of days with migraine attacks/month*	8.73 (7.36, 10.09)	6.80 (5.29, 8.31)	7.28 (5.64, 8.93)	0.01
3. Total intensity scores*	15.15 (13.11, 17.19)	10.37 (8.07, 12.68)	11.28 (9.02, 13.55)	0.001
4. Total severity scores**	134.93 (93, 176.79)	72.33 (41.47, 103.19)	88.82 (54.1, 123.53)	0.001
5. Total duration scores**	90.57 (62.9, 118.24)	54 (30.49, 77.59)	64.91 (37.83, 91.98)	0.002

† HF: Hands-free use group

‡ Non HF: Non hands-free use group

* Sphericity Assumed

** Wilks' Lamda

4.3.2 Comparison of primary outcomes between each pair

For the number of migraine attacks per month, no significant mean difference was shown between baseline and the hands-free use group with 95% CI: -0.15**;** 1.17 (P = 0.18); or baseline and the non hands-free use group with 95% CI: -0.005; 1.02 (P = 0.05). The number of days with migraine attack had a lower significant mean in the hands-free use group than baseline with 95% CI: 0.23**;** 3.63 (P = 0.02); but there was no significant mean difference between baseline and the non hands-free use group with 95% CI: -0.39; 3.28 (P = 0.17). On the other hand**,** total intensity scores and total severity scores revealed a far lower significant mean in the hands-free use group than in the non hands-free use group when compared to the baseline with 95% CI: 1.71**;** 7.84 and 0.58; 7.15 (P = 0.001 and P = 0.016), and 27**;** 98.15 and 5.56; 86.65 (P = 0.001 and P = 0.021)**,** respectively. However, total duration scores in only the hands-free use group had a lower significant mean than the baseline with 95% CI: 12.18**;** 60.88 (P = 0.002). Nevertheless, there was no significant mean difference between baseline and the non hands-free use group (see Table 4.11).

Table 4.11 Mean difference of primary outcomes between each pair (n=45)

Primary Outcomes	Between groups	Pairwise comparisons: Mean diff. (95% CI)[§]	Reduction (%)	P-value
1. Number of migraine attacks/month	▪ Baseline* HF[†]	0.51(-0.15; 1.17)	19.8	0.18
	▪ Baseline*Non HF[‡]	0.51(-0.005; 1.02)	19.8	0.05
2. Number of days with migraine attacks/month	▪ Baseline* HF[†]	1.9(0.23; 3.63)	21.76	0.02
	▪ Baseline* Non HF[‡]	1.4(-0.39; 3.28)	16	0.17
3. Total intensity scores	▪ Baseline* HF[†]	4.7(1.71; 7.84)	31	0.001
	▪ Baseline* Non HF[‡]	3.8(0.58; 7.15)	25	0.01
4. Total severity scores	▪ Baseline* HF[†]	62.6(27; 98.15)	46.39	0.001
	▪ Baseline* Non HF[‡]	46.1(5.56; 86.65)	34.16	0.02
5. Total duration scores	▪ Baseline* HF[†]	36.5(12.18; 60.88)	40.3	0.002
	▪ Baseline* Non HF[‡]	26.5(-2.31; 53.64)	29.25	0.08

[†] HF: Hands-free use group

[‡] Non HF: Non hands-free use group

[§] Mean diff. (95% CI): Mean difference 95% confidence interval

4.3.3 Comparison of outcomes between the hands-free use and non hands-free use group in sequence 2

Some primary and secondary outcomes could not be tested by the repeated ANOVA, due to the carry over effect between baseline to period 1. Therefore, these outcomes could be tested only in period 2 between the hands-free use and non hands-free use group by non parametric statistics (Mann-Whitney U test and Fisher's Exact Test); because data was not normally distributed in each group.

Amount of acute medication and number of days with acute medication showed no significant mean difference between the hands-free use and non hands-free use group (P = 0.83 and P = 0.81). For secondary outcomes, patient's global assessment and investigator's global assessment also revealed no a significant mean difference between the hands-free use and non hands-free use group (P = 0.65 and P = 0.73). Also, there was no significant difference between the two groups in the number of responders having treatment, with a relative risk of 1.75 and 95% CI: 0.94**;** 3.23 (P = 0.08) (see Table 4.12).

Table 4.12 Comparison of outcomes between the hands-free use and non hands-free use group in sequence 2 (n=24 and 21)

Outcomes	HF† (Median ± IQR)*	Non HF‡ (Median ± IQR)*	P-value**
Primary outcomes			
1. Amount of acute medication	2 ± 6.5	3 ± 6	0.83
2. Number of days with acute medication	2 ± 3.5	2.5 ± 4.75	0.81
Secondary outcomes			
3. Patient's Global Assessment	3 ± 1	2.5 ± 1	0.65
4. Investigator's Global Assessment	3 ± 1	2.5 ± 1	0.73
	Relative risk	**95% CI**	
5. Number of responders having treatment	1.75	(0.94; 3.23)	0.08

* IQR: Interquartile Range

** Mann-Whitney U test

† HF: Hands-free use group

‡ Non HF: Non hands-free use group

4.3.4 Comparison of other factors between each period

There was no significant difference between some covariate factors from the Wilcoxon Signed Rank Test comparison, which may enable stimulation and aggravation of migraine attack and severity of migraine headache between the baseline and sequence 1, and baseline and sequence 2 of group A and group B. These factors for migraine consist of coffee and alcohol consumption, microwave use, watching TV, listening on an MP3, and using a computer for continuous variables. However, anxiety scores showed a significant difference between baseline and sequence 1 in group A, and depression scores revealed a significant difference between sequence 1 and sequence 2 in group B.

For categorical variables including food intake for the past month, hot weather stimulation, lack of sleep over the past month, stress over the past month, long travel > 6hr , and smell stimulation over the past month, only smell stimulation showed a significant difference between baseline and sequence 1 ($P = 0.03$) in group B. However, other factors revealed no significant difference between baseline and sequence 1, or sequence 1 and sequence 2 (see Table 4.13).

Table 4.13 Covariate factors for migraine

Covariate factors	P-value	
	Baseline * Sequence 1	**Sequence 1* Sequence 2**
Group A		
Continuous variables [δ]		
1. Number of cups of coffee	0.08	> 0.05
2. Number of glasses of alcohol	0.2	0.2
3. Hours using a microwave	0.1	> 0.05
4. Hours watching TV*	0.2	0.8
5. Hours listening on an MP3	> 0.05	> 0.05
6. Hours using a computer	0.3	> 0.05
7. Anxiety scores*	0.03	0.7
8. Depression scores*	0.08	0.4
Category variables[§]		
9. Past month's food stimulation	0.2	> 0.05
10. Past month's stress stimulation	0.7	> 0.05
11. Past month's lack of sleep Stimulation	> 0.05	> 0.05
12. Past month's long travel > 6hr stimulation	> 0.05	> 0.05
13. Past month's smell stimulation	0.3	> 0.05
14. Past month's hot weather stimulation	> 0.05	0.06

Table 4.13 (Continued)

Covariate factors	P-value	
	Baseline * Sequence 1	Sequence 1* Sequence 2
Group B		
Continuous variables [δ]		
1. Number of cups of coffee	0.6	0.6
2. Number of glasses of alcohol	0.2	0.1
3. Hours using a microwave	0.1	> 0.05
4. Hours watching TV	0.4	0.6
5. Hours listening on an MP3	0.8	0.1
6. Hours using a computer	0.5	0.5
7. Anxiety scores*	0.7	0.08
8. Depression scores*	0.6	0.02

Table 4.13 (Continued)

Covariate factors	P-value	
	Baseline * Sequence 1	Sequence 1* Sequence 2
Category variables[§]		
9. Past month's food stimulation	0.6	>0.05
10. Past month's stress stimulation	0.1	> 0.05
11. Past month's lack of sleep stimulation	> 0.05	> 0.05
12. Past month's long travel > 6hr stimulation	> 0.05	> 0.05
13. Past month's smell stimulation	0.03	0.5
14. Past month's hot weather stimulation	0.06	0.07

[δ] Wilcoxon Signed Rank Test

[§] McNemar Test

***** Paired t-test

4.3.5 Comparison of mean difference in primary outcomes after adjusting covariate factors

After anxiety scores, depression scores and past month's smell stimulation, which showed a significant difference between baseline and sequence 1, sequence 1 and sequence 2 of group A and B were adjusted as covariate factors in a repeated ANOVA model for primary outcomes including number of days with migraine attack, total intensity scores, total severity scores and total duration scores. These demonstrated a significant mean difference between each pair by comparison. Primary outcomes, as mentioned above, showed a significant mean difference between each group comparison, with the p-value as follows: 0.02, 0.001, < 0.001, and 0.002, respectively (see Table 4.14).

Table 4.14 Adjusted mean difference of primary outcomes for each group by comparison (n=45)

	Mean (95% confidence interval)			
Primary outcomes	**Baseline**	**HF†**	**Non HF‡**	**P-value**
1. Number of days with migraine attacks/month*	8.73 (7.37; 10)	6.8 (5.3; 8.29)	7.28 (5.62; 8.95)	0.02
2. Total intensity scores*	15.15 (13; 17.25)	10.37 (8, 12.7)	11.28 (9, 13.48)	0.001
3. Total severity scores*	134.93 (93.99; 175.87)	72.33 (40.63; 104)	88.82 (55.3; 122.34)	< 0.001
4. Total duration scores**	90.57 (63.29; 117.85)	54 (29.97; 78.11)	64.91 (37.58; 92.23)	0.002

† HF: Hands-free use group

‡ Non HF: Non hands-free use group

* Sphericity Assumed

** Wilks' Lamda

For a comparison of primary outcomes between each pair after adjusting covariate factors by repeated ANOVA, the number of days with migraine attack still had a lower significant mean in the hands-free use group than in baseline with 95% CI: 0.16; 3.69 (P = 0.02); but there was no significant mean difference between baseline and the non hands-free use group with 95% CI: -0.38; 3.27 (P = 0.16). Furthermore, total intensity scores and total severity scores also revealed a greater significant mean among the hands-free use group than in the non hands-free use group when compared to the baseline with 95% CI: 1.68; 7.87 and 0.64; 7 (P = 0.001 and P = 0.01), and 28.72; 96.47 and 8.1; 84.12 (P = < 0.001 and P = 0.01), respectively. However, total duration scores in only the hands-free use group, again, had a lower significant mean than in baseline with 95% CI: 12.45; 60.61 (P = 0.001). In addition, there was no significant mean difference of total duration scores between baseline and the non hands-free use group with 95% CI: -0.89; 52.22 (P = 0.06) (see Table 4.15).

Table 4.15 Adjusted mean difference of primary outcomes between each pair (n=45)

		Pairwise comparisons		
Primary Outcomes	**Between groups**	**Mean diff. (95% CI)[§]**	**Reduction (%)**	**P-value[(a)]**
1. Number of days with migraine attacks/month	▪ Baseline*HF[†]	1.9[δ](0.16; 3.69)	21.76	0.02
	▪ Baseline*Non HF[‡]	1.4(-0.38; 3.27)	16	0.16
2. Total intensity scores	▪ Baseline* HF[†]	4.7 [δ](1.68; 7.87)	31	0.001
	▪ Baseline* Non HF[‡]	3.8 [δ](0.64; 7)	25	0.01
3. Total severity scores	▪ Baseline* HF[†]	62.6 [δ](28.72; 96.47)	46.39	< 0.001
	▪ Baseline* Non HF[‡]	46.1 [δ](8.1; 84.12)	34.16	0.01
4. Total duration scores	▪ Baseline* HF[†]	36.5 [δ](12.45; 60.61)	40.3	0.001
	▪ Baseline* Non HF[‡]	25.6(-0.89; 52.22)	29.25	0.06

[δ] The mean difference is significant at the .05 level

[(a)] Adjustment for multiple comparisons: Bonferroni

[†] HF: Hands-free use group

[‡] Non HF: Non hands-free use group

[§] Mean diff. (95% CI): Mean difference 95% confidence interval

There was no a significant mean difference between the hands-free use group and non hands-free use group in all primary and secondary outcomes. Therefore, these results are not shown in the tables of mean difference comparisons for primary outcomes in each group or comparisons between pairs.

4.3.6 Comparison in subgroup analysis

In further analysis, this study also compared the mean difference of outcomes in each group (group A and group B) between baseline and sequence 1, and between groups in sequence 1, in order to find whether there was a mean difference of outcomes in subgroup analysis. However, these outcomes were not compared between baseline and sequence 2, because the comparison of mean difference for outcomes in Table 4.10, 4.11, 4.14 and 4.15 showed prophylaxis treatment effect in the long term. Consequently, the outcomes were not performed in sequence 2.

4.3.6.1 Group A estimation between baseline and the hands-free use group

The results showed that there was no significant mean difference in the number of migraine attacks and number of days with migraine attack between baseline and the hands-free use group with the p-value as follows 0.39 and 0.66. However, total intensity scores and total severity scores had a significant mean difference between baseline and the hands-free use group (P = 0.018 and P= 0.04) Nevertheless, total duration scores, amount of acute medication and number of days with acute medication showed no significant mean difference between baseline and

the hands-free use group (P= 0.07, P= 0.39 and P= 0.36). Patient's global assessment and investigator's global assessment demonstrated a significant mean difference between baseline and the hands-free use group with the p-value as follows 0.04 and 0.04 (see Table 4.16).

Table 4.16 Comparison of outcomes between baseline and the hands-free use group in group A

Outcomes	P-value[§]
Primary outcomes	
1. Number of attacks	0.39
2. Number of days with attack	0.66
3. Total intensity scores	0.018
4. Total severity scores	0.04
5. Total duration scores	0.07
6. Amount of acute medication	0.39
7. Number of days with acute medication	0.36
Secondary outcomes	
8. Patient's global assessment	0.04
9. Investigator's global assessment	0.04

[§] Wilcoxon Signed Rank test

4.3.6.2 Group B estimation between baseline and the non hands-free use group

The findings showed that there was no significant mean difference in the number of migraine attacks, number of days with migraine attack, and total intensity scores between baseline and the non hands-free use group (P= 0.2, P= 0.16 and P= 0.19). However, total severity scores, total duration scores, amount of acute medication and number of days with acute medication showed a significant mean difference between baseline and the non hands-free use group with the p-value as follows 0.012, 0.011, 0.004 and 0.006.. Patient's global assessment and investigator's global assessment demonstrated no significant mean difference between baseline and the non hands-free use group (P= 0.39 and P= 0.27) (see Table 4.17).

Table 4.17 Comparison of outcomes between baseline and the non hands-free use group in group B

Outcomes	P-value[§]
Primary outcomes	
1. Number of attacks	0.2
2. Number of days with attack	0.16
3. Total intensity scores	0.19
4. Total severity scores	0.012
5. Total duration scores	0.011
6. Amount of acute medication	0.004
7. Number of days with acute medication	0.006

Table 4.17 (Continued)

Outcomes	P-value[§]
Secondary outcomes	
8. Patient's global assessment	0.39
9. Investigator's global assessment	0.27

[§] Wilcoxon Signed Rank test

4.3.6.3 Comparison between groups A and B in sequence 1

These results showed that there was no significant mean difference between the hands-free use group (group A) and non hands-free use group (group B) in sequence 1 of all outcomes including number of migraine attacks, number of days with migraine attack, total intensity scores, total severity scores, total duration scores, amount of acute medication, number of days with acute medication, patient's global assessment and investigator's global assessment (data not shown).

4.4 Correlation of mobile phone use and primary outcomes

There was a significant correlation between duration grading of mobile phone use and number of attacks in the non hands-free use group (r =0.41, P = 0.005). However, there was no significant correlation of the number of days with migraine attack, total intensity scores, total severity scores, total duration scores, amount of

acute medication, number of days with acute medication and duration of mobile phone use in all groups. On the other hand, the number of migraine attacks and number of days with migraine attack had a significant correlation with the frequency of mobile phone use in the hands-free use group (r = 0.3, P = 0.03 and r = 0.35, P = 0.017). Nevertheless, the frequency of mobile phone use showed no significant correlation with total intensity scores, total severity scores, total duration scores, amount of acute medication, and number of days with acute medication (see Table 4.18 and 4.19 and Figure 4.11, 4.12 and 4.13).

From Pearson correlation, there was also a significant correlation in the time of a call on a mobile phone, the number of migraine attacks in the baseline period and the non hands-free use group (r = 0.34, P = 0.02 and r = 0.30, P = 0.04) (see Table 4.20 and Figure 4.14 and 4.15).

Table 4.18 Correlation of mobile phone use duration grading and primary outcomes (Spearman's correlation)

Duration grading of mobile phone use	**Correlation (p-value)**		
Primary outcomes	**Baseline**	**HF†**	**Non HF‡**
1. Number of attacks	0.12 (0.4)	0. 22 (0.1)	0.41 (0.005)
2. Number of days with attack	-0.07 (0.6)	-0.01 (0.9)	0.1 (0.4)
3. Total intensity scores	-0.14 (0.3)	0.04 (0.7)	0.29 (0.05)
4. Total severity scores	-0.23 (0.1)	-0.19 (0.2)	-0.06 (0.6)

Table 4.18 (Continued)

Duration grading of mobile phone use	Correlation (p-value)		
Primary outcomes	**Baseline**	**HF†**	**Non HF‡**
5. Total duration scores	-0.21 (0.1)	-0.18 (0.2)	-0.12 (0.4)
6. Amount of acute medication	-0.01 (0.9)	-0.02 (0.8)	0.1 (0.5)
7. Number of days with acute medication	0.04 (0.7)	0.02 (0.8)	0.12 (0.4)

† HF: Hands-free use group

‡ Non HF: Non hands-free use group

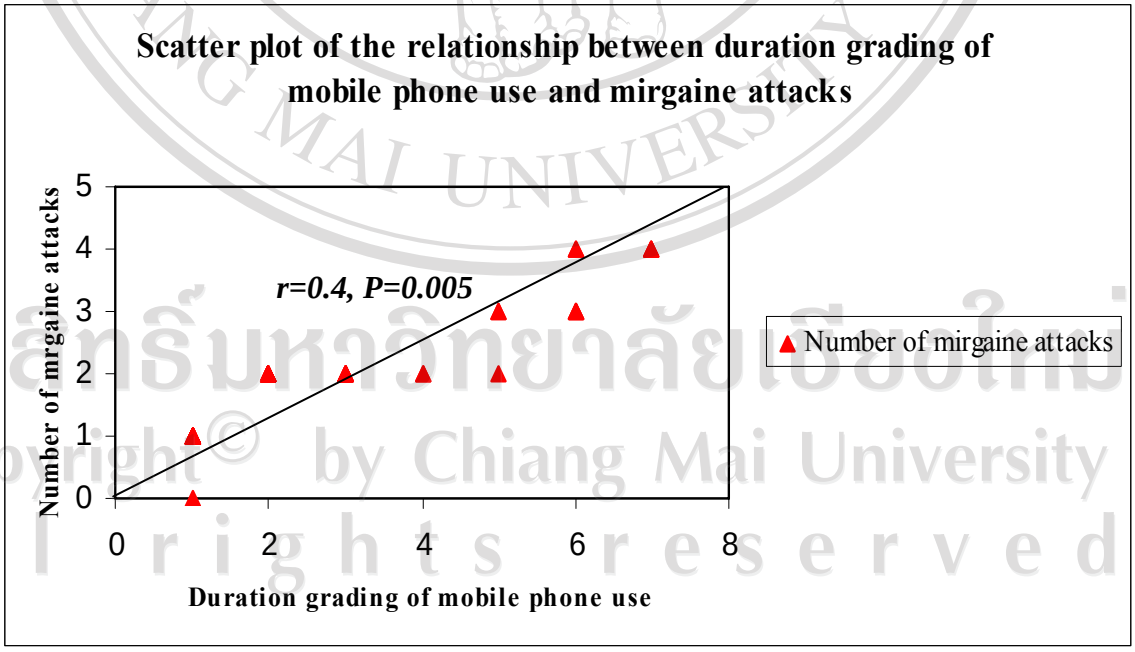


Figure 4.11 Scatter plot showed the relationship between duration grading of mobile phone use and migraine attacks in the non hands-free use group.

Table 4.19 Correlation of mobile phone use frequency and primary outcomes (Spearman's correlation)

Frequency of mobile phone use	Correlation (p-value)		
Primary outcomes	**Baseline**	**HF†**	**Non HF‡**
1. Number of attacks	0.48 (0.7)	0.3 (0.03)	0.15 (0.3)
2. Number of days with attack	0.09 (0.5)	0.35 (0.017)	0.2 (0.17)
3. Total intensity scores	0.04 (0.7)	0.29 (0.05)	0.2 (0.17)
4. Total severity scores	-0.22 (0.1)	0.08 (0.5)	0.02 (0.8)
5. Total duration scores	-0.2 (0.1)	0.09 (0.5)	-0.01 (0.9)
6. Amount of acute medication	-0.04 (0.7)	0.08 (0.5)	-0.11 (0.4)
7. Number of days with acute medication	-0.03 (0.8)	0.18 (0.2)	-0.11 (0.1)

† HF: Hands-free use group

‡ Non HF: Non hands-free use group

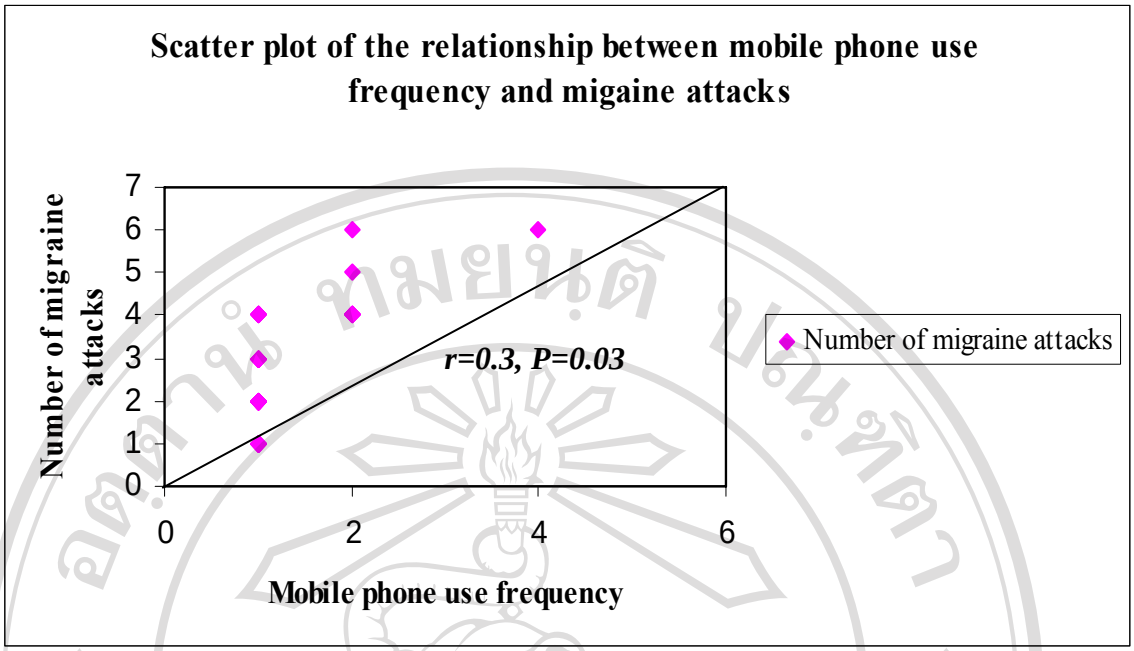


Figure 4.12 Scatter plot showed the relationship between mobile phone use frequency and migraine attacks in the hands-free use group.

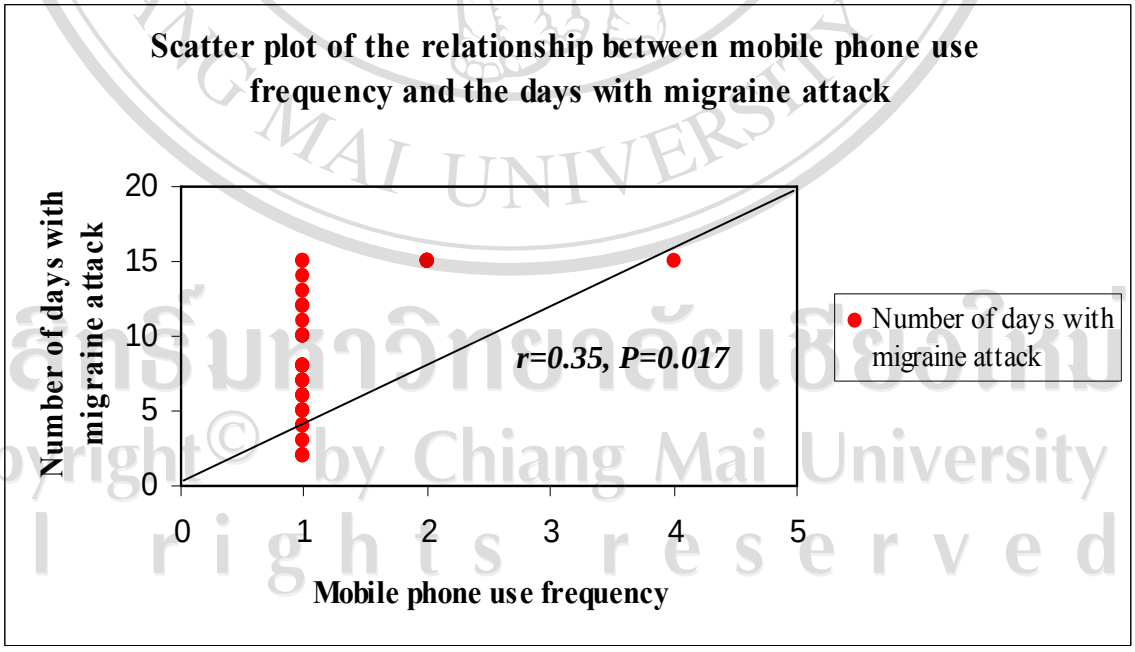


Figure 4.13 Scatter plot showed the relationship between mobile phone use frequency and the days with migraine attacks in the hands-free use group.

Table 4.20 Correlation in the time of a call on a mobile phone and primary outcomes (Pearson's correlation)

Frequency of mobile phone use	Correlation (p-value)		
Primary outcomes	**Baseline**	**HF†**	**Non HF‡**
1. Number of attacks	0.34 (0.02)	0.21 (0.16)	0.3 (0.04)
2. Number of days with attack	-0.14 (0.3)	-0.16 (0.2)	-0.02 (0.8)
3. Total intensity scores	-0.08 (0.5)	-0.05 (0.7)	0.18 (0.2)
4. Total severity scores	-0.28 (0.05)	-0.2 (0.1)	-0.16 (0.2)
5. Total duration scores	-0.29 (0.05)	-0.21 (0.1)	-0.15 (0.3)
6. Amount of acute medication	0.03 (0.8)	-0.1 (0.4)	0.11 (0.4)
7. Number of days with acute medication	0.15 (0.3)	-0.03 (0.8)	0.15 (0.3)

† HF: Hands-free use group

‡ Non HF: Non hands-free use group

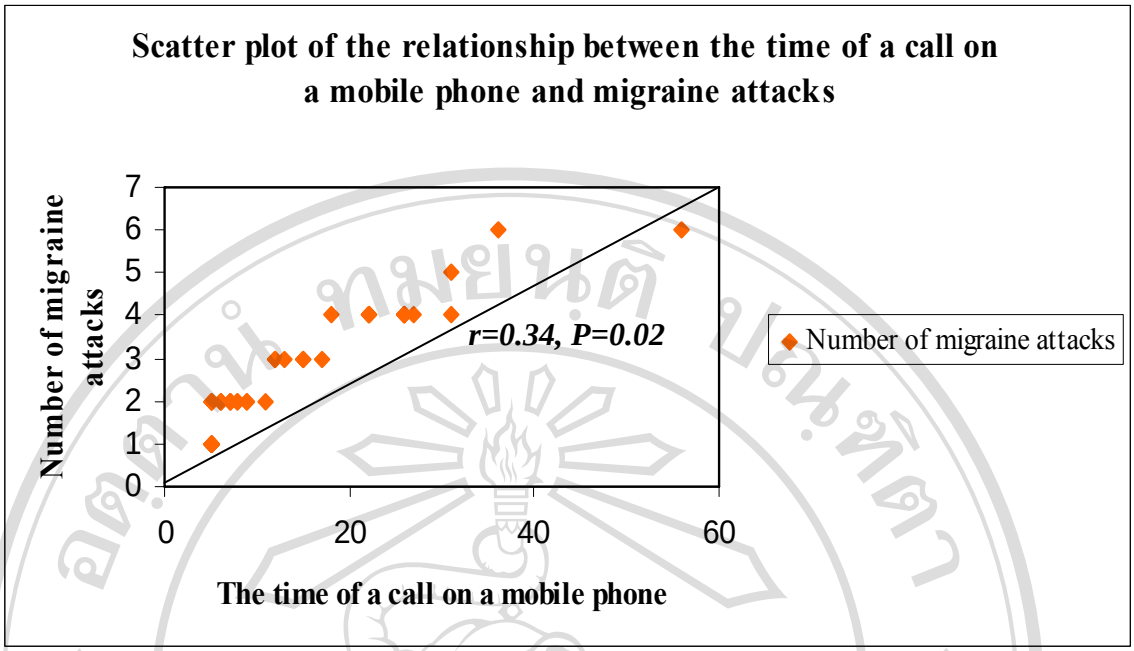


Figure 4.14 Scatter plot showed the relationship between the time of a call on a mobile phone and migraine attacks at the baseline phase.

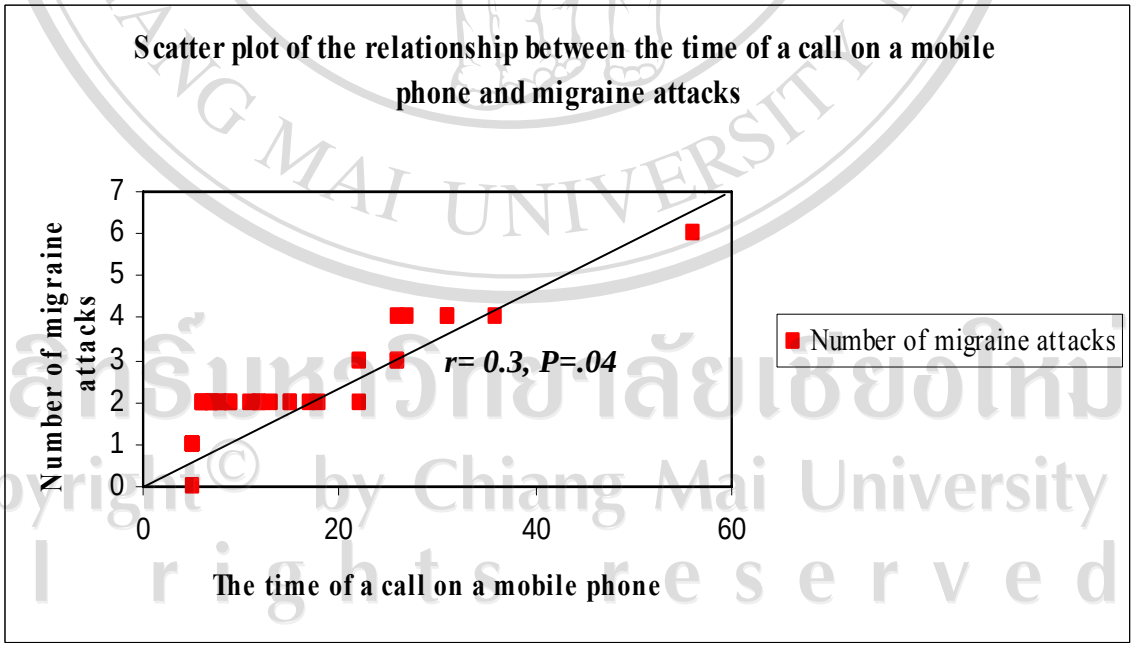


Figure 4.15 Scatter plot showed the relationship between the time of a call on a mobile phone and migraine attacks in the non hands-free use group.