International Journal of Behavioral Medicine

Real-time assessment of the effect of biofeedback therapy with migraine: a pilot study.

--Manuscript Draft--

Manuscript Number:	JBME-D-14-00219R2
Full Title:	Real-time assessment of the effect of biofeedback therapy with migraine: a pilot study.
Article Type:	Full length manuscript
Keywords:	migraine; Ecological Momentary Assessment; Biofeedback; Psychological stress; Headache-related disability; Multilevel model
Corresponding Author:	Miyuki Odawara, M.S. JAPAN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
First Author:	Miyuki Odawara, M.S.
First Author Secondary Information:	
Order of Authors:	Miyuki Odawara, M.S.
	Masahiro Hashizume, M.D., Ph.D.
	Kazuhiro Yoshiuchi, M.D., Ph.D.
	Koji Tsuboi, M.D., Ph.D.
Order of Authors Secondary Information:	
Abstract:	Purpose Biofeedback therapy has been reported to be effective in the treatment of migraine. However, previous studies have assessed its effectiveness using paper-and-pencil diaries, which are not very reliable. Therefore, the objective of the present pilot study was to investigate the feasibility of using computerized ecological momentary assessment (EMA) for evaluating the efficacy of BF treatment for migraine in a randomized controlled trial. Methods The subjects comprised one male and 26 female patients with migraine. They were randomly assigned to either biofeedback or wait list control groups. Patients were asked to carry a palmtop-type computer to record momentary symptoms for 4 weeks before and after biofeedback treatment. The primary outcome measure was headache intensity. The secondary outcome measures included psychological stress, anxiety, irritation, headache-related disability and the frequency (number of days per month) of migraine attack and of headache of at least moderate intensity (pain rating ≥50). Results Headache intensity showed significant main effects of period (before vs. after therapy, $p = 0.02$) and group (biofeedback vs. control groups, $p = 0.42$) and a significant period × group interaction ($p < 0.001$). Biofeedback reduced the duration of headaches by 1.9 days, and the frequency of days when headache intensity was ≥50 by 2.4 times. In addition, headache-related disability, psychological stress, depression, anxiety, and irritation were significantly improved. Conclusions The present study used computerized EMA to show that biofeedback could improve the symptoms of migraine, including psychological stress and headache-related disability.
Response to Reviewers:	

Title

Real-time assessment of the effect of biofeedback therapy with migraine: a pilot study.

Author names

Miyuki Odawara M.S.[1*]

Masahiro Hashizume M.D., Ph.D. [1]

Kazuhiro Yoshiuchi M.D., Ph.D.[2]

Koji Tsuboi M.D., Ph.D. [1]

Affiliations and addresses of the authors

1. Department of Psychosomatic Medicine, Faculty of Medicine, Toho University
   6-11-1 Omorinishi, Ota-ku, Tokyo 143-8541, Japan
2. Department of Psychosomatic Medicine, Faculty of Medicine, the University of Tokyo
   7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Corresponding author

Miyuki Odawara

mykodawara@med.toho-u.ac.jp

Phone: +81337627547 Fax: +81337627547

Abstract

Purpose

Biofeedback therapy has been reported to be effective in the treatment of migraine. However, previous studies have assessed its effectiveness using paper-and-pencil diaries, which are not very reliable. Therefore, the objective of the present pilot study was to investigate the feasibility of using computerized ecological momentary assessment (EMA) for evaluating the efficacy of BF treatment for migraine in a randomized controlled trial.

Methods

The subjects comprised one male and 26 female patients with migraine. They were randomly assigned to either biofeedback or wait list control groups. Patients were asked to carry a palmtop-type computer to record momentary symptoms for 4 weeks before and after biofeedback treatment. The primary outcome measure was headache intensity. The secondary outcome measures included psychological stress, anxiety, irritation, headache-related disability and the frequency (number of days per month) of migraine attack and of headache of at least moderate intensity (pain rating $\geq$50).

Results

Headache intensity showed significant main effects of period (before vs. after therapy, $p = 0.02$) and group (biofeedback vs. control groups, $p = 0.42$) and a significant period × group interaction ($p < 0.001$). Biofeedback reduced the duration of headaches by 1.9 days, and the frequency of days when headache intensity was $\geq$50 by 2.4 times. In addition, headache-related disability, psychological stress, depression, anxiety, and irritation were significantly improved.

Conclusions

The present study used computerized EMA to show that biofeedback could improve the symptoms of migraine, including psychological stress and headache-related disability.

Keywords:

Migraine, Ecological Momentary Assessment, Biofeedback, Psychological stress, Headache-related disability, Multilevel model

Introduction

Migraine is a neurological disorder that affects 18% of women and 6% of men in the United States [1] and 12.9% of women and 3.6% of men in Japan [2]. Frequent migraines have a significant effect on work or school, home, and social activities [3-5]. Although effective drugs for migraine treatment exist [6], they are not suitable for a substantial portion of patients due to medical contraindications (e.g., due to poor tolerance, during pregnancy), inadequate response to acute medications, and significant side effects caused by acute medications. These effects also hinder long-term prevention through prophylactic medication [7]. Sleep, meals, alcohol, caffeine, and psychological stress are known to trigger migraine [8].Psychological stress is an especially important factor for the onset and exacerbation of migraine symptoms [9-11]. Therefore, treatments for migraine consist of non-pharmacological interventions with or without pharmacological treatments.

All patients with headache could benefit from the following non-pharmacological treatments: education about headache and its management, identification of headache triggers via headache diaries, trigger management, lifestyle modification, and knowing how and when to use headache medication to optimize its efficacy [12]. Among non-pharmacological treatments, biofeedback (BF) therapy has been investigated in randomized controlled trials on patients with migraine, and a meta-analysis has proved its efficacy [13-15].

An effectiveness of BF for migraine has been reported by previous studies. Therefore, this study was designed, as a feasibility study, to examine effectiveness of computerized EMA which is a recording device with higher reliability. The reason why we need to use computerized EMA was to exclude recall bias and faked compliance. Previous studies evaluated the efficacy of BF therapy using a questionnaire and/or paper-and-pencil diaries, which were reported to have problems in reliability and validity [16, 17]. Recently, ecological momentary assessment (EMA) has been proposed as an appropriate method for evaluating and recording events or subjective symptoms in daily settings. EMA is a sampling method developed "to assess phenomena at the moment they occur in natural settings, thus maximizing ecological validity while avoiding retrospective recall" [16]. When applying EMA to symptoms such as pain, paper-and-pencil diaries have often been used as recording devices. Using paper-and-pencil diaries, it would be possible to record symptoms at times other than those designated. In such a case, the compliance would seem very good, which has been called "faked compliance" [17], although the true compliance for recoding symptoms at designated times would be bad. Computerized EMA using electronic devices such as

palm-top type computer devices could overcome the problem of faked compliance because the input time could be also recorded automatically in computerized EMA.

However, there are no studies using computerized EMA on BF treatment for migraine. The objective of the present pilot study was to investigate the feasibility of using computerized EMA for evaluating the efficacy of BF treatment for migraine in a randomized controlled trial.

Methods

Subjects

The trial was conducted at the Toho University Medical Center Omori Hospital and was approved by the institutional review board.

Recruitment was conducted from April 2006 to March 2009 via an advertisement on the departmental website. Applicants were interviewed and screened by the authors (M.H., K.T.). Inclusion criteria for the study were diagnosis of any type of migraine according to the criteria of the International Headache Society (IHS) [18]. Exclusion criteria were either the presence of psychiatric disease at the time of application; history of paranoia, schizophrenia, panic disorder, personality disorders, or severe physical illnesses; or diagnosis of analgesics abuse headache according to the criteria of the IHS [18]. Of the 66 applicants, 47 met the eligibility criteria, and 32 were finally enrolled in the study. All subjects provided written informed consent to participate.

Study design and treatments

In this prospective randomized study, patients were randomly assigned to either BF or wait list control groups using an envelope method. We prepared 35 envelopes for each group, which included a piece of paper on which "treatment" or "control" was written. Subjects were asked to choose one envelope and open it in front of the therapist. The group assigned to the participant was revealed to the therapist and the subject at this time.

The BF group was subjected to electromyogram (EMG) and temperature BF with Jacobson's progressive muscle relaxation (eight guided sessions) accompanied by home practice of Jacobson's progressive muscle relaxation for 10 weeks. This method was conducted based on previous studies [e.g. 19], and many of them used a combination of three methods (EMG-biofeedback, temperature-biofeedback, and relaxation training) [13]. BF training consisted of 30-minute sessions utilizing standard EMG feedback from trapezius muscles and temperature from the first finger of the dominant hand by

polygraph (NeXus-4; MindMedia BV., Herten, The Netherland). Subjects were provided both EMG and temperature information according to visual feedback. During treatment and follow-up, all groups were permitted to use medications for acute pain (usually analgesic medication and/or triptans), and patients' medication intake was not changed during the study period. Subjects were asked not to begin any new therapy after enrollment so that no other psychological intervention was provided.

Outcome measures

Subjects were asked to carry a palmtop-type computer device to provide real-time entries into a computerized EMA system for 4 weeks before and after BF treatment.

To record momentary headache intensity, psychological stress, anxiety, irritation, and headache-related disability, palmtop-type computers (ZAURUS, 430g; SHARP Instruments Inc., Tokyo, Japan) were used as electronic diaries. The computer was equipped with a screen measuring 65 × 85 mm and a touch panel input system. Before beginning the study, subjects were given manuals and detailed instructions on the use of the device. They also practiced manipulating the device with one of the authors (either M.O or M.H) until they were accustomed to its use.

Signal-contingent recordings were prompted with a beep as a start signal and were programmed to be made randomly within an interval of 30 min from 8:45 to 9:15, 13:45 to 14:15, and 19:45 to 20:15. Recordings not made within 30 min were cancelled. Subjects were also asked to record their headache intensity when they woke up and went to bed by making a selection from the menu, such as "waking up" or "going to bed." Signal-contingent recordings and recordings upon waking up and going to bed were treated as scheduled recordings. Event-contingent recordings were those started by the subjects themselves when a particular migraine attack occurred. In this study, subjects were asked to make an event-contingent recording every time their migraine attack exacerbated, with or without taking analgesics. The recording schedule is shown in Figure 1. In both scheduled- and event-contingent recordings, headache intensity and other headache related symptoms were rated according to a visual analogue scale (VAS) from 0–100 displayed on the screen. The words "headache intensity" was displayed with a VAS as a question. The VAS was accompanied by the anchor words "none" and "most intense" at both ends. Using a touch pencil, subjects adjusted the length of the bar so that it corresponded to their headache intensity at that moment. The other headache related symptoms were recorded using the same procedure as that for headache intensity.

Headache intensity was used as the primary outcome measure for recorded

headache. Secondary outcome measures were psychological stress, anxiety, irritation, headache-related disability and frequency (number of days per month) of migraine attack (days of analgesic medication consumption), and frequency of headache of at least moderate intensity (pain rating ≥ 50) [20, 21].

Statistical analysis

In order to assess headache intensity, maximum headache intensity of the day, psychological stress, anxiety, irritation, and headache-related disability, we investigated the temporal difference between the BF and control groups using multilevel modeling as follows:

Level 1 equation:

$Y_{ij} = \pi_{0i} + \pi_{1i}Per_{ij} + \varepsilon_{ij}$

Level 2 equation:

$\pi_{0i} = \gamma_{00} + \gamma_{01}GROUP_i + \zeta_{0i}$

$\pi_{1i} = \gamma_{10} + \gamma_{11}GROUP_i + \zeta_{1i}$

where Yij is one of the outcome measures, Per_{ij} is period before and after treatment, and GROUP refers to the BF treatment or control group.

In addition, we used a t-test to investigate the temporal differences between BF and control groups after treatment, as measured by frequency of a headache of at least moderate severity or a migraine attack. All statistical analyses were conducted using SPSS (IBM Japan, Tokyo, Japan) version 19.0 for Windows.

Results

Participant characteristics

The flow of participants through the trial is described in Figure 2. Of the 66 patients approached, 47 met all eligibility criteria and were randomly distributed into the BF or wait-list control group. Retention was excellent, with 68% of the patients completing the trial and follow-up visits. Demographic and clinical characteristics for the 27 participants are listed in Table 1. The mean age of BF group subjects was 41.4 years (SD 9.6 years) and of wait-list control group subjects was 37.6 years (SD 5.6).

Recording profiles

For all subjects, there were 7220 scheduled recordings consisting of 3736 signal-contingent recordings, 1389 recordings upon waking, and 1272 recordings at bedtime. The mean compliance rate for signal-contingent recordings was 82.4%. Twenty-seven subjects added 822 event-contingent recordings.

Headache symptoms (Table 2)

Headache intensity showed significant main effects of PERIOD ($p = 0.02$) and a significant GROUP × TIME interaction ($p < 0.001$). Maximum intensity of headache in a day showed a significant GROUP × TIME interaction ($p = 0.004$). PERIOD of maximum intensity and GROUP of both did not show significant effect. Figure 3 presents the results from pre-treatment to post-treatment for headache intensity. From pre-treatment to post-treatment, BF resulted in a decrease in duration of headache by 1.9 days versus an increase to 0.7 days in the control group (change score difference, 2.6 [95% CI, 0.1-5.1] days; $p = 0.043$; Table 3). The frequency of headaches of intensity $\geq$ 50 decreased by 2.4 times with BF versus 0.2 times in the control group (change score difference, 2.0 [95% CI, 0.2–4.2] times; $p = 0.035$). These measures were improved in the BF group. In contrast, the wait-list control group worsened or experienced no remarkable change after the observation period.

Psychological symptoms and headache-induced disability of daily life (Table 4, Fig 4)

Psychological stress showed significant main effects of PERIOD ($p < 0.001$) and a significant GROUP × TIME interaction ($p < 0.001$). Depressive mood showed significant main effects of PERIOD ($p < 0.001$) and a significant GROUP × TIME interaction ($p < 0.001$). Anxiety showed significant main effects of PERIOD ($p = 0.03$) and a significant GROUP × TIME interaction ($p < 0.001$). Irritation showed a significant GROUP × TIME interaction ($p < 0.001$). Headache-related disability showed significant main effects of PERIOD ($p < 0.001$) and a significant GROUP × TIME interaction ($p < 0.001$). There were no significant effect in PERIOD of irritation and GROUP of all measures. Figure 3 presents the results from pre-treatment to post-treatment for disability of daily life. These results indicate that the BF group had improved psychological symptoms and headache-related disability after treatment.

Discussion

This is the first randomized clinical study using computerized EMA to evaluate the efficacy of BF treatment for migraine. As a pilot study, the results of the present study showed that computerized EMA might be feasible to evaluate the efficacy of BF

treatment for migraine, and that BF treatment could reduce the severity and frequency of migraine attacks and the degree of headache-related disability, psychological stress, depression, anxiety, and irritation by evaluation using computerized EMA.

Our results using computerized EMA that BF therapy reduces the intensity and frequency of migraine headache attacks were consistent with those of a previous meta-analysis study [13-15]. However, previous studies on the efficacy of BF therapy used questionnaires or paper-and-pencil diaries, which were reported to have problems in reliability and validity [16, 17]. Therefore, the present results might be more reliable. In addition, the mean compliance rate for signal-contingent recordings was 82.4%, which showed that computerized EMA might be feasible for evaluating the efficacy of BF treatment for migraine.

BF therapy reduced the degree of headache-related disability, psychological stress, depression, anxiety, and irritation. Migraine is known to be related to psychological stress and to impair one's quality of life. For example, depression, anxiety, and alteration in self-efficacy due to headache were improved by BF in previous studies [22, 23]. In addition, BF has also been used for patients with high blood pressure or undergoing rehabilitation for symptoms associated with paralysis or obesity [24, 25]. These studies showed improvement of the major symptoms and a decrease in depression and anxiety [26]. In some cases, BF might not to be used to improve the main symptoms directly, but rather to reduce secondary symptoms such as anxiety (e.g., for decreasing anxiety during pregnancy or in a patients with eating disorders) [27, 28]. Our findings support these previous studies. This might be because BF might help patients have a sense of controlling oneself easily, which might lead to improve their self-efficacy. We did not measure self-efficacy in the present study. Therefore, such a measurement should be needed in the future studies.

Other behavioral strategies such as cognitive behavioral therapy have been reported as useful in the management of headache [29]. Therefore, computerized EMA could be applied to confirm the efficacy of these behavioral strategies.

There were a few limitations to this study. Firstly, the sample size was relatively small. Therefore, further studies with larger sample sizes will be required to confirm the results. Secondly, the baseline of headache intensity varies within each group. It could be possible that the distribution of patients with more intense headaches was skewed towards one group. Therefore, it is recommended that future studies randomize the sample after forming a hierarchy based on the results of baseline intensities. Thirdly, the exact duration of headache was unknown. Measuring equipment such as a stopwatch could be used to take accurate measurements by pressing a button when a headache

attack starts and ends. Fourthly, the BF group used a combination of three methods (EMG-biofeedback, temperature-biofeedback, and relaxation training). Therefore, it was impossible to inspect the independent effect of each treatment. Fifthly, the mean age of the present study was low. Compliance might be reduced among older age groups while one of our previous studies in terminal cancer patients with median age of 62 years (range 43-70) reported that overall compliance of recording data in palm-top type devices was 90.3% [30] . Finally, there was a prevalence of females in the present study like previous studies [e.g. 31]. The prevalence of females in the present study might influence the results.

In conclusion, computerized EMA methods might be feasible to evaluate the efficacy of BF therapy in natural settings, which could improve symptoms of migraine, including psychological stress and headache-related disability.

Ethical Standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study

Conflict of Interest

Miyuki Odawara, Masahiro Hashizume, Kazuhiro Yoshiuchi and Koji Tsuboi declare that they have no conflict of interest.

Reference

1. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007; 68:343–349.
2. Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. Cephalalgia. 1997; 17(1):15-22.
3. Buse DC, Manack AN, Fanning KM, Serrano D, Reed ML, Turkel CC, Lipton RB. Chronic migraine prevalence, disability, and sociodemographic factors. Headache. 2012; 52(10):1456-1470.
4. Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche MA, Maynard MK.. PedMIDAS: development of a questionnaire to assess disability of migraines in children. Neurology. 2001; 57(11):2034-2039.
5. Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in childhood migraines. Pediatrics. 2003; 112(1 pt 1):e1-e5.
6. Oldman AD, Smith LA, McQuay HJ, Moore RA. Pharmacological treatments for acute migraine: quantitative systematic review. Pain.2002; 97:247–57.
7. Yoon M, Savidou I, Diener H, Limmroth V. Evidence-based medicine in migraine prevention. Expert Rev Neurother.2005; 5:333–41.
8. Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia. 2007; 27(5):394-402.
9. Blackburn-Munro G, Blacburn-Munro RE. Chronic pain, chronic stress and depression: coincidence or consequence? J Neuroendocrinol. 2001; 13:1009-1023.
10. Wöber C, Wöber-Bingöl C. Triggers of migraine and tension-type headache. Handb Clin Neurol. 2010; 97:161-172.
11. Yadav RK, Kalita J, Misra UK A. study of triggers of migraine in India. Pain Med. 2010; 11:44-47.
12. Nicholson RA, Buse DC, Andrasik F, Lipton RB. Nonpharmacologic treatments for migraine and tension-type headache: how to choose and when to use. Curr Treat Options Neurol. 2011; 13(1):28-40.
13. Nestoriuc Y, Martin A. Efficacy of biofeedback for migraine: a meta-analysis. Pain. 2007; 128(1-2):111-27.
14. Goslin RE, Gray RN, McCrory DC, Penzien D, Rains J, Hasselblad V. Behavioral and Physical Treatments for Migraine Headache. Technical Review 2.2. Rockville: Agency for Health Care Policy and Research; 1999.
15. Nestoriuc Y, Martin A, Rief W, Andrasik F. Biofeedback treatment for headache

disorders: A comprehensive efficacy review. Applied Psychophysiology and Biofeedback 2008; 33:125–140.
16. Stone AA, Shiffman SS. Ecological momentary assessment (EMA) in behavioral medicine. Ann Behav Med. 1994; 16:199–202.
17. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. BMJ 2002; 324:1193–4.
18. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004; 24(suppl 1):9-160.
19. Nicholson NL, Blanchard EB. A controlled evaluation of behavioral treatment of chronic headache in the elderly. Behav Ther 1993;24:395–408.
20. Holroyd K, Stensland M, Lipchik G, Hill K, O'Donnell F, Cordingley G. Psychosocial correlates and impact of chronic tension-type headaches. Headache. 2000; 40:3–16.
21. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination. JAMA. 2001; 285(17):2208-2215.
22. Rokicki LA, Holroyd KA, France CR, Lipchik GL, France JL, Kvaal SA. Change mechanisms associated with combined relaxation/EMG biofeedback training for chronic tension headache. Appl Psychophysiol Biofeedback. 1997; 22(1):21-41.
23. Kang EH, Park JE, Chung CS, Yu BH. Effect of biofeedback-assisted autogenic training on headache activity and mood states in Korean female migraine patients.J Korean Med Sci. 2009; 24(5):936-40.
24. Hemmen B, Seelen HA. Effects of movement imagery and electromyography-triggered feedback on arm hand function in stroke patients in the subacute phase. Clin Rehabil. 2007; 21: 587-594.
25. McGrady A. Effects of group relaxation training and thermal biofeedback on blood pressure and related physiological and psychological variables in essential hypertension. Biofeedback Self Regul. 1994; 19(1):51-66.
26. Beckham AJ, Greene TB, Meltaer-Broday S. A pilot study of heart rate variability biofeedback therapy in the treatment of perinatal depression on a specialized perinatal psychiatry inpatient unit. Arch Womens Ment Health. 2012; 2:59–65.
27. Scolnick B, Mostofsky DI, Keane RJ. Pilot study employing heart rate variability biofeedback training to decrease anxiety in patients with eating disorders. J Eat Disord. 2014; 2:17.
28. Eccleston C, Morley S, Williams A, Yorke L, Mastroyannopoulou K. Systematic

review of randomized controlled trials of psychological therapy for chronic pain in children and adolescents, with a subset of meta-analysis pain relief. Pain. 2002;99:157–65.
29. Pistoia F, Sacco S, Carolei A. Behavioral therapy for chronic migraine. Curr Pain Headache Rep. 2013;17(1):304.
30. Hachizuka M, Yoshiuchi K, Yamamoto Y, Iwase S, Nakagawa K, Kawagoe K, Akabayashi A. Development of a personal digital assistant (PDA) system to collect symptom information from home hospice patients. J Palliat Med. 2010; 13(6):647-51.
31. Ndao-Brumblay SK, Green CR. Predictors of complementary and alternative medicine use in chronic pain patients. Pain Med. 2010; 11(1):16-24.

Table 1. Demographic and medical characteristics of the subjects

	Biofeedback group (n=16)	Wait list control group (n=11)
Age, mean (SD), y	41.44 (9.56)	37.55 (5.56)
Sex		
Male	1	0
Female	15	11
Occupation		
Office worker	10	8
Part-time worker	2	2
House wife	4	1
Pain characteristics		
With aura	9	5
Pulsating	16	11
Photophobia	14	9
Phonophobia	14	10
Nausea	14	9
Duration of migraine (years)	20.91 (6.93)	17.90 (5.57)
With Tension type headache	4	4

Table 2

Multilevel model estimates for headache symptoms

Variable	(Total record number =7220)	Mean (S.E.) effect	*p* value
Headache intensity	Intercept (γ_{00})	12.2 (2.1)	<0.001
	PERIOD (γ_{01})	-1.7 (0.7)	0.02
	GROUP (γ_{10})	-2.3 (2.3)	0.42
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	6.0 (0.9)	<0.001
Maximum intensity of headache	Intercept (γ_{00})	24.0 (3.1)	<0.001
	PERIOD (γ_{01})	-2.1 (4.0)	0.60
	GROUP (γ_{10})	-1.4 (2.0)	0.49
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	7.5 (2.6)	0.004

Table 3 Changes in Headache Frequency at Post treatment

	BF (n=17)			Control (n=11)					
	Pre-treatment	Post-treatment	Change score	Pre-treatment	Post-treatment	Change score	Group Mean Difference in Change Scores (95% Cl)	t	p value
Headache Frequency Mean (SD)	6.2 (3.3)	4.3 (2.9)	-1.9 (2.4)	5.8 (3.7)	6.5 (4.4)	0.7 (3.8)	2.6 (0.1-5.1)	2.1	.043
Pain rating ≥50 Mean (SD)	6.1 (3.3)	3.8 (2.3)	-2.3 (3.0)	5.3 (3.1)	5.1 (2.7)	-0.2 (1.4)	2.2 (0.2-4.2)	2.2	.035

Table 4

Multilevel model estimates for psychological symptoms and headache-related disability

Variable	(Total record number =7220)	Mean (S.E.) effect	*p* value
Psychological stress	Intercept (γ_{00})	19.1 (4.5)	<0.001
	PERIOD (γ_{01})	-3.8 (0.7)	<0.001
	GROUP (γ_{10})	-4.8 (5.9)	0.42
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	7.2 (0.8)	<0.001
Depressive mood	Intercept (γ_{00})	8.4 (3.0)	0.01
	PERIOD (γ_{01})	-1.2 (0.5)	0.03
	GROUP (γ_{10})	0.9 (3.9)	0.83
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	5.5 (0.7)	<0.001
Anxiety	Intercept (γ_{00})	9.1 (2.8)	0.003
	PERIOD (γ_{01})	-3.4 (0.5)	<0.001
	GROUP (γ_{10})	-1.0 (3.6)	0.78
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	5.8 (0.6)	<0.001
Irritation	Intercept (γ_{00})	11.6 (3.4)	0.002
	PERIOD (γ_{01})	-1.0 (0.6)	0.10
	GROUP (γ_{10})	-0.1 (4.4)	0.98
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	2.9 (0.8)	<0.001
headache-related disability	Intercept (γ_{00})	10.7 (2.2)	<0.001
	PERIOD (γ_{01})	-2.1 (0.6)	<0.001
	GROUP (γ_{10})	-2.4 (2.9)	0.42
	PERIOD (γ_{01}) ×GROUP (γ_{10}) interaction (γ_{11})	4.2 (0.8)	<0.001

Figure Legends

Figure 1. Sampling schedule of outcome measures by computerized EMA in a study of biofeedback treatment for migraine. Scheduled recordings consist of three times of signal-contingent recordings, "waking up" and "going to bed". Signal-contingent recordings were prompted with a beep as a start signal and were programmed to be made randomly within an interval of 30 min from 8:45 to 9:15, 13:45 to 14:15, and 19:45 to 20:15. Subjects were asked to keep all event-contingent recordings by themselves when a particular migraine attack occurred.

Figure 2. CONSORT flow diagram of participants in a study of biofeedback treatment for migraine.

Figure 3. Temporal changes in headache intensity scores after 4 weeks in subjects with biofeedback treatment and waiting list control subjects estimated by multilevel modeling. There were significant main effects of the PERIOD ($p = 0.02$) and a significant PERIOD × GROUP interaction ($p < 0.001$). Solid line indicated scores of subjects with biofeedback treatment, and dotted line indicated scores of waiting list control subjects. Error bars showed standard error of means of headache intensity scores and headache-related disability.

Figure 4. Temporal changes in headache-related disability scores after 4 weeks in subjects with biofeedback treatment and waiting list control subjects estimated by multilevel modeling. There were significant main effects of the PERIOD ($p < 0.001$) and a significant PERIOD × GROUP interaction ($p < 0.001$). Solid line indicated scores of subjects with biofeedback treatment, and dotted line indicated scores of waiting list control subjects. Error bars showed standard error of means of headache intensity scores and headache-related disability.

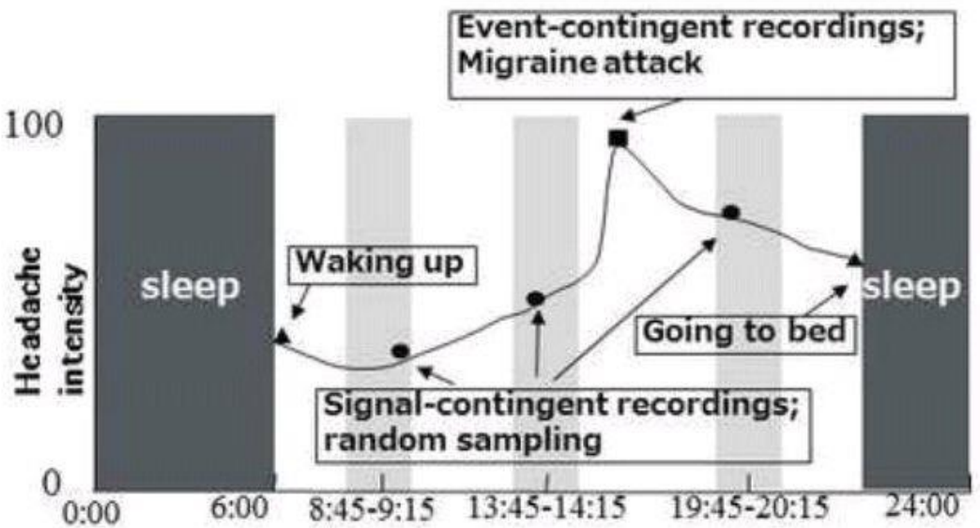
Event-contingent recordings;
Migraine attack
100
Headache intensity
0
sleep
Waking up
sleep
Going to bed
Signal-contingent recordings;
random sampling
0:00
6:00
8:45-9:15
13:45-14:15
19:45-20:15
24:00

Figure 1

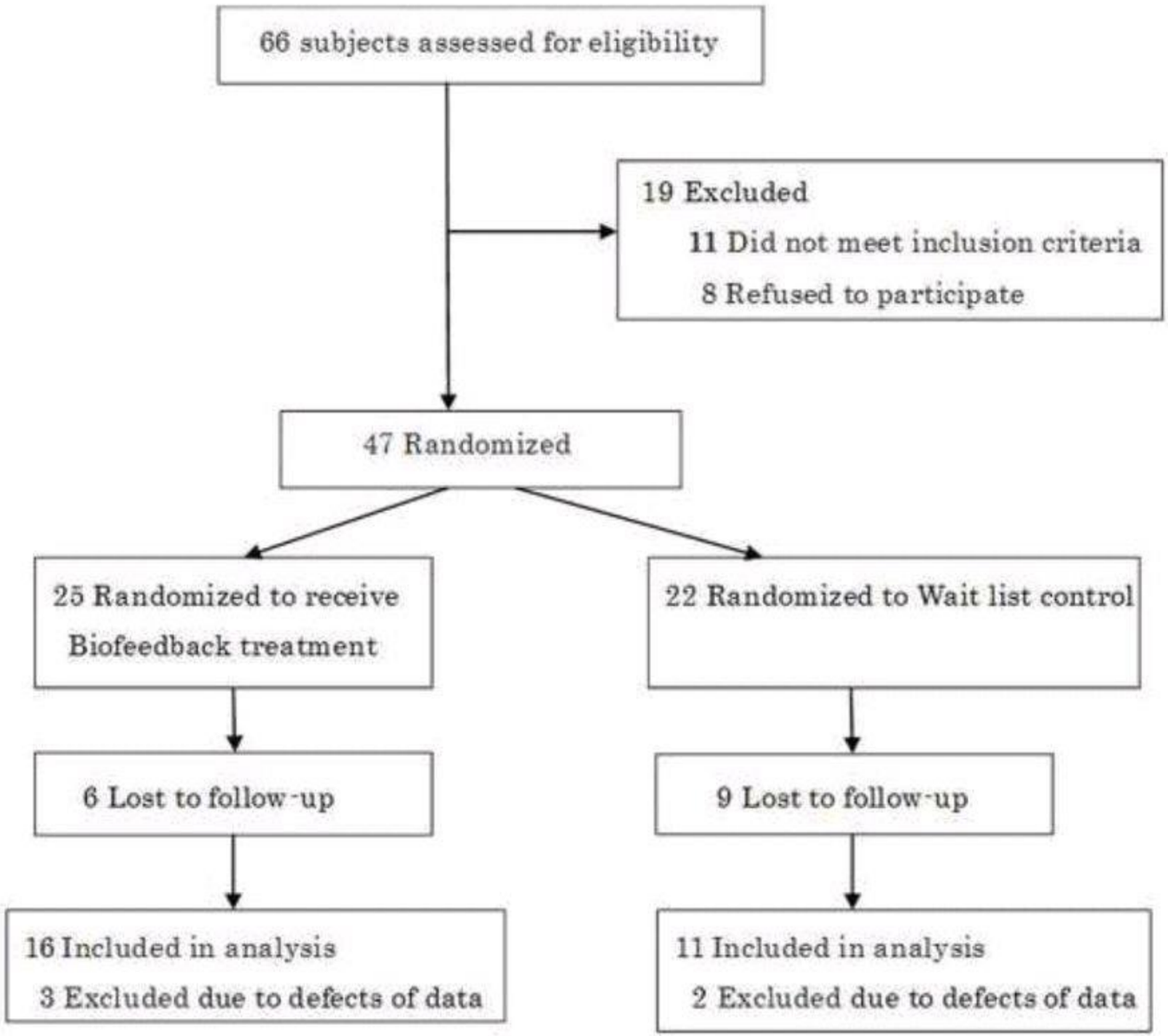
66 subjects assessed for eligibility
19 Excluded
11 Did not meet inclusion criteria
8 Refused to participate
47 Randomized
25 Randomized to receive Biofeedback treatment
22 Randomized to Wait list control
6 Lost to follow-up
9 Lost to follow-up
16 Included in analysis
3 Excluded due to defects of data
11 Included in analysis
2 Excluded due to defects of data

Figure 2

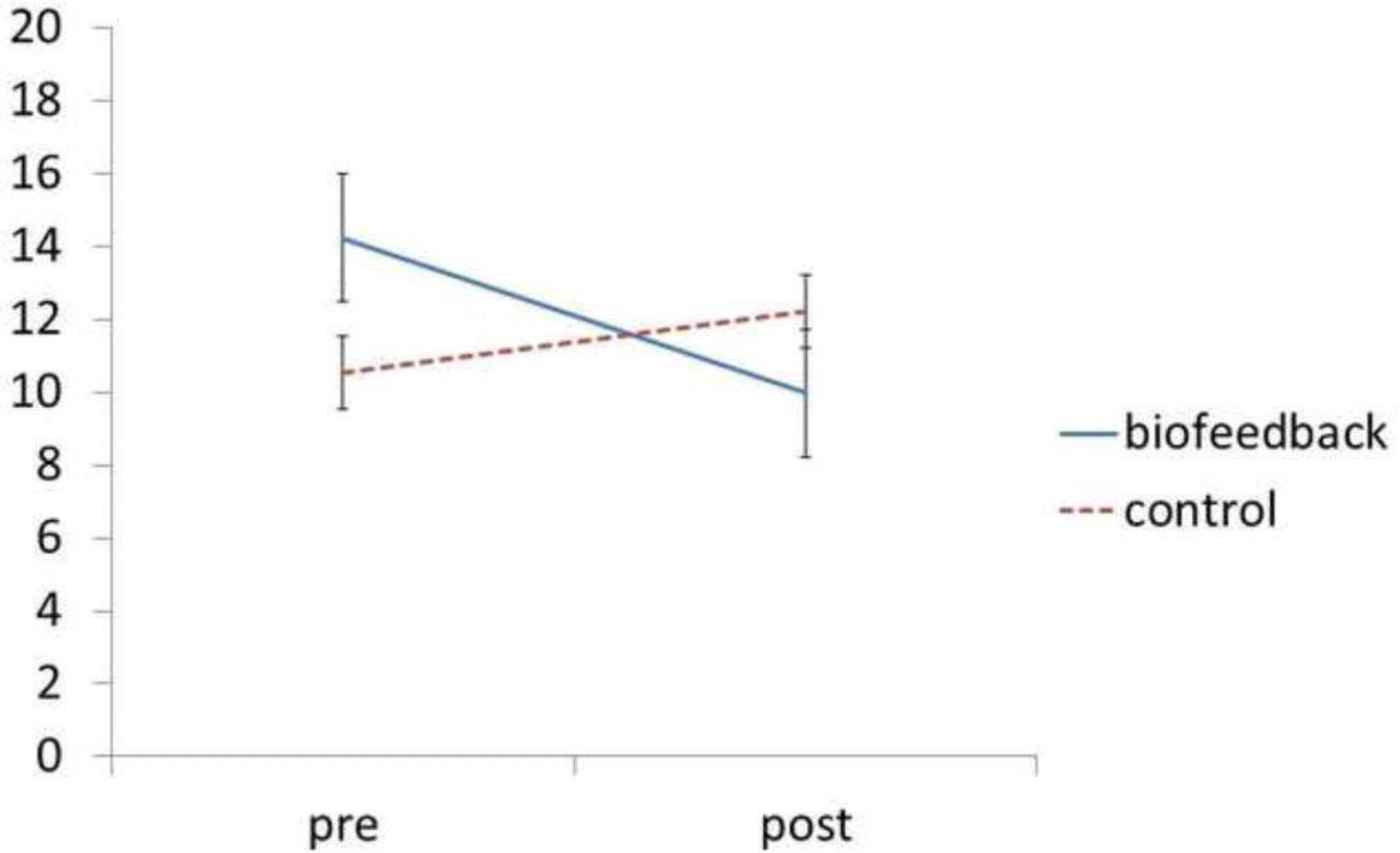

Figure 3

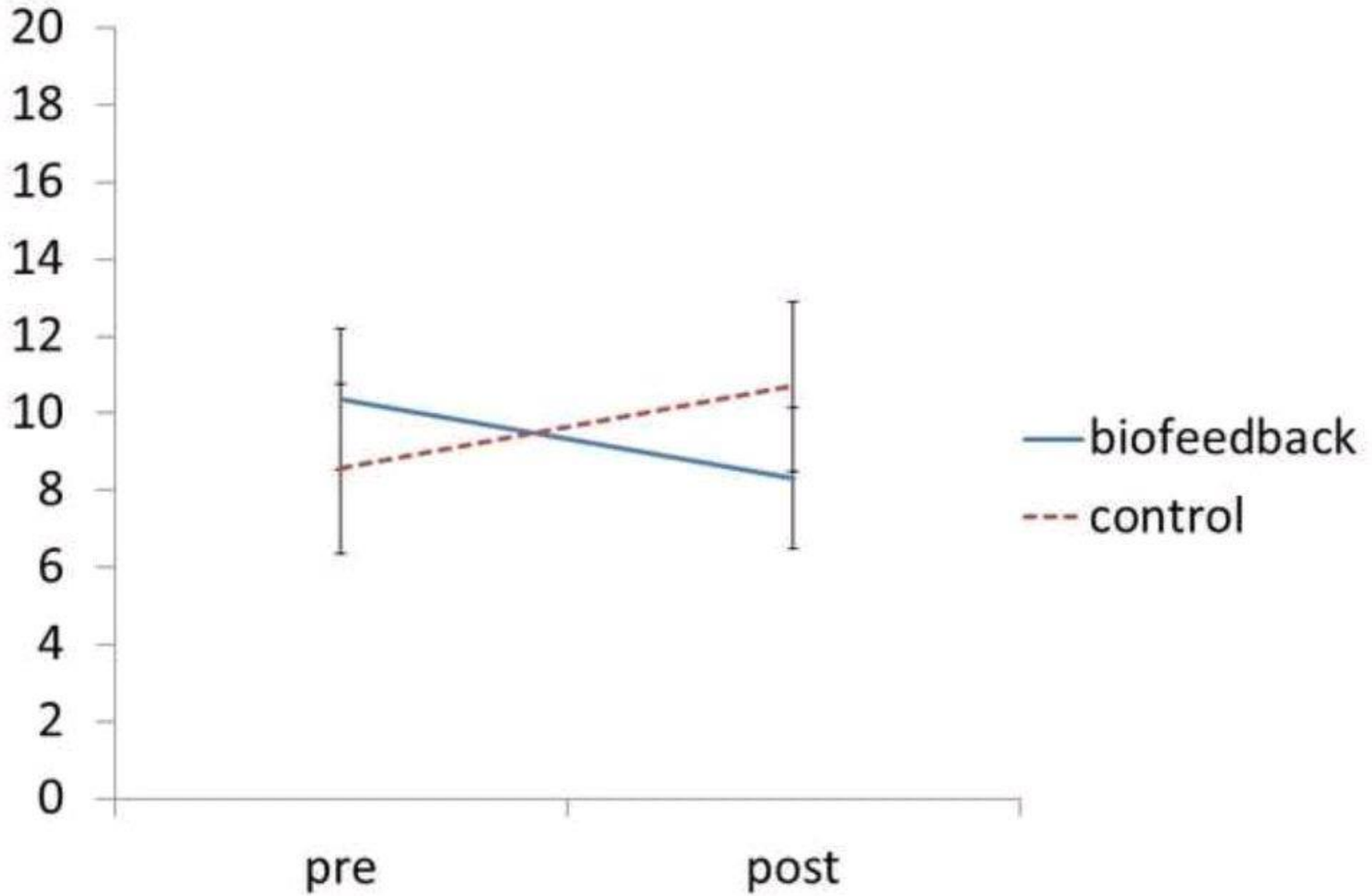

Figure 4