Effectiveness of Jogging, Eye Movement Exercises, and Diaphragmatic Breathing in Reducing Migraine Symptoms: A Randomized Controlled Trial

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Abstract

Background: electrophysiological dysresponsiveness (ED) is apparent in a migraine brain. Various methods have been suggested to regulate ED, including electrochemical transduction or regulation of Nitric Oxide (NO) and Brain-Derived Neurotrophic Factor (BDNF), jogging, eye movement exercises, and diaphragmatic breathing.

Objectives and methods: A three-group, double-blind, and randomized design with pre-test, post-test, and follow-up assessment was used to test the effectiveness of jogging, eye movement exercises, and diaphragmatic breathing in the treatment of patients with episodic migraine. International Classification of Headache Disorders 3rd edition (ICHD-3) was used to diagnose the migraine patients, who were randomly assigned to one of the three study groups to perform either 12 consecutive weeks of (a) jogging and eye movement exercises (n = 22) ;(b) jogging and diaphragmatic breathing (n = 19); or (c) treatment as usual (TAU), receiving prescribed medication (n = 22) group.

Results: The results of a series of MANCOVA showed that, compared to the TAU group, patients in the two experimental groups showed significant reductions in the frequency, duration, and intensity of their episodic migraine attacks. Moreover, the frequency of menstrual cycle-dependent headache attacks and over the counter drugs use were reduced, and the quality of sleep and drinking water were improved at post-test and a 12-month follow-up.

Conclusion: The results suggest that jogging and eye movement exercises or jogging and diaphragmatic breathing can be used as effective alternative interventions in the treatment of episodic migraine.

Trial registration retrospectively: [Ir.mums.fm.rec.1396.362](https://www.clinicaltrials.gov/ct2/show/study?term=Ir.mums.fm.rec.1396.362)

Introduction

Dynamic dysfunctions within the pain matrix, abnormal modulation in pain circuits, altered pain inhibition, and electrophysiological dysresponsiveness (ED) hint a migraine brain (1–3). Moreover, the dysfunctions could be exacerbated by the reciprocal connectivity or bidirectional impacts of neural, endocrine, immune, and humoral alterations in response to daily life stressors. Examples of such links could be observed in the sensory dysfunction or metabolism dysregulation, specific spontaneous oscillations, and maladaptive stress responses in several networks of a migraine brain including hypothalamus and the brain stem (4). For instance, eye-brain electrochemical transduction and retinal nerve fiber alterations seem to play a key initiating role in a migraine brain (e.g., through choroidal thinning and thickening or retinal vasospasm) (5). As a state of hypoxia, these changes also appear to be initiated by Nitric Oxide (NO)-mediated vasodilator responses or by endothelin-1 (ET-1)-mediated vasoconstrictive responses in a migraine brain (6, 7). Furthermore, structural and functional abnormalities in the endothelial progenitor cells have been reported in patients with migraine (8). The domains or interlinks between mitochondrial energy production, reactive oxygen species (ROS) availability, and ion homeostasis (e.g., calcium influx) have been clearly shown in a migraine brain (9).

Under these circumstances, ionic dysregulation (e.g., anoxic depolarization) appears to share several links with a hyperexcitable migraine brain (10). Therefore, depending on the quantity, duration, or presence of other elements, a biomolecule (e.g., NO or Brain-Derived Neurotrophic Factor; BDNF) can play various roles in these networks or domains. The key roles that NO plays in the brain consist of (a) regulating cerebral blood flow (CBF) or vascular tone; (b) modulating cells communications; and (c) acting as an antioxidant agent (11, 12). In addition, both NO and BDNF are pleiotropic and pain modulators (13, 14). Homeostatic dysregulation of these biomolecules during migraine attacks is another implication in the pathophysiology of the migraine disease (15, 16). Therefore, regulation and availability of NO or BDNF are essential during health and illness, including migraine attacks, as stressful insults to the brain (17, 18).

The regulation of NO or BDNF gene expression as a neuroprotective strategy appears to offer a promising method for decreasing the load of the insults. Although migraine-specific, antidepressants, and anti-epileptic drugs directly target these types of expressions (because of similar molecular features of the drugs or identical structural features of the cells), most of these medications have drug-drug sharing and target-related induced undesirable side effects (11). Therefore, given the vital role of NO and BDNF biomolecules, the direct targeting of their expressions can have detrimental side effects both for brain function and vascular tone (13, 18, 19). For example, in the presence of triptans or morphine, NO boosts the activation of trigeminal pathways or increases the risk of medication overuse headache (MOH) (20, 21). Another interesting instance of over-expression is the elevated level of BDNF. Interlinks of epilepsy, migraine, and neuronal hyperexcitability are obvious. Recent evidence suggests links between elevated levels of BDNF and neuronal hyperexcitability (22). Moreover, the upregulation of BDNF compensates for pain hypersensitivity (23). Nevertheless, the chronic administration or high doses of antidepressants suppress the expression of these biomolecule genes (24). Moreover, the manipulation of BDNF gene expression may contribute to the development of other diseases and disorders including anxiety, depression, or chronification of migraine (25). Considering these endogenous biomolecule deteriorations that are caused by direct-target interventions in a hypersensitive migraine brain, developing novel, safe, multidimensional, and non-direct or non-pharmacological interventions is vital to the treatment of a multifactorial disease like migraine (26).

Based on previous studies (27–29) that have shown the effect of regular aerobic exercises or progressive relaxation techniques on pain processing or migraine, the present study proposes that regular aerobic exercises relieve pain experience possibly through a cascade of facilitative mechanisms, including the reduction of N-Methyl-D-Aspartate (NMDA) receptors or regulation of serotonin or glutamate excitatory signaling (30–32). Moreover, NO inhibits the excess presence of NMDA receptors through using a positive feedback loop and facilitation of glial cells function, and hence regulates the excitotoxic effect of accumulative glutamate following a disease like migraine (33–35). In the same vein, regular exercise maintains the brain homeostasis and improves the brain function by promoting the gene expression of BDNF (36). Exercise-induced BDNF reduces excitotoxins through a negative feedback loop (37). Therefore, as a regulator of homeostatic response, BDNF protects the brain against glutamate-induced toxicity during migraine attacks (38–40). Furthermore, to regulate the hypoxia-induced alterations in a

migraine brain (41), exercise-induced, nasal, or diaphragmatic breathing can offer a promising adjunctive method. By passing through nasal mucosa and influencing olfactory neuroepithelium receptors, the nasal breathing facilitates autonomic nervous system, hormonal systems, and psychological constructs, all of which are closely related to a migraine brain (42). Naturally, regular physical exercise improves nasal breathing (43). The visual exercise, through cortical re-arrangement and oscillatory feedback signaling between cranial motor nerves, brain stem, thalamus, hypothalamus, and motor cortex regulates local and cortical endothelium releasing factors including NO and BDNF (44–48). To conclude, regulating several reciprocal feedback mechanisms between neuronal and vascular interactions, including hormones (e.g., melatonin, irisin), biomolecules (e.g., NO, and BDNF), organelles (e.g., mitochondria), axis (e.g., hypothalamus-pituitary-adrenal (PHA)), and systems (e.g., immune and metabolism), regular physical exercises or other progressive regulatory techniques including eye movement exercise and diaphragmatic breathing can alleviate pain processing in a migraine brain (49–54).

Methods

Study population

The present study was performed on 53 right-handed (55) Persian-speaking female patients (56, 57) (mean age = 31.19; $SD = 5.67$; range of 19–40) with episodic migraine (33.3% with aura (MwA); 66.7% without aura (MwoA)) selected from a population of 764 patients with migraine who were admitted to several local state hospitals between September 2015 and August 2016. After eligibility assessment (the study flowchart below), 353 individuals did not meet the study criteria (below) and 276 were unwilling or unable to participate in the study. Another 72 participants were discontinued from the study for being unpunctual, and 10 were missed during the follow-up. Participation in the study was voluntary. During their enrolment, participants filled out a questionnaire on demographic information, history of migraine, socioeconomic status, and migraine type (Table 1).

Table 1

Mean and SDs for demographic information, history of migraine, and distribution of participants based on socioeconomic status and type of migraine in study groups.

<i>Groups</i>						
Variables		Eye movement	Diaphragmatic Breathing	Control	<i>F</i> (2,60)	<i>χ</i> ² <i>p</i>
<i>Mean (SD)</i>	Age	31.15 (6.40)	31.61 (4.87)	30.73 (5.88)	.09	.90
	Weight	61.95 (7.51)	61.39 (7.77)	62.07 (8.08)	.03	.96
	Height	163.75 (6.98)	162.50 (5.53)	162.93 (6.79)	.18	.83
	HM	5.00 (3.06)	4.39 (2.63)	4.93 (3.36)	.22	.80
N	SES*	4:14:2	3:13:2	5:8:2		1.70 .79
	MT	8:12	3:15	6:9		2.97 .22
Note. HM = History of Migraine, SES = Socioeconomic Status (*high: middle: Low), and MT = Migraine Type (MwA = Migraine with aura or MwoA = Migraine without aura) in study groups. The groups did not significantly differ in demographic characteristics, SES, and MT.						

Inclusion criteria were (a) 18–50 years of age (58); (b) a confirmed diagnosis of episodic migraine based on the International Classification of Headache Disorders (ICHD) criteria (59); and (c) a history of migraine over the last 12 months regardless of the migraine type (i.e., with aura (MwA) or without aura (MwoA)). Exclusion criteria were (a) a history of any other neurological, gut, or respiratory-related diseases including concomitant diagnosis of other headache disorders especially medication overuse headache (MOH) (60); (b) any kind of surgery that restricts their ability to jog, perform eye movement exercises, and/or breath; or (c) cardiovascular-related diseases, e.g., blood pressure abnormalities. The use of pain medication was allowed between post-test and the follow-up assessment for the patients in the control group. Patients in the experimental groups agreed not to take pain medications or any other interventions for at least three months in advance of and during the present study. However, if they were experiencing severe pain, they could use limited medication prescribed by their physician. Flowchart shows flow of the present study from 2016 to 2019.

Experimental design

The present study (3×3 factorial design; three groups and three dependent variables) is a randomized double-blind controlled trial that aimed to investigate whether jogging plus eye movement exercises or jogging plus diaphragmatic breathing could be effective in alleviating episodic migraine symptoms compared to a control group that use prescribed medications for migraine (treatment as usual).

All of participants had to meet the inclusion criteria and be flexible about the terms of the study after their diagnosis was confirmed by two consultant neurologists at a local state hospital based on ICHD criteria (59). The sample was tested and selected over a 46-week period between August 2016 and July 2017. The sample was screened for frequency, duration, and intensity of attacks in the last three months. Next, participants were randomly (1:1:1) assigned to one of the experimental groups, i.e., eye movement exercises (n = 22) or diaphragmatic breathing (n = 19) or to the control group (n = 22). All the data were recorded by an experimenter who was blind to the study design. The data analysis was also conducted by one of the co-authors, who was blind to the study design and its hypotheses.

Randomization procedure

Because the present study was based on a double-blind design, clinicians, and experimenters who were working with the patients were not aware of the nature of the study design and procedures. Participants were informed only about what they were expected to do but not about their group allocation and other participants in the study, and the study design and goals. To reduce the risk of prediction for a sample size of $n > 50$, we used telephone (secure) allocation of participants by an independent person in line with instructions for simple randomization method (61). Before proceeding to the next stage, the inclusion and exclusion criteria of the present study were monitored and checked. For example, if a participant was on a prescribed or non-prescribed medication, she was recommended to stop her medication in a tapering manner (i.e., over a 6-week period). Moreover, patients were monitored and screened for any types of smoking (e.g., the participants who smoked cigarettes were instructed to stop smoking; otherwise, they were excluded from the experiment). Smoking was discouraged to help with the patients' physical exercise routine.

A written informed consent was obtained from the participants.

The study was approved by the ethical committee of Mashhad University of Medical Sciences (Ir.mums.fm.rec.1396.362).

One experimenter was randomly assigned to each group to execute the participants' enrollment and interventions' assignments in each group during study. Experimenters were instructed and scheduled to monitor and record medications, menstrual cycles, sleeping, drinking water, and exercise intolerance behaviors in the experimental and control groups. The participants were told that their participation was voluntary, and they could withdraw from the experiment at their will. They were told that they are part of a study on the migraine. A written informed consent was obtained from the participants. The study was approved by the ethical committee of Mashhad University of Medical Sciences (Ir.mums.fm.rec.1396.362).

Interventions

Jogging plus eye movement exercises or jogging plus diaphragmatic breathing instruction

There were two experimental groups. The first experimental group performed *jogging plus eye movement exercises*. The second experimental group performed *jogging plus diaphragmatic breathing instruction*.

During the jogging, they were instructed to follow a breathing rhythm that required two relaxed, deep nasal inhalations, a repose, and two deep oral exhalations.

Jogging required circling around the outer ring of a local public park for 3.2 km ($\approx$ 25-min). During the jogging, they were instructed to follow a breathing rhythm that required two relaxed, deep nasal inhalations, a repose, and two deep oral exhalations. The jogging was exercised every other day (between 5:00 p.m. and 7:00 p.m.) over a period of 12 weeks.

The eye movement exercises included horizontal (dextroversion / levoversion) and vertical (sursumduction / deorsumduction) conjugated eye movements (62). Participants performed a 5-min eye movement exercise 30-min before having their breakfast every morning and 30-min before going to bed at night for 12 weeks. The 5-min bedtime phase was initiated by 15-round movements of the right-hand index finger, followed by 15-round left-hand index finger movements in the horizontal visual field, which was followed by the same procedure in the vertical visual field with a front-forward, fixed head with the eyes following the finger in a constantly controlled manner (Fig. 3). The 5-min morning phase was initiated, sustained, and terminated with the same procedure, but instead of moving the index finger in the visual field, the head was moved horizontally (30 rounds laterally) and then vertically (30 rounds up and down) with fixed eyes on a fixed index finger in the visual field (Fig. 4) (63, 64). Figures 2 and 3 show participants' hands and head-guided eye movement exercises in the experimental groups.

Participants were persuaded to focus on their breathing while inhaling and exhaling (65, 66).

The diaphragmatic breathing practice required a deep nasal inhalation, a two-second repose, and a long, deep oral exhalation three times a day around 7:00 a.m., 2:00 p.m., and 9:00 p.m. for 5-min for 12 consecutive weeks (Fig.

The diaphragmatic breathing practice required a deep nasal inhalation, a two-second repose, and a long, deep oral exhalation three times a day around 7:00 a.m., 2:00 p.m., and 9:00 p.m. for 5-min for 12 consecutive weeks (Fig. 2). Participants were persuaded to focus on their breathing while inhaling and exhaling (65, 66).

During the eye movement exercises and diaphragmatic breathing practice, participants were asked to sit in an upright position and plant their feet on the ground at a 90-degree angle to match the extension of their shoulders. Moreover, they were instructed to fix their head horizontally, leveled with their body. They were also asked to arch their back completely and slouch forward. The position was followed by rolling shoulders back and dropping them down. The preparation phase was ended by a deep breath and relaxation (Fig. 1) (67).

Control group

As stated before, the control group was receiving medical treatment as usual, which solely consisted of common prescribed medication to help with the migraine symptoms. Because there were a variety of

prescribed medications and their effect on the migraine symptoms was not a goal of the present study, it was not necessary to keep a record of the type of medication that participants in the control group were using over the two-year of the present study. Therefore, we monitored this group of patients and like the experimental groups, we administered all the study measures with them at the baseline, post-test, and the follow-up assessments.

Procedure

However, none of the participants in the experimental groups reported referring to their physician or resuming the use of migraine prescribed or non-prescribed medication at any of phone calls or follow-up assessments.

The telephone calls also helped minimize the participants' dropouts.

Moreover, weekly telephone follow-ups were made to enquire about the participants' experiences of pain, use of prescribed or non-prescribed medication, menstrual cycle, sleeping pattern, drinking water, or other related behaviors.

To measure the duration, frequency, and intensity of pain, the study measures were administered at the baseline, post-test, and a 12-month follow-up. Moreover, weekly telephone follow-ups were made to enquire about the participants' experiences of pain, use of prescribed or non-prescribed medication, menstrual cycle, sleeping pattern, drinking water, or other related behaviors. The telephone calls also helped minimize the participants' dropouts. Participants were also reassured that they could have control visits during the study in case of experiencing migraine attacks or complications that could affect the intake of regular prescribed or non-prescribed medication. However, none of the participants in the experimental groups reported referring to their physician or resuming the use of migraine prescribed or non-prescribed medication at any of phone calls or follow-up assessments. Therefore, there was no data on prescribed or non-prescribed medication relapse for the experimental groups. The same experimenters administered all study measures at the baseline, post-test, and the follow-up assessments.

Measures

Headache diary

The Headache diary was used (68, 69) to record the frequency, (i.e., one attack per four weeks, one attack in two weeks, two or three attacks per week, or more than three attacks per week), duration (i.e., 4, 4–24, or 24–72 hours per attack), and the intensity of pain (i.e., moderate (1–3), severe (4–7), and worse possible case (8–10)) per migraine attack during the past four weeks. The measure has desirable reliability and validity indices (68, 69).

Compliance with intervention

Based on recorded data and the present study protocols, which included 36 sessions of jogging and 72 sessions of eye movement exercises or 72 sessions of diaphragmatic breathing for each study group, compliance with the intervention was assessed as follows: $36/36 \times 100 = \% \text{ compliance}$ or $72/72 \times 100 = \% \text{ compliance}$ for each study group (70). During 36 sessions of jogging and 72 sessions of eye

movement exercises or diaphragmatic breathing, each group of participants could skip sessions for a maximum of three (with a minimum compliance of 91.6%) or six (with a minimum compliance of 95.8%) sessions. Because there were no reports beyond the minimum compliance with interventions, further reports of the factor deemed unnecessary in the present study.

Menstrual cycle, OTC, sleep, changes of drinking water, and exercise intolerance behaviors

Prior to the study, an experimenter recorded information on (a) menstrual cycle; (b) over the counter (OTC) drug use; (c) sleep regimens (sleep and wake-up patterns), sleeping hours, and wake-up mode (71); (d) drinking water; and (e) exercise intolerance from the participants (Table 3). Menstrual cycle involved presence or absence of any effects on headache characteristics prior to, during, or after a menstrual period. Sleeping pattern involved going to sleep on time (between 9:00 p.m. and 11:00 p.m.) or late at night (after 11:30 p.m.). Sleeping hours included sleeping less than or more than seven hours per night (between 10:00 p.m. and 7:00 a.m.) (72, 73). In addition, drinking water was also recorded for the participants (74). However, any incidents of muscle cramps, fatigue, chronic dizziness, and vomiting, which were related to exercise intolerance were recorded. The data was recorded every other day during the experiment and every week during the 12-month follow-up. The rationale for recording and analyzing this data was to test whether the interventions influenced such variables beside migraine pain characteristics (Table 3).

Data analysis

To test the relative effect of jogging plus eye movement exercises or jogging plus diaphragmatic breathing, three multivariate analyses of covariance (MANCOVA) were conducted. To ensure that there were no missing data, initial data evaluation was performed for experimental and control groups. Next, assumptions of homogeneity, linearity, and normality of variance-covariance matrices were calculated and a p -value $\geq .05$ was set for all analyses. The results of models' fitness tests did not reveal any violation of underlying assumptions. In each model, group (three levels) was entered into the model as factor, pain characteristics (i.e., frequency, duration, and intensity of pain) at baseline were entered as covariates, and pain characteristics at the post-test and follow-up were entered into the model as dependent variables. Moreover, as secondary analyses, Cochran's tests were calculated to measure the effects of the two types of interventions on menstrual cycle, OTC, sleep, and drinking water as behavioral outcomes from baseline to post-test and the 12-month follow-up.

Results

Table 2 shows means and SDs of frequency, duration, and intensity of pain in each study group at baseline, post-test, and the 12-month follow-up assessments.

Table 2

Mean and SDs for frequency, duration, and intensity of migraine pain in each study group across three assessment points.

Groups; Mean (SD)	Frequency			Duration			Intensity		
	Pre-test	Post-test	Follow-up	Pre-test	Post-test	Follow-up	Pre-test	Post-test	Follow-up
EM	9.15 (2.68)	2.40 (1.46)	2.70 (1.21)	8.10 (3.29)	1.80 (1.36)	1.95 (0.99)	6.50 (1.67)	1.20 (0.83)	2.20 (0.95)
DB	8.22 (4.00)	1.61 (1.24)	1.44 (1.79)	6.50 (2.77)	0.89 (0.67)	1.11 (1.41)	6.11 (1.32)	0.94 (0.72)	1.50 (1.29)
Control	8.80 (2.48)	8.33 (2.66)	9.20 (4.34)	8.07 (3.97)	8.00 (3.87)	7.80 (3.07)	7.07 (1.79)	6.80 (1.56)	6.20 (1.29)
Note. EM = Eye movement exercises; DB = Diaphragmatic Breathing									

Primary data analyses

In each MANCOVA model, group showed a significant multivariate effect on the frequency ($Wilk's = .20$; $F_{(4, 96)} = 28.93$; $p = .001$; η^2 (Cohen's d) = .54 (2.16)), duration ($Wilk's = .16$; $F_{(4, 96)} = 34.34$; $p = .001$; η^2 (Cohen's d) = .58 (2.35)), and intensity ($Wilk's = .09$; $F_{(4, 96)} = 53.14$; $p = .001$; η^2 (Cohen's d) = .68 (2.91)) of the pain at the post-test and follow-up assessments. Pairwise comparisons showed that, compared to the control group, the experimental groups showed significant improvements in all pain characteristics at the post-test and follow-up assessments (Table 3). There was no significant difference between the two experimental groups on any of the pain characteristics. The effect sizes for all models were greater than Cohen's $d = .80$ for a large effect size (Table 3). Figure 4 shows changes in the migraine pain across assessment points for each group.

Table 3

Results of three MANCOVA models testing inter-group effects at post-test and a 12-month follow-up.

			Main effects				Pairwise comparisons
DVs		Assessment	<i>Wilks' λ</i> (4, 96)	<i>F</i> (4, 96)	<i>p</i>	η^2 (Cohen's d)	(<i>p</i> < .001)
Migraine attacks	Frequency	Post-test	0.20	78.59	.001	.79 (3.55)	ME&DB < Ctrl
		Follow-up		50.93	.001	.67 (2.84)	ME&DB < Ctrl
	Duration	Post-test	0.16	89.28	.001	.78 (3.76)	ME&DB < Ctrl
		Follow-up		77.40	.001	.76 (3.55)	ME&DB < Ctrl
	Intensity	Post-test	0.09	166.81	.001	.87 (5.17)	ME&DB < Ctrl
		Follow-up		69.53	.001	.73 (3.28)	ME&DB < Ctrl

Secondary data analysis

The results of a series of Cochran's tests were used to test changes in the patients' menstrual cycle, OTC, sleep pattern, and drinking water across the assessment points and showed significant improvements for the experimental groups but not for the control group (Table 4). None of the participants in the experimental groups complained of adverse effects like muscle cramps, fatigue, chronic dizziness, or vomiting on exertion or after exercise.

Table 4

Results of Cochran's Q models testing inter-group effects at post-test and a 12-month follow-up.

Frequency							
Variables	Factors	Groups	Pre-test	Post-test	Follow-up	Cochran's Q	P
Menstrual Cycle	No Effect: Increase	EM	13 : 5	18 : 0	18 : 0	10.00	.007
		DB	15 : 5	20 : 0	20 : 0	10.00	.007
		Control	10 : 5	11 : 4	14 : 1	6.50	.03
Over the Counter	No Use : Use	EM	0 : 18	2 : 16	4 : 14	4.80	.09
		DB	0 : 20	7 : 13	4 : 16	9.25	.01
		Control	2 : 13	1 : 14	1 : 14	.66	.71
Wake_up_Mode	Refreshed : Sleepy or Tired	EM	5 : 13	18 : 0	18 : 0	26.00	.001
		DB	0 : 20	19 : 1	18 : 2	34.30	.001
		Control	3 : 12	1 : 14	0 : 15	4.66	.09
Sleep Hours	Less than Seven Hours :	EM	16 : 2	9 : 9	12 : 6	5.69	.05
	More than Seven Hours	DB	18 : 2	14 : 6	12 : 8	4.30	.11
		Control	13 : 2	13 : 2	13 : 2	0.00	1.00
Sleeping Pattern	On time : Late	EM	4 : 14	12 : 6	15 : 3	14.92	.001
		DB	3 : 17	14 : 6	13 : 7	13.87	.001
		Control	2 : 13	1 : 14	1 : 14	0.66	.71
Drinking water	No : Yes	EM	14 : 4	1 : 17	0 : 18	24.40	.001
		DB	19 : 1	3 : 17	6 : 14	24.11	.001
		Control	14 : 1	13 : 2	13 : 2	.66	.717
Note. EM = Eye movement; DB = Diaphragmatic breathing							

Given the loss of participants from post-test to the follow-up (see Flowchart), we did not have full compliance with the present study intervention protocols; the compliance rates were: $53/63 \times 100 = 84.1\%$ compliance for the total sample; $20/22 \times 100 = 90.9\%$ compliance for the jogging plus eye movement exercises group; $18/19 \times 100 = 94.7\%$ compliance for the jogging plus diaphragmatic breathing; and $15/22 \times 100 = 61.1\%$ compliance for the control group.

Discussion

The present study tested the effectiveness of jogging, eye movement exercises, and diaphragmatic breathing in patients with migraine pain. The first experimental group received jogging plus eye movement exercises and the second experimental group received jogging plus diaphragmatic breathing, whereas the control group only received treatment as usual. The results showed significant effects of the interventions on the patients' symptoms in the experimental groups (Fig. 4 and Table 3). Therefore, regular aerobic exercises (i.e., jogging) and practicing body-mind awareness (i.e., eye movement exercises and diaphragmatic breathing) appear to elucidate the negative effects of stressful insults in the brain, on the body muscles, respiratory rate and depth, and the flow of biomolecules and hormones (i.e., Nitric Oxide (NO), brain-derived neurotrophic factor (BDNF), and adenosine monophosphate-activated protein kinase (AMPK)). These effects could stem from various possible mechanisms, including (a) brain-gut and neuroimmune axis (e.g., hypothalamus-pituitary-adrenal (HPA); (b) brain-brain reciprocal interlinks (e.g., hippocampus-anterior cingulate cortex and medial-prefrontal cortex (mPFC) oscillations); and (c) circadian disruption and biomolecular dysregulation (e.g., oxidative stress and neurogenic inflammation), each of which may play a key initiating role in spurring migraine-related symptoms (75–78).

Although the results of a meta-analysis (29) suggested that the effect of aerobic exercise on patients with migraine is only related to the frequency of the attacks, in a recent study (79), aerobic exercises are assumed to influence all aspects of migraine pain including frequency, duration, and intensity. The paradoxical findings in the literature on the effectiveness of aerobic exercise could be related to the following reasons. *First*, based on the International Headache Society (IHS) recommendations (69, 80), one major drawback of previous studies is heterogeneity in applying headache-related outcome measures. *Second*, some studies have failed to adequately address issues related to blinding, sample size, designing, and randomization. *Third*, no study has compared the outcomes of aerobic exercises on patients with migraine without aura (MwoA) and patients with migraine with aura (MwA). *Forth*, evidence was scarce for comparing the outcomes of aerobic exercises and pharmacological treatment of migraine pain. *Fifth*, in no study so far aerobic exercise has been complemented with another non-medication intervention; therefore, this was the first study that, based on findings from the migraine brain studies, combined jogging with eye movement exercises or diaphragmatic breathing to decrease kinesiophobia or sensitivity to movements in migraine patients (81, 82).

As a diagnostic criterion, patients with migraine have a fear of movement or kinesiophobia (83–85). To develop readiness for and potentiate neural responsiveness to a full-body exercise and to improve body awareness (65, 66), the present study provided the patients with eye movement exercises or diaphragmatic breathing (86–88). Considering the neural or Hebbian learning, stimulating brain on a regular basis adjusts brain functions at the molecular level (e.g., signaling mechanisms and memory formation) (89). Eye movement exercises are identified to activate widespread, interconnected cortical and subcortical networks such as superior colliculus, oculomotor network (ON) in the brain stem, dorsolateral prefrontal brain cortex, basal ganglia, subthalamic structures, substantia nigra pars reticulata, visuo-motor, parietal, and posterior cingulate cortices (90–94). Each of these networks plays an excitatory or inhibitory role in pain processing (95, 96). Therefore, performing eye movement exercises on a regular basis stimulates or potentiates almost all major parts of the brain that are important in the

experience of the pain. The corneoretinal potential (CRP) transduction by eye movement exercises is a bioelectrical signal, which is produced by two modes of polarities during eye movement exercises: a positively charged end (cornea) and a negatively charged end (retina) (97). The conjugated eye movement exercises (i.e., from right to left or from top to bottom and the *vice versa*) transduces sequential negative or positive electrical charges on the retina (98). These types of training-induced transduction should potentiate synaptic plasticity and facilitate myelination mechanisms by (a) regulating signal transmission (i.e., neuromodulation of ion channels and neurotransmitters); (b) synchronizing oscillations (i.e., frequency, amplitude, or phase); and (c) cortical reorganization or enhancement of timing within related cortical-cortical or cortical-subcortical brain networks (i.e., enhancement of memory, visuospatial accuracy, decision-making, or task switching) (99–103).

In the present study, another essential guided behavior was diaphragmatic breathing.

In the present study, another essential guided behavior was diaphragmatic breathing. It should be noted that jogging itself may increase exercise-induced stress insults in migraine brain; however, diaphragmatic breathing helps with promoting stress-response control indices and potentiating cortical readiness prior to jogging (104, 105). Diaphragmatic breathing can improve brain function via the following mechanisms: (a) chemical, which involves the regulation of biomolecules such as adenosine, melatonin, orexin, or calcitonin-gene-related peptide (CGRP); (b) mechanical, which involves enhancing the rate, length, or intensity of breathing at the cortical level; and (c) cortical-subcortical control, which is related to shared breathing centers and headache-related networks such as brainstem and medullary centers (106–109). Together, jogging, eye movement exercises, and diaphragmatic breathing may induce mitochondrial oxidative phosphorylation, electrical transduction, ionic, and biomolecule homeostasis that can explain primary and secondary outcomes of the present study.

All participants in the present study were female patients with episodic migraine. This may limit the generalizability of our findings to male patients with migraine. Subsequently, the same study should be also conducted with male migraine patients. Moreover, heterogeneity in the rate of prescribed and OTC medication use in the control group was another limitation of the present study. Moreover, we did not ask patients in the control group to keep a journal of any medication that they were taking for their pain because, there is no single or specific medication with consistent or long-term effect for migraine, hence even recording the rate of medication use over a two-year by the patients in the control group deemed an unviable goal and could not help with interpreting the study outcomes. Furthermore, given that the present study was conducted in a Middle Eastern country with a different environment and culture, future studies can replicate the study with patients from different cultural, racial, and ethnical backgrounds. Future studies can also examine the outcomes of the present interventions for other types of headache, migraine-related comorbidities (e.g., epilepsy, tinnitus, chronic dizziness or vertigo, sleep apnea, or restless leg syndrome), and even for psychopathologies like depression and anxiety.

Conclusion

The primary outcomes of the present study can be summarized as positive effects of jogging plus eye movement exercises or jogging plus diaphragmatic breathing on decreasing the frequency, duration, and intensity of pain in patients with migraine. The secondary outcomes could be summarized as decreased headache attacks associated with menstrual cycle and use of OTC medication, and on improving sleep and drinking water. Together, interventions used the present study offer promising prophylactic and therapeutic outcomes for patients with migraine.

Clinical implications

Performing 12-week jogging (every other day $\approx$ 25-min) either with eye movement exercises (60 rounds early in the morning / 60 rounds before the bedtime) or diaphragmatic breathing (3 times a day, each time for $\approx$ 5-min)

- can significantly reduce the measured aspects of episodic migraine pain characteristics.
- offers a safe and convenient intervention.
- produces no short-term or long-term undesirable side effects.

Abbreviations

ED

electrophysiological dysresponsiveness

NO

Nitric Oxide

BDNF

Brain-Derived Neurotrophic Factor

ICHD-3

International Classification of Headache Disorders 3rd edition

TAU

Treatment as usual

CBF

Cerebral blood flow

MOH

Medication overuse headache

NMDA

N-Methyl-D-Aspartate

PHA

Hypothalamus-pituitary-adrenal

MwA

Migraine with aura

MwoA

Migraine without aura

OTC

Over the counter drugs

CRP

corneoretinal potential

EM

Eye movement

DB

Diaphragmatic breathing

Declarations

Availability of data and material

All data generated or analyzed during the present study are included in this manuscript and its supplementary information files will be available on demand.

Ethics declarations

Ethics approval

The study was approved by the ethics committee of Mashhad University of Medical Sciences (Ir.mums.fm.rec.1396.362).

Consent for publication

All subjects provided written informed consent for publication prior to the present study enrolment.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Mohammad Dawood Rahimi: Conceptualization, Methodology, Data curation, Investigation, Project administration, Writing-original draft. Fatemeh Alidoosti: Formal analysis. Pouriya Hassani: Investigation. Mohammad Mahdi Ghasemi: Resources, Supervision. Javad Salehi Fadardi: Supervision, Reviewing & Editing

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Figures

Figure 1

Flow of study population from 2016 to 2019.

Figure 2

Participants posture during eye movement exercises or diaphragmatic breathing: a = upright back; b= fixed, leveled, and high-up head; c = rolled backed shoulders; d = planted feet on the ground at a 90-degree angle to the extension of shoulders; e = slouched forward breast.

Figure 3

Shows participants eye movement exercises for experimental groups: first row shows right hand-guided eye movement exercises; second row shows left hand-guided eye movement exercises.

Figure 4

Shows participants eye movement exercises for experimental groups: first row shows vertical head-guided eye movement exercises; second row shows horizontal head-guided eye movement exercises.

Figure 5

Migraine pain (frequency; ranges 1-9 attacks, duration; ranges 1-8 hours/attack, and intensity; ranges a scale of 1-7/attack during the last four-week) changes in each study (EM = eye movement exercises, DB = diaphragmatic breathing, control) group across three assessment points (pre-test, pot-test, and follow-up).