Original Article

Yoga intervention on blood NO in female migraineurs

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Abstract

Background: The current survey investigates the effect of 12 weeks yoga training on headache frequency, severity, duration and blood nitric oxide levels as well as headache impacts on female migraineurs' lives.

Materials and Methods: Thirty-two female patients with migraine took part and were randomly divided into two groups. The control group (n = 14) received medication and the yoga group (n = 18) participated in 12 weeks yoga training in addition to receiving the same medication as that of the control group. Frequency and duration of headache were assessed by a questionnaire. Visual Analogue Scale was used to measure the severity of headache, and the metabolite of NO also was measured by Griess reaction. Headache Impact Test (HIT-6) was also used to assess the impact of headache on patients' lives. Data were analyzed by t-test mean variance.

Results: After 3 months intervention, in the yoga group, there was a significant reduction in the impact of headache on patients' lives, headache frequency, and severity and a non-significant reduction in headache duration in the yoga group. There was no significant difference in the plasma levels of NO between yoga and control groups before and after the study.

Conclusion: Based on the results, yoga could be recommended as a complementary method to migraine patients.

Key Words: Asana, headache impact, migraine, NO, pranayama, shavasana

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INTRODUCTION

Migraine headaches are often a debilitating condition which affects millions of people throughout the world. Migraine is a serious neurological disorder which is unilateral, repeated alternatively, and occurs usually along with vomiting, nausea, photophobia, and phonophobia.[1] Although the prevalence of migraine may be slightly different in different societies, it is strikingly higher in females than in males and its ratio is changing from 2:1 to 3:1, especially between the ages of 25 and 55 years.[2] Studies show that migraine can not only be a risk factor of cardiovascular diseases and ischemic stroke, but it also has a relationship with brain structural injuries and lesions like those of brain circulation which lead to brain stroke.[3,4] The majority of the studies show a kind of depression in women migraine sufferers.[5] Food intolerance and allergies,[6] structural problems,[7] hormonal

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imbalances,[8] low blood sugar,[9] hard work,[10] brain tumors,[11] cerebrovascular hypoxia caused by reduced blood supply to the brain vessels,[12] depression,[13] high blood pressure,[14] neck trauma,[15] and many other unmentioned factors can cause migraine or make it more severe. Based on genetic evidences, it is strongly believed that changes in blood vessels, disruption in endocrine system, and some micro metabolism can create a dysfunction in neurovascular function and cause cortex depression.[16,17] There are important mediators like the neuropeptides substance P, calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP), which lead to a severe impairment in cerebral cortex function, vessel expansion, and cause migraine or primary headaches.[18] At that time, an electrical current moves to the frontal lobe at a certain speed and causes headache.[19]

Nitric oxide (NO) is an endothelium-derived relaxing factor (EDRF)-like substance which plays a key role in regulating brain metabolism and cerebral circulation, and vascular smooth muscle function.[20] It is one of the responsible factors for cerebral blood flow modulation in response to changes in oxygen gas and carbon dioxide; hence, it is not unlikely that impairment in NO production causes several pathological conditions of brain such as migraine, Alzheimer's and Huntington's, and even inflammation.[21] Repeated exercise helps NO to be kept in higher levels in the blood between exercise sessions. However, in apparent contrast, some surveys have suggested that some kinds of exercise may intensify migraine attacks due to excess NO production.[22] Yoga, as a Complementary and Alternative Medicine (CAM), is a popular alternative form of mind-body therapy. Due to higher prevalence of migraine in women and the popularity of yoga among them, in this survey, the effects of this kind of exercise on the frequency, severity, and duration of headache, the impact of headache on patient's life, and the blood NO levels of female patients with migraine have been studied.

Study design and setting

This study was a randomized, controlled trial conducted at the Physiology Research Center, University of Medical Sciences, Isfahan, Iran, from April to June 2012. The Ethical Committee of Isfahan University of Medical Sciences approved the project and the protocol. Filled out the consent form before baseline assessment and randomization.

MATERIALS AND METHODS

Patients were selected from a Neurological Institute under the supervision of a neurologist. All potential subjects were informed that we were conducting a study of migraine treatment that was intended to reduce its negative effects on their personal, family, and social lives. Evaluations (with diagnosis) were performed by neurologists, and detailed case histories were taken by trained interviewers. The criteria for selection of the subjects among the other migraineurs were according to the definition of the International Headache Society (IHS).[23] All the patients were in menstrual age and have not had any experience of yoga training before. They also were under a same pharmacological treatment and did not have any other exercise during the treatment period.

Eighty-five patients agreed to participate in the program. Forty-three patients were excluded. Seventeen of them were excluded as they were receiving different medical treatments. Seven migraineurs were crossed out due to coexisting diseases and nineteen patients did not meet the inclusion criteria. The rest of the migraine patients were accidently divided into two groups (yoga group and control group). A computer-generated random number list allocated patients to either case or control group. In the control group, four patients left the intervention because of worsening of their symptoms, two refused to participate in blood test, and one left the program because our exercise time overlapped with her work schedule. In the experimental group, one patient refused to continue because of drugs' side effects and two patients left the treatment due to unknown reason. Thirty-two patients were finally analyzed. The steps are shown in Figure 1.

Procedure

Patients were informed of the details of the treatment plan. The initial examination and medication were performed by a neurologist who confirmed the diagnosis of migraine. Personal information, family headache history, frequency and duration of headache, and medication were recorded.

Severity of headache

Visual Analogue Scale (VAS) was also used to measure the severity of headache pain. The VAS has been shown to be reliable and valid for measuring pain. It is also applied in different clinical surveys including migraine, low back pain, colon cancer, etc.[24-27] Each subject expresses her headache intensity on a 100-mm VAS that ranges from no pain (0) to very severe pain.[28]

The headache impact test

The headache impact test (HIT-6) was developed to measure a wide range of factors contributing to the burden of headache, and it has shown utility for producing quantitative and pertinent information on

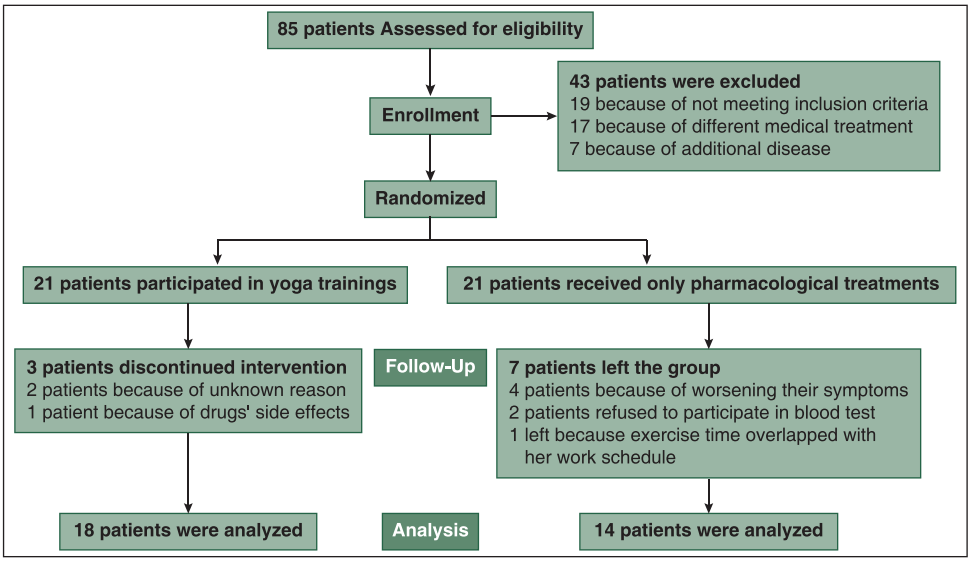

Figure 1: Flow diagram of patient participation through the study

the impact of headache. The HIT-6 consists of six items: Pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. The patient answers each of the six related questions with one of the following five responses: "Never", "rarely", "sometimes", "very often", and "always". These responses are summed to produce a total HIT-6 score that ranges from 36 to 78, where a higher score indicates a greater impact of headache on the daily life of the respondent. Scores can be interpreted using four groupings that demonstrate the severity of impact of headache on the patient's life. Extensive testing has shown the HIT-6 to be highly reliable and internally consistent, and it has been translated into various languages. The HIT-6 also exhibits excellent accessibility and ease of use. Although HIT-6 is a very promising instrument, little data exists for comparing HIT-6 scores with the real amount of disability, which would help in interpreting the results when creating a management plan.[29]

Serum nitrite measurement

The level of serum nitrite (stable NO metabolite) was measured using a colorimetric assay kit (R&D Systems, Minneapolis, MN, USA) that involves the Griess reaction. Briefly, serum was added into wells (96-well enzymatic assay plate). Sulfanilamide solution was added to all experimental samples, and after incubation, *N*-1-naphtylethylenediamine dihydrochloride solution was added. Then, the absorbance was measured using a microreader at 540 nm wavelength. The sample's nitrite concentration was determined on comparing it to a nitrite standard reference curve. The detection limit was 0.25 μM nitrite.

Serum NOx and nitrate measurement

For measuring the total nitrite (NOx) concentration in serum samples, total NO/nitrite/nitrate assay kit (R & D Systems) was used which is based on the enzymatic conversion of nitrate to nitrite by nitrate reductase. The reaction is followed by colorimetric detection of nitrite as an azo dye product of the Griess reaction. Briefly, serum samples were added into wells (96-well enzymatic assay plate). Then equal volume of NADH and dilute nitrate reductase were added to all wells. The samples were incubated for 30 min at 37°C. At the end of this step, nitrate in the samples gets reduced to nitrite. Then the concentration of nitrite in the samples was measured as mentioned above. For determining the nitrate concentration in the sample, the endogenous nitrite concentration was subtracted from the NOx concentration.[30]

Patients were randomly divided into two groups (yoga and control groups). The control group received only medication for 12 weeks and the yoga group was placed in a yoga training program that consisted of three sessions per week (each session 75 min) in addition to the same medical treatment. During 3 months, the control group was under the supervision of a neurologist, medically and mentally. Yoga program was chosen from Hatha yoga Pradipika. It included asanas (yoga movements), pranayama (breathing exercises), and shavasanas (relaxation). Asanas largely dealt with the positions related to head and neck, although lower extremity, arms, and shoulder exercises were also involved. Eye-related exercises, pavanmoktasana, pre-pranayama and pranayama, positions in lying, sitting, and standing status, palming, Neti exercises, and Shavasana were the kinds of exercises which were done under the supervision of a trainer. Surya

namaskar was another part of the program, which includes 12 positions itself, and it is mainly used for warm up, stretch, strength, and increasing flexibility. The protocol details are given in Table 1.

Blood test was performed for all patients in the physiology research center at Isfahan Faculty of Medicine between 8 a.m. and 10 a.m. in a fasting condition. In the first session of exercises, patients were asked to mark their headache frequency during these 3 months in a table to which they were given.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 16.0. All data were normally distributed and presented as mean ± SD. Independent *t*-test was used to compare the mean differences between groups before and after training. Differences of $P \leq 0.01$ were considered significant for all statistical analyses.

RESULTS

The mean age was 35.4 ± 7.9 years in the exercise group and 34.9 ± 8.37 years in the control group. The body mass index (BMI) in the yoga group was 66.8 ± 4.47 and in the control group was 63.8 ± 6.19. When comparing yoga and control groups after 12 weeks, the results showed a reduction in headache severity, frequency, and headache impact on patients' lives after the intervention in the yoga group [Figures 2-4]; however, the changes in the control group were not significant. Duration of headache also reduced after 12 weeks in the yoga group, but the results were not significant [Figure 5]. A non-significant increase was seen in blood NO level in both groups after treatment [Figure 6]. The mean, standard deviation, and independent *t*-test and other results which are related to this study are shown in Table 2.

DISCUSSION

The aim of this research was to investigate the effectiveness of yoga-based intervention on migraine headache and endothelial dysfunction. Although the reduction in duration of headache was not significant in this study, yoga was found to have a beneficial effect on various migraine parameters (frequency, intensity, duration of attack, medication score, and the nature of the pain).[31,32]

Table 1: Details of selected yoga exercises during 3 months

Exercises	Effects on body
Eye-related exercises	Stimulates the nerves of the eye, produces alpha waves in the brain, and calms the mind and body down
Backward bending exercises	Give calmness to the related muscles with a direct effect on the neck and lumbar parasympathetic nervous system
First pavanmoktasana	Rheumatism anti-locker and is the most important method for mind confliction, especially in the area of wrist and ankle. This is the most important method to release blocked energies in the body
Second pavanmoktasana	Carminative. Non-normative nutrition, lack of proper function in digestive system, and other causes related to these disorders, blocks energy in this area, because the concentration of this energy creates a discomfort in head and neck that can lead to headache. Yoga can affect beneficially by removing negative energy.
Third pavanmoktasana	Anti-locker includes 12 main asanas. Regulates hormones and body energy
Pre-pranayama yoga	Increases respiratory volume along with serratus muscle stretching, stimulates the nerves in the region, the alpha wave production in the brain, and causes tranquility
Standing–sitting and lying out screw position	Stretches vertebras, releases blocked energy of the region, and prevents muscle spasm and pain
Palming	Causes facial muscles and eyes getting relaxed, makes relaxation deeper, defeats nervous tension, gives vitality to the skin and eyes, cools the brain down, and helps in depression, stress, and anxiety
Neti exercises	Helps to prevent infection, asthma, bronchitis, chronic pain caused by sinusitis, and chronic diseases, in addition to clearing the facial area. This is one of the most effective methods in treating migraine
Shavasana or relaxation	Done at the end of one session. Different senses are reinforced in different sessions. Auditory sense is reinforced by listening to different sounds in the environment. Touching sense is reinforced by palming, feeling the skin, face and body limbs. The sense of smell is reinforced by movement of air through the nose and diagnoses the odors. Tasting sense also is reinforced by imaging basal tastes.

Table 2: Mean ± SD of the results before and after intervention in the study groups

Groups variable	Yoga group (n = 15)		Control group (n =15)		Significance value	t
	Pre-test Mean ± SD	Post-test Mean ± SD	Pre-test Mean ± SD	Post-test Mean ± SD		
Severity of headache	7.67±1.8	5.27±2.09	6.64±2.01	6.73±2.41	0.002*	−3.561
Headache frequency	5.07±4.77	2.27±1.49	3.72±2.61	5.09±2.98	0.007*	−2.962
Duration of headache (days)	1.67 ±.48	1.4±0.51	2.09±0.07	1.82±0.87	0.98	0.025
Headache impact (HIT-6)	64±10.5	55.67±8.15	64.18±6.4	64.36±5.85	0.001*	−3.741
Blood NO level (μM)	2.34±0.65	2.55±1.63	1.91±0.13	2.02±0.44	0.84	0.2

*Significant difference between two groups, $P < 0.001$

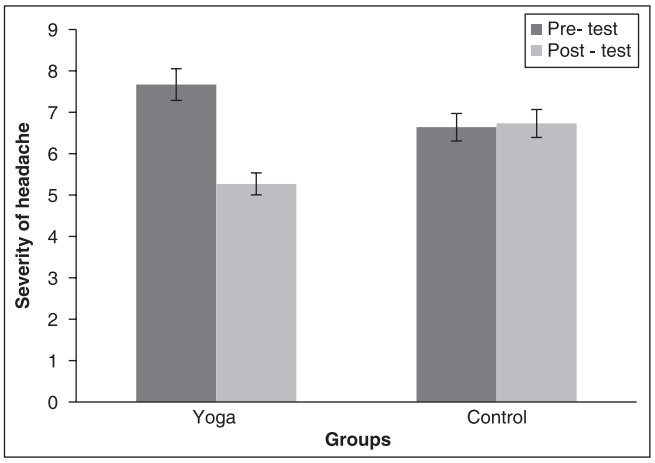

Figure 2: Severity of headache before and after yoga training between yoga and control groups

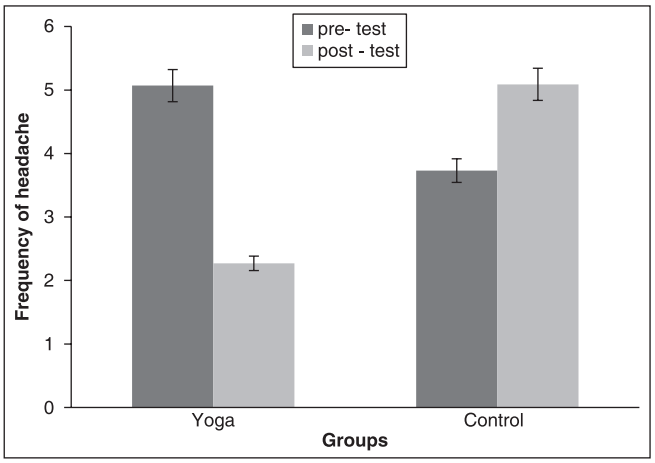

Figure 3: Frequency of headache before and after yoga training between yoga and control groups

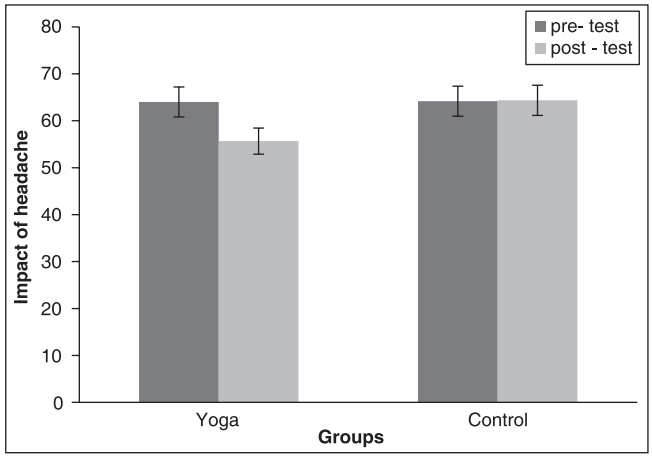

Figure 4: Impact of headache before and after yoga training between yoga and control groups

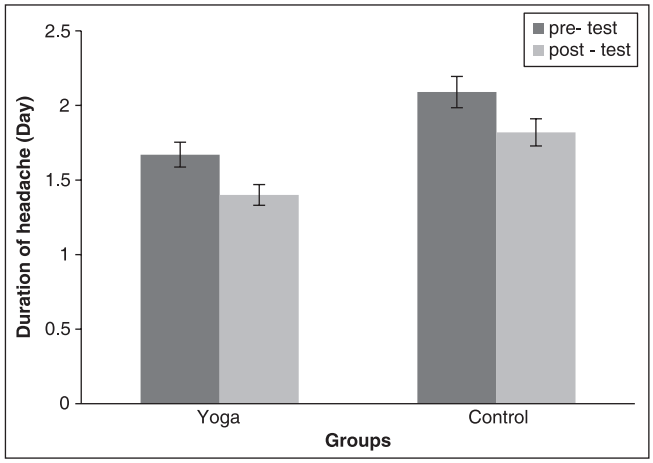

Figure 5: During of Headache before and after yoga training between yoga and control groups

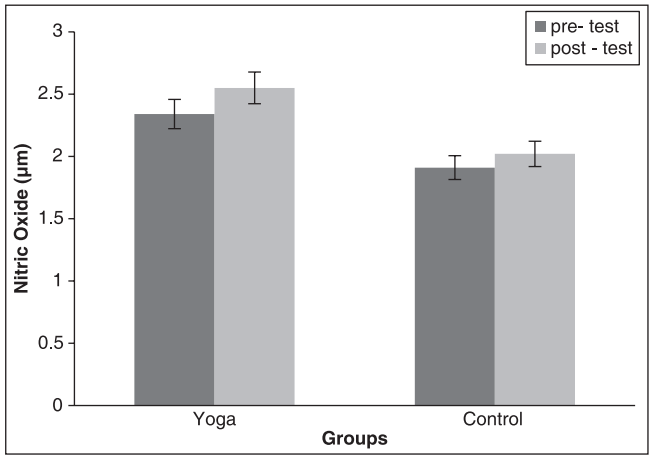

Figure 6: Nitric Oxide before and after yoga training between yoga and control groups

One contemporary theory of how migraines occur states that the arteries that feed the brain narrow temporarily due to a variety of factors, with stress and muscular tension being the two common ones. For a migraine sufferer, there is a sudden shift in the blood vessels and they abruptly dilate, increasing the blood flow to the head. This occurrence results in the severe pain of the migraine episode. If patients can somehow keep their body's nervous system more relaxed daily, the initial narrowing of the blood vessels that predisposes someone to a migraine might be eliminated and the chance of the migraine is minimized.[33-35]

Many surveys and experiments have shown that aerobic exercise significantly leads to cardiovascular fitness improvement, regulates vessel tone regulation, and decreases migraine attacks.[36]

Yoga also affect psychological parameters like anxiety and depression which are the causes of the headache impact on the life of migraine sufferers.[37] Yogic breathing is useful for balancing the autonomic nervous system and has a special influence on psychological and stress-related disorders.[34] Certain

mechanisms which describe a state of calm alertness include increased parasympathetic drive, calming of stress response systems, neuroendocrine release of hormones, and thalamic generators.[32]

If done correctly, yoga can significantly release tensions accumulated around the areas of pain (forehead, temples, neck, and shoulders) and also loosen the tight muscles, especially in the back and neck. Since tight muscles can trigger headaches, yoga could potentially assist.[38]

Nasal water cleansing (Kriya-Jalaneti) which is followed by forced exhalation (Kapalbhanti) goes beyond stimulating and regulating the nerve tone, glands, and organs of the entire nasal and cranial area, including the eyes, sinuses, ears, and cranium.[39]

During pranayama, baseline O_2 consumption increases which could be due to the increased sympathetic stimulation of the adrenal medulla. Since hypoxia is one of the risk factors of migraine, increasing the O_2 consumption by pranayama can be a solution.[40] We suggested that the NO was also increased in our survey, although the levels were not significant. Vascular endothelial function is vital for maintenance of health of vessel walls and for vasomotor control. Regular exercises have been demonstrated to regulate the expression of the endothelial nitric oxide synthase (NOS) gene in the vascular tissue.[41-43] On the other hand, it is also known that relatively intense exercises can provoke migraine headache or worsen it.[44-46] Some investigators have opined that this might be linked to an acute rise in the blood NO level. Some other studies demonstrated increased l-arginine/NO pathway activity in platelets from patients with migraine, and this influence is particularly noticeable during the attacks.[20] The non-significant levels of blood NO in our study may be due to the low intensity of exercises compared with aerobic exercises. So, it is recommended to make a comparative survey between the effects of aerobic exercises and yoga training.

On the basis of above remarks, the mind-body activities in yoga enhance vascular health and promote a feeling of well-being.[47,48] In addition, yoga asanas also improve the body's physical and mental fitness which may help control blood pressure, respiration, and heart and metabolic rates.[49] On the other hand, yoga training helps patients to get over stress and anxiety, the factors which are known to intensify migraine setup, its severity, and also the frequency.[46] Yogic theory and practice lead to increased self-knowledge. This knowledge is not merely that of the practical kind related to techniques, but especially of a spiritual sort pertaining to grasping something about the nature of the self at rest.

CONCLUSION

It is too early to recommend yoga for treatment or prevention of migraines. However, there is some evidence showing that taking up yoga could enhance overall health. It controls the negative impacts of migraine and helps patients lead a healthy lifestyle, be more effective and live happier. It also eliminates the modifiable risk factors for the other diseases.[25]

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