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A RANDOMIZED CASE-CONTROL STUDY ON PLASMA SEROTONIN, NITRIC OXIDE AND FREQUENCY OF MIGRAINE ATTACKS IN PATIENTS, ON PRACTICE OF INTEGRATED AMRITA MEDITATION (IAM) TECHNIQUE

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ABSTRACT **Objective** We focused on the effect of IAM technique on frequency of migraine attacks and neurotransmitters. **Methods** Patients were randomly divided in to IAM and control groups (n = 39 each) using table of random numbers. The frequency of migraine attacks, neurotransmitter levels were assessed at baseline, 3 months, and 6 months of IAM practice regularly. **Results** A reduction in the frequency of migraine significantly was found in the IAM group after 3 months, which sustained for 6 months (p value =0.000) whereas in the control group significant change was not seen. The changes seen in IAM group were statistically significant when compared to the control group after 3 and 6 months (p = 0.065, 0.005). Within IAM group there was an increase in the differences in mean values of plasma levels of serotonin after 3 and 6 months (p =0.001 and 0.002) and decrease in nitric oxide (NO) after 3 and 6 months (p value 0.000). In the control group, there was a significant decrease in the mean values of serotonin (p value0.003 and 0.001) and increase in NO levels after 6 months (p 0.034). When the two groups were compared, there was significant difference between groups in serotonin (p =0.000 and 0.001) and NO values (p value 0.000). **Conclusion** Our study proved that practice of IAM technique regularly can decrease the migraine frequency with increase in serotonin and decrease in nitric oxide levels significantly.

KEYWORDS : Migraine, Serotonin, Nitric Oxide, Yoga, Meditation, IAM

1. INTRODUCTION

Migraine is a severe neurological disease that causes intense discomfort on either side of the head. Migraine symptoms include hemi-cranial pulsating pain, vomiting, and greater responsiveness to sounds and light, with or without transitory neurological symptoms[1].It has been discovered that migraine is the second greatest cause of disability worldwide. [2].Migraine is a common primary headache illness that affects 13% of the world's inhabitants [1].The overall incidence of migraine is higher in women with a female to male ratio 3:1 , while it is more in males than in females before puberty.[3]

Migraine development is heavily influenced by diet and social variables [4] .Since negative emotions such as anxiety, anger, depression, tension and stress can trigger migraine headaches, treatments methods that can help in this regard must be employed. [5]. Preventive therapy can reduce the frequency of migraine attacks. Other benefits are improved response to treatments in acute stages and better patient's cognitive function and reduction of impairments. [6] In preventive methods, non-pharmacological methods such as yoga, massage, acupuncture, etc. are commonly used. Yoga and meditation techniques are beneficial for migraines, as it reduces stress, the most common migraine trigger. Practising meditation and yoga can assist people manage the psychological aspects of persistent pain by lowering stress, anxiety, and tension. When it comes to neurotransmitters, it has already been proven that yoga and meditation can influence their levels in the body. Serotonin is a mood-uplifting hormone and it increases after doing yoga and meditation techniques. [2]Serotonin and nitric oxide have broad functions in our body, and its fluctuations in the body during migraine are evident. Serotonin helps in controlling mood and behaviour, vasoconstriction and vasodilatation, and maintaining activities of different systems of the body, such as neurological functions, respiratory and cardiac health, endocrine, gastro-intestinal tract,genito-urinary and reproductive systems. Low serotonin levels are known to dilate blood vessels and cause migraines.[7]NO also has a significant role in migraine pathogenesis. High levels of NO can cause acute migraine attacks. Some other studies of NO levels in migraine are also found in the literature. Nitric oxide aids general immune defences against viral, bacterial, fungal, and worm diseases, hence preventing inflammation in the body. Nitric oxide enhances respiration and relieves the symptoms of bronchial asthma, and it also modulates the levels of serotonin, norepinephrine, glutamate, and the other key neurochemicals implicated in the neurological process. [8]

1.1. Objectives of the study

We conducted a randomized controlled unblinded trial (RCT) with an objective of evaluating of the effect of the technique Integrated Amrita Meditation (IAM) on the frequency of migraine episodes along with changes in neurochemical levels of serotonin and nitric oxide. We made a long- term follow- up (6 months) for the subjects.

2. MATERIALS AND METHODS

We executed a pilot clinical trial as there was no previous study on the effect of IAM in migraine patients for estimating sample size. According to the study outcomes, the minimum sample size was estimated as 30 in both groups.

Our study got approval from Human Ethics Committee of the institute.96 patients with chronic migraine were initially screened from Amrita hospital with the support of the Neurology Department, and among them, 78 patients volunteered to participate. 17 patients discontinued the study due to personal reasons (9 from IAM and 8 from control) and 61 patients (30 in IAM and 31 in control) completed the study. Age group of study subjects were in the range of 18 -60 years with male female ratio as M: F =15:46. Nobody had undergone any specialised yoga and meditation practices previously and were willing to to participate in the study. Informed consent was taken from them. Patients above 65 years and below 15 years, those with other destructive neurological disorders, those could not perform yogic practises due to muscular or joint pain, pregnant women, , and those who were practising other forms of yoga and meditation were excluded from the research.

2.1. Patient screening and classification procedure

Using a random number table, participants were allocated at random to one of two groups.

Group A consisted of 39 patients who received regular medical care and employed the IAM Technique (test group). Group B consists of 39 patients who obtain only regular medical care and refrain from practising yoga or meditation (control group). Everyone in Group A was taught the IAM technique and told to practise it for twenty minutes every day. Individuals who had been trained in the IAM technique and recognised as teachers by Mata Amritanandamayi Devi delivered the technique. Blood samples were obtained from every subjects in the morning (at 9 a.m.) using vacutainers in order to assess plasma levels

of neurochemicals using enzyme-linked immunosorbent assay (ELISA). The plasma from the bloodstream was separated using a centrifuge, and serum was stored in 2ml storage vials and kept in a deep freezer at minus 80 degrees Celsius. Samples were obtained before the trial began (before any IAM practise was offered to group 1), three months later, and six months later, when the study completed.

Group A participants were given a diary to record their daily practise before the study began. This was done to determine compliance with IAM technique. Good compliance was defined as using the IAM technique at least five times per week. All participants were encouraged to do yoga and meditation on a regular basis and were followed up on for six months. In the IAM group, statistical analysis revealed that compliance was at 82.8%.

2.2. Intervention tool

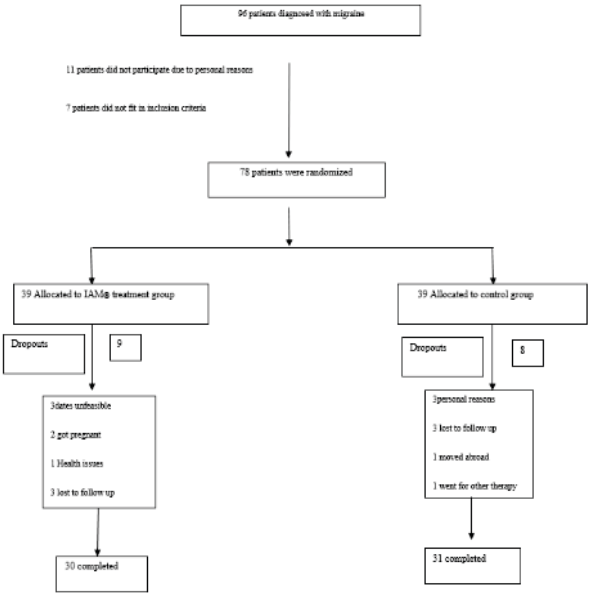
Mata Amritanandamayi Devi, a world-renowned humanitarian, created the IAM technique. It is an intended and copyright-protected synthesis of yoga, meditation, and breathing techniques. The IAM approach includes up to eight minutes of yoga postures, two minutes of tranquilly, and ten minutes of meditation. At the completion of the technique, the patients are required to stay calm for 5 minutes. Anyone can practise the IAM technique, which is taught by certified instructors, for just twenty minutes every day. The method is a blend of conventional, established methods that have been adapted to the cognitive state, time limits, and needs of modern man. Yoga postures, relaxation techniques, exercise for breathing, and awareness of themselves are the main components of the approach. The final part concentrates on the movement of the breath. This strategy is thought to reduce stress and broaden thinking, allowing the individual to be more innovative.[9,10,11,12,13]

2.3. Questionnaires and blood plasma analysis

Migraine headache questionnaire: A questionnaire was developed and standardised, which was used to analyse the frequency of migraine. (Cronbach's Alpha=0.760). The frequency of migraine was assessed by the scale of the number of times in which migraine occurs in a month where numbers are indicated for less than 5 times, 5 times, greater than 8times, and greater than 15 times. The levels of serotonin and nitric oxide in the blood were measured using an enzyme-linked immune absorbent assay (ELISA) kit from Elabsciences of Western Kits Company. For the assays, the supplier's procedure was utilised. [13]

2.4. Statistical analysis

Statistical analysis was done using IBM SPSS 20 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are given in Mean±SD or median (Q1-Q3) and for categorical variables as percentages. To compare the pre and post mean±SD or Median (Q1,Q3) difference of numerical variables between groups, independent sample 't' test was applied for parametric data and Mann Whitney U test for non-parametric data. To compare the mean±SD or Median (Q1,Q3) difference of parameters among the follow up, Paired t test was applied for parametric data and Wilcoxon signed-rank test for non-parametric data. A 'p' value less than 0.05 was considered statistically significant (*P<0.05) and 'p' value less than 0.001 was considered as highly significant (**P <0.001).



3. RESULTS

Table 1 shows the socioeconomic variables of the individuals in both of the study groups. In terms of age, gender, and body weight, the groups proved to be comparable. A questionnaire was developed and standardised, which was used to analyse the frequency of migraine. It was statistically analysed with Cronbach's Alpha=0.760.

3.1. Variation in neurochemicals

Variations in plasma levels of serotonin and NO within the two study groups at different time periods are shown in table 3 and graphically represented in Figure 1 & 2. When the two groups were compared, a significant increase in difference in mean values of serotonin after 3 months (p value=0.000) and after 6 months (p value=0.001) was observed. The difference between the mean values of the baseline visit and after 3 months are -27.016±48.233 ng/ml and after 6 months is -10.907±30.93 ng/ml. A significant decrease in NO after 3 months and 6 months was seen with p value 0.000 between the IAM and control group (Table3). The differences between the mean values of visit after 3 months are 128.00±102.73 µmol/L and after 6 months is 159.316±120.58 µmol/L.

There was an increase in the mean values of plasma levels of serotonin after 3 months from 78.969±77.06 ng/ml to 105.985±109.48 ng/ml (p value=0.001) and after 6 months from 78.969±77.06 ng/ml to 89.876±90.78 ng/ml (p value=0.002) within the IAM® group. Within the same group, NO levels decreased significantly after the 3 month interventional period from 451.276±187.03 µmol/L to 323.276±181.65 µmol/L and after 6 months from 451.276±187.03 µmol/L to 291.959±133.37 µmol/L with p value 0.000. In the control group, there was a significant decrease in the mean values of serotonin from 96.010±120.34 ng/ml to 81.999±101.09 ng/ml (p value=0.003) after 3 months and from 96.010±120.34 ng/mlto 75.666±77.68 ng/ml (p value=0.001) after 6 months. Mean values of NO were found to have increased from 478.073±182.26 µmol/Lto 507.992±185.03 µmol/L after 3 months. After 6 months, a significant increase in NO plasma levels was observed from 478.073±182.26 µmol/L to 506.440±168.99 µmol/L (p value=0.034) (Table 2).

3.2. Variation in frequency of migraine attacks

A significant decrease in frequency of migraine was seen after 3 months from 2.0667±0.907 to1.4000±0.621 and after 6 months from 2.0667±0.907 to 1.3333±0.907 in patients of IAM group with p value 0.000 (Table 4). In the control group, there was no significant reduction in the frequency of migraine after 3 months and after 6 months (Table 4).

When the 2 groups were compared, there was a significant difference in the frequency of migraine after 3 months with p value 0.065and after 6 months with p value 0.005(Table 5).

Table 1: Comparison of socio-demographic characteristics of patients with migraine in the trial of the practise of Integrated Amrita Meditation (IAM) Technique

Socio-demographic characteristics	Groups (mean ±SD)		P value
	IAM (n=30)	Control (n=31)	
Age in years	36.80±9.17	35.80±7.57	0.646
Gender	1.73±0.450	1.77±0.425	0.717
Body Weight in kilograms	61.73±12.44	62.32±12.63	0.855
Height in centimetres	162.13±8.45	158.45±9.18	0.109

Table 2: Plasma levels of serotonin and nitric oxide at different time periods in patients with migraine in the Integrated Amrita Meditation (IAM) group and control group

Variables	Visitm	IAM (n=30)			Control (n=31)		
		Mean± SD	Median (Q1,Q3)	p value	Mean± SD	Median (Q1,Q3)	p value
Serotonin b ng/ml	Baseline	78.969 ±77.06	49.535 (32.200,102.310)	-	96.010± 120.34	59.300 (28.100,122.790)	-
	3	105.985±109.48	71.385 (50.200,126.200)	0.001 **	81.999± 101.09	46.900 (23.285,108.300)	0.003 **
	6	89.876 ±90.78	57.490 (35.260,102.100)	0.002 **	75.666± 77.68	51.520 (24.760,109.500)	0.001 **

Nitric Oxide (NO)µ mol/L	Baseline	451.276±187.03	434.600 (301.660,593.300)	-	478.073 ±182.26	506.430 (368.170, 633.135)	-
	3	323.276±181.65	289.155 (206.500,414.300)	<0.001 **	507.992 ±185.03	493.530 (371.250, 645.140)	0.104
	6	291.959±133.37	271.205 (169.600,391.100)	<0.001 **	506.440 ±168.99	499.310 (415.965, 612.000)	0.034 **

** Statistically significant; m for months

Table 3: Comparison of difference between mean values of plasma levels of neurotransmitters between patients with migraine who regularly practiced Integrated Amrita Meditation Technique (IAMgroup) and control group at different time periods

Variables	Visits m	IAM (n=30)		Control (n=31)		p value
		Mean differences± SD	Median (Q1,Q3)	Mean differences± SD	Median (Q1,Q3)	
Serotonin ng/ml	Baseline -3 months	-27.016±48.233	-10.835 (-25.920,-1.770)	14.011±39.12	11.750 (3.795,21.900)	<0.001 **
	Baseline -6 months	-10.907±30.93	-5.005(-12.680,6.350)	20.344±51.54	8.790 (2.365,17.735)	0.001**
Nitric Oxide µmol/L	Baseline -3 months	128.00±102.73	142.290 (37.200,204.180)	-29.919 ±94.75	-47.870(-109. 580, 42.055)	<0.001 **
	Baseline -6 months	159.32±120.58	168.065 (22.960,272.800)	-28.367±87.43	-45.100(-79. 390,9.780)	<0.001 **

** Statistically significant; m for months

Table 4: Changes of variation in frequency of migraine attacks in patients with migraine in the Integrated Amrita Meditation (IAM) group and control group

Variables	Visits m	Groups (Mean±SD)			
		IAM (n=30)	p value	Control (n=31)	p value
Frequency	Baseline	2.0667± 0.90719	-	2.2258± 1.02338	-
	3	1.4000± 0.62146	<0.001**	1.9677± 0.94812	0.133
	6	1.3333± 0.90719	<0.001**	2.0323± 0.91228	0.110

** Statistically significant; m for months

Table 5: Changes of variation in frequency of migraine attacks in patients with migraine who regularly practiced Integrated Amrita Meditation Technique (IAM group) and control group at different time periods

Variables	Visits m	Groups (Mean± SD)		p value
		IAM (n=30)	Control (n=31)	
Frequency	Baseline	2.067±0.907	2.226±1.023	-
	3	1.400±0.622	1.968±0.948	0.065**
	6	1.333±0.606	2.032±0.913	0.005**

** Statistically significant; m for months

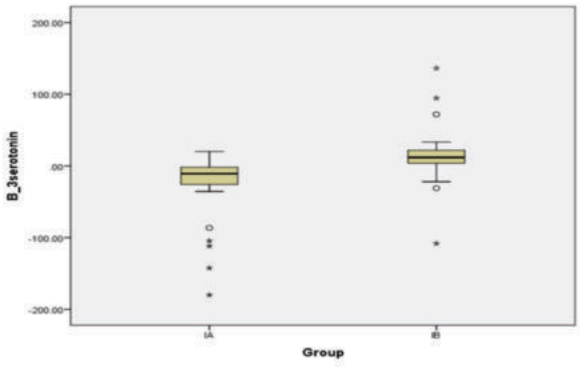


Fig 1: Plasma levels of serotonin

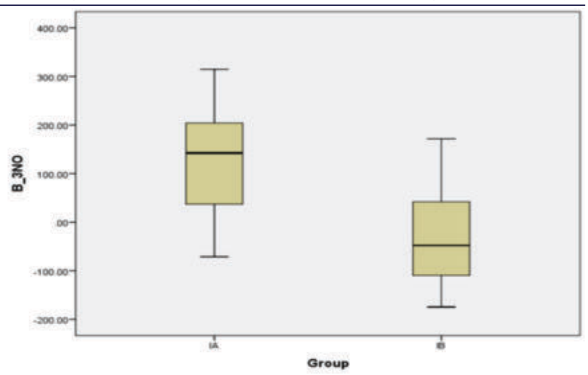


Fig 2: Plasma levels of nitric oxide

4. DISCUSSION

The present research was done to determine the effect of IAM technique on the frequency of migraine and changes in serotonin and NO on comparing with the control group. The socio- demographic characteristics of the study participants were equitable on the basis of gender, age, and weight (Table1). Our study was RCT and comparison between the groups was done based on the percentage changes. The results obtained from this study found a significant reduction in migraine frequency in the IAM group after 6 months of intervention (Table 4). Long-term follow-up studies in migraine are uncommon, which distinguishes our study. The current study result is consistent with other previous study results where patients who received meditation had improvements in discomforts associated with headache-, standard of life, management of pain, and frequent attacks of pain and uneasiness. [2]Even though many yoga and meditation studies have been done on migraine, ours is significant because of the special features of the tool- the IAM technique. It is a fusion of yogic postures in standing, sitting, and lying positions and can be considered as a capsule form of Ashtanga yoga along with meditation and pranayama. It is taught free throughout the world by trained IAM instructors. So the reproducibility of this technique adds more value to the relevance of this study.[11]Spiritual meditation can help to reduce usage of medications including analgesics. The benefits of analgesic usage reduction include decrease in medication-overuse headaches and its addiction and also helps to lower expenses related with it.[14]This can be done at all stages of migraine and ensures a long- term benefit. Our primary aim is to give relaxation to the patients through the act of yoga and meditation, as symptoms of migraine reduces along with the stress. People interested in yoga and meditation practises will benefit greatly from the proper application of the IAM technique. In a previous study, the author, Anand Kumar,etal., found that proper yoga and meditation practise give us a state of calm state to the mind by suppressing stress response systems , increases parasympathetic drive and influences release of neuroendocrine hormones.[15] Another study of the effect of yoga on migraine using clinical profile and cardiac autonomic functions observed that yoga has shown a reduction in blood pressure and stress levels of patients, facilitating vasodilatation and their migraine symptoms were also reduced which was also observed, in our study results too .

The percentage differences of serotonin and nitric oxide from baseline to 6 months were compared between IAM and the control group, and variations were seen in serotonin and NO. (Table 2&3). In this study, we observed that after the IAM technique, serotonin levels increased and migraine pain subsided. (Table2&3). Similar study results were observed in our pilot study.[13] According to a previous study author Milan Aggarwal, **said** about the pain initiating events by neurotransmitters that take place in the trigeminovascular system. It has been found that serotonin vasoconstricts the nerves and blood vessels and affects nociceptive pain.[2] The serotonin agonists promote vasoconstriction and block pain pathways in the brain. [16] Dilatation of blood vessels occurs due to low levels of serotonin and can result in migraine. Insufficient serotonin due to changes in its production and release as well as receptor function in the brain and throughout the body may contribute formation migraine.[17]. Here, by the mechanism of yoga and meditation, the values of serotonin always rise and prevent the attack and causes of migraine, which was evident from our results also. So, in this manner, treatment can be given to its root cause.[2]Some other studies postulate that increased serotonin levels may result in migraine. Their result, which are in contrast with the current

hypothesis that migraine is a syndrome of low brain serotonin levels.[18] However this type of serotonin level variations was not observed in our study. We observed better results in migraine symptoms when serotonin values were raised.

Nitric oxide levels were found to be reduced after the IAM technique and thus helped in alleviating the pain of patients with migraine in the current study. (Table 2 &3). NO can provoke migraine attacks and its duration. Previous studies proved that inhibition of NO synthases (NOS) is effective in the acute treatment of migraine headache, which is consistent with our study results. .In that study of NO on migraine headaches, the author JesOlesen clearly concluded the presence of high levels of NO in migraine patients after studying on migraine.[19]Similarly in another study of NO, its role in stress, memory, and psychologycal impairments of chronic migraine has been explored. Migraine patients may have impaired memory, visual and verbal problems, absent- mindedness, and low attention. Inhibition of NO can reverts the condition. Similarly, here in our study, we observed that yoga and meditation help in overcoming stress and NO levels and thus help in alleviating migraine symptoms.[20]In another study, the author hypothesised that NO, may help in reducing migraine attacks[21] This study supports the statement that increased levels of NO can reduce migraine symptoms, but which was not observed in our results. In our study results we observed increased serotonin levels and decreased NO levels after migraine relief through the consistent practise of IAM technique.

5. CONCLUSION

This study concluded that practise of IAM technique on a regular basis can decrease the frequency of migraine attacks and is also associated with increase in plasma levels of serotonin and decrease in nitric oxide significantly. We strongly recommending the practice of IAM regularly as a preventive and holistic treatment method for patients with migraine headache.

6. Limitations

We could not track the changes in medicine intake in the migraine patients during the study. Here we only assessed the variation in frequency, serotonin and nitric oxide that are observed in the migraine patients irrespective of the medicines they had taken. More scientific studies need to be done in future to check the stress management strategies such as yoga and meditation in migraine management and thereby can confirm the role of further parameters in migraine pathology and which in turn help in its treatment techniques.

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8. Authors' contribution:

The contribution of Vandana Balakrishnan, the Principal investigator of the project, includes the development of the idea for research topic , conduct of the study , manuscript draft and writing. Contribution of Anand Kumar includes development of concept, method, and manuscript review. Contribution of Aryalakshmi includes data collection, literature search ,the conduct of the study, and manuscript writing. The contribution of Greeshma CR includes statistical data analysis of the study.

9. Conflicts of interest: The authors have no conflicts of interest.

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List of abbreviations

IAM:Integrated Amrita Meditation

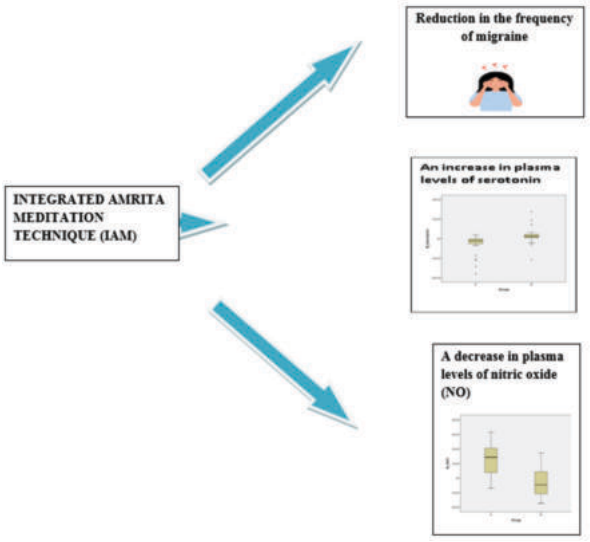
NO:Nitric Oxide

ELISA: Enzyme-Linked Immune Sorbent Assay

Highlights

- This stands first study about the Integrated Amrita Meditation (IAM) Technique in migraine patients on the frequency of migraine attacks and plasma levels of serotonin and nitric oxide
- We observed significant improvement in values of serotonin and nitric oxide after 3 months which sustained till 6 months of IAM practise in migraine patients
- The frequency of migraine attacks of patients found to be significantly reduced after regular practise of IAM Technique.

Graphical abstract -



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