

## A RANDOMIZED CASE-CONTROL PILOT STUDY ON THE NEUROCHEMICAL BASIS OF PAIN MODULATION IN PATIENTS WITH MIGRAINE, WHO PRACTICED INTEGRATED AMRITA MEDITATION TECHNIQUE

VANDANA BALAKRISHNAN<sup>1\*</sup>, ANAND KUMAR<sup>2</sup>, ARYALAKSHMI CS<sup>1</sup>, MRUDULA M<sup>1</sup>, RENJU RAJAN<sup>1</sup>,  
GREESHMA C RAVINDRAN<sup>3</sup>

<sup>1</sup>Department of Physiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India. <sup>2</sup>Department of Neurology, Amrita Institute of Medical Sciences, Kochi, Kerala, India. <sup>3</sup>Department of Statistics, Amrita Institute of Medical Sciences, Kochi, Kerala, India.  
Email: vandanabalakrishnan@aims.amrita.edu

Received: 19 January 2022, Revised and Accepted: 25 February 2022

### ABSTRACT

**Objective:** The objective of the study was to determine the changes in duration and intensity of headache and associated changes in the plasma levels of neurochemicals, serotonin, glutamate, vasoactive intestinal peptide (VIP), and nitric oxide (NO) in patients with migraine after 6 months of regular practice of integrated Amrita meditation (IAM).

**Methods:** Sixteen patients aged 18–50 with migraine were randomly assigned to 2 groups, one with standard medical care and IAM, and the other only standard medical care. Data were collected before IAM, after 3 and 6 months of IAM practice.

**Results:** After 6 months, a significant decrease in the duration of headache from 2.4±0.54 to 1.4±0.54 (p=0.034) hours and intensity of pain from 3.6±0.54 to 2.6±0.89, (p=0.035) was seen in patients who practiced IAM. Plasma levels of serotonin within the IAM group increased (47.29±26.85 to 53.85±29.73ng/ml), where as there was decrease in glutamate (38.47±8.2 to 29.68±12.57µg/ml), VIP (28.01±13.64 to 22.23±7.79pg/ml) and NO levels (642.26±167.42 to 423.18±97.96µmol/L). A correlating trend was seen in comparison with control group after 6 months showing a statistically significant difference in plasma Serotonin (p value 0.007) and NO (p value-0.023) levels.

**Discussion:** The results of our study have been discussed with other migraine and meditation-related studies.

**Conclusion:** Regular practice of IAM reduces the intensity and duration of headache in migraine patients and is associated with alterations in the neurotransmitter levels.

**Keywords:** Headache, Migraine, Yoga, Meditation, Neurotransmitters.

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### INTRODUCTION

Migraine is a common neurological disorder characterized by recurrent attacks of debilitating pulsating headache with varying intensity. The headache which can be triggered by several factors may last for several hours or days and is aggravated by physical activity [1].

More than 213 million people in India were found to be suffering from migraine. Sixty percent of them were reported to be women. An increase in migraine cases was reported among people of the lower socioeconomic status. Patients with migraine have an increased risk for mental illness and other comorbid illnesses [2].

Migraine headaches are associated with depressive and anxiety symptoms which can affect pain tolerance and positive feelings towards life. Stress is recognized to be a primary trigger for migraine attacks and a factor that can aggravate the intensity, duration as well as frequency of migraine attacks. Yoga and meditation are considered to reduce the negative traits associated with migraine headaches and also to aid in the decrease of stress, anger, tension, depression, and anxiety, as well as to improve the quality of life in patients with migraine [3]. An earlier study found that regular practice of Yoga helps in the reduction of headache [4].

We present here the effect of regular practice of a technique Integrated Amrita Meditation (IAM) on the duration and intensity of headache in

patients with migraine. Given the known alterations in the plasma levels of serotonin, glutamate, vasoactive intestinal peptide (VIP), and nitric oxide (NO) in patients with migraine, we have analyzed the relationship between the observed improvement in headache in patients with the changes in the blood levels of the neurochemicals before and after IAM practice.

### METHODS

Our study comprised of a randomized controlled unblinded trial aimed at evaluation of the impact of a technique IAM, on the duration and intensity of migraine episodes. IAM® technique was designed by the world-renowned humanitarian Mata Amritanandamayi Devi (MAM).

Since there has been no earlier study on the effect of IAM in patients with migraine, we conducted a pilot trial. Our study was approved by the Institutional Human Ethics Committee. Sixteen patients with chronic migraine were selected after the initial screening of 30 patients. Study subjects were in the age group of 18–50 years (males: Females=6:10). None of them had previously undergone any specialized yoga and meditation practices and they volunteered to participate in the study. Patients with other concomitant neurological disorders and those who were unable to perform yoga due to muscle or joint pain were excluded from the study. Subjects were randomly assigned to two groups using the table of random numbers. Group 1 consisted of seven patients receiving standard medical care and who practiced the IAM Technique (test

group). Group 2 consisted of patients receiving only standard medical care and not practicing either yoga or meditation (control group). All those in Group 1 were trained to practice the IAM technique and were advised to practice IAM for twenty minutes every day. IAM technique was taught by individuals who were well versed with the technique and approved as teachers by MAM. The study design is represented in Fig. 1.

Blood samples were collected in morning (at 9 AM) from all participants for analysis of plasma levels of serotonin, glutamate, VIP, and NO by enzyme-linked immune absorbent assay (ELISA using commercial kits of Elabsciences of Western kits company). The manufacturer's protocol was followed for the assays. Patients were instructed not to consume coffee or tea from the previous night of sample collection. They were also asked to relax for 5 min before the collection of blood samples. Samples were collected before initiation of the study (before any training was given to group 1), after 3 months, and at 6 months when the study concluded. Plasma was separated and stored at minus 80°C in a deep freezer.

Before initiation of the trial, Group 1 participants were given a questionnaire and a diary for self-recording daily practice, to assess compliance to IAM. Practicing IAM at least 5 times/week was taken as good compliance. The *migraine headache questionnaire* was a standardized pro forma to assess the history, frequency, duration, and severity of migraine. The intensity of pain was assessed by visual analog scale where numbers are indicated for mild, moderate, and severe ranges of migraine headache. Duration of pain was assessed by the scale of time in hours where numbers are indicated for 2 h, 4 h, 12 h, and 24 h.

All participants were motivated by frequent phone calls to practice yoga and meditation regularly and followed up for a total duration of 6 months.

#### 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 test statistical significance Student's "t" test was applied for parametric data and the Mann-Whitney U test non-parametric data. For comparison of numerical variables between groups and post-trial, paired t-test was applied for parametric data and Wilcoxon signed-rank test for non-parametric data.  $p < 0.05$  was considered statistically significant. ( $*p < 0.05$ ) and  $p < 0.001$  was considered as highly significant ( $**p < 0.001$ ).

## RESULTS

Socio-demographic characteristics of the participants in both study groups are given in Table 1. The groups were found to be comparable in age, sex, and body weight. A standardized questionnaire was used to analyze intensity and duration (Cronbach's Alpha=0.760).

Changes in blood levels of neurotransmitters within the two study groups at different time periods are given in Table 2 and graphically represented in Figs. 2-5. When the two groups were compared, a significant increase in serotonin ( $p=0.050$ ), and decrease in glutamate ( $p=0.010$ ), and NO ( $p=0.023$ ) were seen in Group 1 (Table 3). Within Group 1, NO levels decreased significantly after intervention ( $p=0.018$ ) (Fig. 3). There was an increase in the mean values for the plasma levels of serotonin (Fig. 2) (though not statistically significant) and a decrease in the mean values for levels of glutamate, (Fig. 5) and VIP (Fig. 4) before and after the practice of IAM. These differences are associated with the significant changes in the intensity and duration of migraine with IAM practice. Continuous practice of IAM for 3 months resulted in lowering plasma levels of glutamate, NO, and VIP. After regular practice of IAM for a period of 6 months, glutamate NO and VIP levels in plasma dropped significantly (Table 3).

In the control group, there were no consistent changes in the plasma levels of glutamate, VIP, and NO either at 3 months or after 6 months. Between the two groups, significant changes in the plasma levels of serotonin ( $p=0.007$ ), glutamate ( $p=0.013$ ), and NO ( $p=0.025$ ) were observed (Table 3).

#### Physiological and psychological variables

A significant difference in intensity of migraine was seen both after 3 months and after 6 months in subjects of Group 1 (Table 4). A significant drop was seen in the duration of headache in Group 1 after 6 months of IAM practice. In the control group, there was no significant reduction in either intensity or duration of migraine after 3 months and after 6 months (Table 4).

Graphical representation of the changes in plasma levels of neurotransmitters in patients with migraine who regularly practiced IAM Technique (IAM group) and control group at different time periods.

There is significant changes in NO with  $p=0.023$  between IAM and control groups. NO value significantly decreased in test groups 642.26–492.24  $\mu\text{mol/L}$  with  $p=0.018$  after IAM intervention. In control group, NO slightly decreased from 570.23 to 542.16  $\mu\text{mol/L}$ .

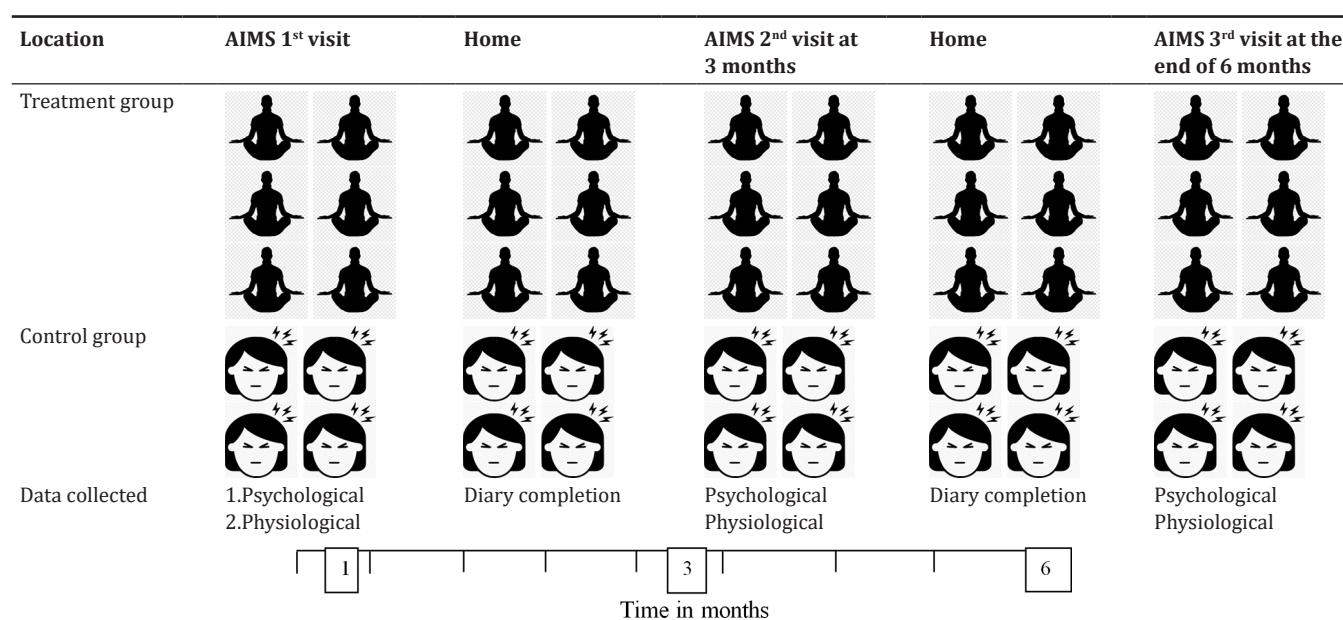


Fig. 1: Schematic representation of the study design in the trial of Integrated Amrita Meditation technique in patients with migraine

## DISCUSSION

We report for the first time that the practice of IAM can reduce the intensity and duration of headache in patients with migraine and that the effect is possibly mediated by alterations in the plasma levels of neurotransmitters such as serotonin, glutamate, NO, and VIP. Our observation is significant given that migraine is a common neurological disorder with recurrent attacks of severe headache and that there is a paucity of effective preventive strategies. Current medications though effective in relieving headaches are known to cause drug dependence or lead to tolerance on continuous usage. Patients with migraine who are on regular medications also have sleepiness and fatigue, racing heartbeat, nausea, and difficulty in thinking as common side effects [5]. Pain killer headache is a secondary headache disorder that commonly develops from the overuse of acute medication to treat migraine attacks [6].

Several forms of alternative medicine therapies which include acupuncture and yoga are on trial as preventive strategies for migraine.

**Table 1: Sociodemographic characteristics of patients with migraine in the trial of the practice of Integrated Amrita Meditation technique**

Sociodemographic characteristics	Mean±SD		p
	IAM (n=7)	Control (n=9)	
Age in years	31.78±9.052	31.00±6.982	0.841
Gender	1.22±0.411	1.11±0.333	0.555
Body weight in kilograms	53.11±10.289	56.22±14.627	0.609

IAM: Integrated Amrita Meditation, SD: Standard deviation

**Table 2: Plasma levels of neurotransmitters at different time periods in patients with migraine in the trial of the practice of Integrated Amrita Meditation technique**

Variables	Visits (months)	IAM group (n=7)			Control group (n=9)		
		Mean±SD	Median (Q1-Q3)	p	Mean±SD	Median (Q1-Q3)	p
Serotonin (ng/ml)	Baseline	47.29±26.858	37.200 (34.05-37.20)	-	31.88±8.079	28.300 (27.30-34.50)	-
	3	83.29±57.127	72.810 (39.60-109.90)	0.237	21.97±4.513	22.260 (18.94-25.35)	0.008**
	6	53.85±29.737	58.000 (27.62-69.20)	0.612	22.76±4.041	23.710 (20.40-25.30)	0.008**
Glutamate (µg/ml)	Baseline	38.47±8.231	41.350 (37.35-42.63)	-	21.77±13.627	17.540 (15.29-36.80)	-
	3	36.51±7.173	38.510 (33.31-38.51)	0.866	27.44±17.022	23.020 (17.50-41.63)	0.011*
	6	29.684±12.507	29.140 (21.69-34.16)	0.091*	27.163±11.43	31.790 (16.10-33.45)	0.260
NO (µmol/L)	Baseline	642.26±167.422	646.200 (578.50-646.40)	-	570.23±118.0	577.700 (524.30-671.50)	-
	3	492.24±235.345	376.600 (351.15-376.60)	0.018**	542.16±87.57	500.000 (439.50-618.40)	0.441
	6	423.17±97.968	391.200 (348.6-483.2)	0.018**	540.59±88.30	604.500 (439.50-608.40)	0.594
VIP (pg/ml)	Baseline	28.01±13.640	26.120 (21.20-27.61)	-	22.20±7.878	21.830 (15.40-25.16)	-
	3	27.50±3.587	25.840 (19.35-29.24)	0.866	22.96±6.316	21.210 (15.07-24.31)	0.678
	6	22.23±7.793	21.780 (17.43-25.13)	0.735	18.32±2.424	19.070 (17.10-19.92)	0.086

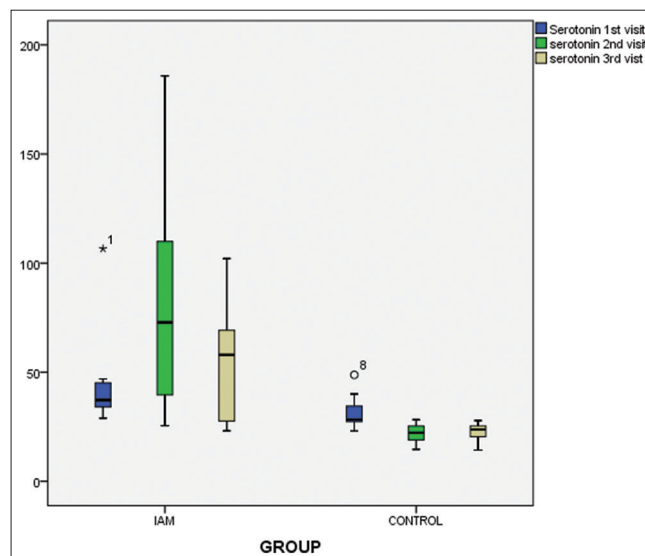
\*Statistically significant, \*\*Statistically significant. NO: Nitric oxide, VIP: Vasoactive intestinal peptide, IAM: Integrated Amrita Meditation, SD: Standard deviation

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

Variables	Visits months	IAM group (n=7)		Control group (n=9)		p
		Mean±SD	Median	Mean±SD	Median	
Serotonin (ng/ml)	Baseline	47.29±26.858	37.200 (34.05-45.10)	31.88±8.079	28.300 (27.30-34.50)	0.050*
	3	83.29±57.127	72.810 (39.60-109.0)	21.97±4.513	22.260 (18.94-25.35)	0.004**
	6	53.85±29.737	58.000 (27.62-69.20)	22.76±4.041	23.710 (20.40-25.30)	0.007**
Glutamate (µg/ml)	Baseline	38.47±8.231	41.350 (37.35-42.63)	21.77±13.627	17.540 (15.29-36.80)	0.010**
	3	36.51±7.173	38.510 (33.31-41.23)	27.44±17.022	23.020 (17.5-41.63)	0.427
	6	29.684±12.50	29.140 (21.69-34.16)	27.163±11.4339	31.790 (16.10-33.45)	0.874
NO (µmol/L)	Baseline	642.26±167.42	646.200 (578.5-696.6)	570.23±118.056	577.700 (524.3-671.5)	0.339
	3	492.24±235.34	376.60 (351.1-638.4)	542.16±87.578	500.00 (488.7-618.4)	0.427
	6	423.17±97.968	391.200 (348.6-483.2)	540.59±88.300	604.500 (439.5-608.4)	0.023**
VIP (pg/ml)	Baseline	28.01±13.640	26.120 (21.21-27.61)	22.20±7.878	21.830 (15.40-25.16)	0.223
	3	27.50±13.587	25.840 (19.35-29.24)	20.96±6.316	21.210 (15.07-24.31)	0.266
	6	22.23±7.493	21.780 (17.43-25.13)	18.32±2.424	19.070 (17.10-19.92)	0.223

\*Statistically significant, \*\*Statistically significant. NO: Nitric oxide, VIP: Vasoactive intestinal peptide, IAM: Integrated Amrita Meditation, SD: Standard deviation

They aim at treating a person as a whole, rather than treating the symptoms of disease and at complete alleviation of the disease with minimal complications or side effects. Several earlier observational studies have suggested the effectiveness of psychological therapy in patients with migraine, specifically with respect to behavioral therapy in the management of headache secondary to the overuse of migraine drugs [7].

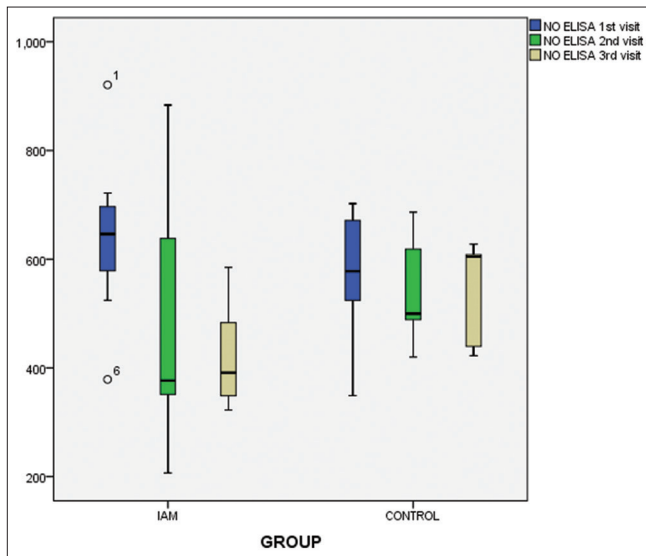
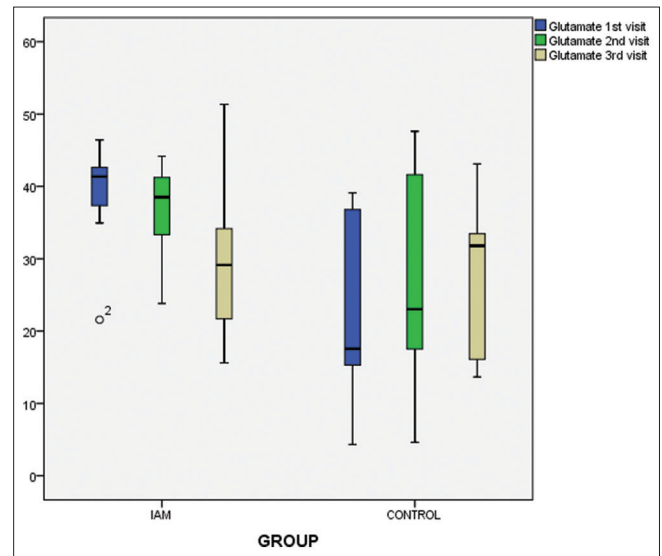
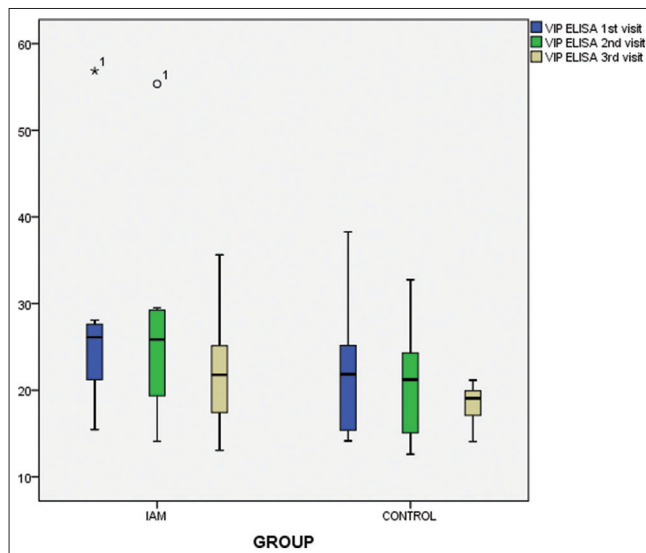


**Fig. 2: Plasma levels of serotonin**

**Table 4: Changes of physiological and psychological variables in patients with migraine who regularly practiced Integrated Amrita Meditation Technique (Integrated Amrita Meditation group) and control group at different time periods**

Variables	Visits (months)	IAM group (n=7), mean±SD	p	Control group (n=9), mean±SD	p
Pain intensity	Baseline	3.600±0.548	-	3.222±0.667	-
	3	2.600±0.894	0.034**	2.778±0.667	0.034**
	6	2.600±1.341	0.089	2.778±0.667	0.035**
Duration	Baseline	2.400±0.548	-	2.111±0.928	-
	3	2.000±0.707	0.178	1.778±0.833	0.195
	6	1.400±0.548	0.034**	1.778±0.833	0.195

\*\*Statistically significant. IAM: Integrated Amrita Meditation, SD: Standard deviation

**Fig. 3: Plasma levels of nitric oxide****Fig. 5: Plasma levels of glutamate****Fig. 4: Plasma levels of Vasoactive intestinal peptide**

Behavior therapy such as yoga and meditation has been shown to control blood pressure, respiratory rate, and heart rate, as well as improve the response to several medicines [8]. In the study reported here, we investigated whether the regular daily practice of yoga and meditation can relieve symptoms of migraine as stress is a known primary triggering factor for migraine headache.

The IAM technique which we evaluated for its effectiveness in patients with migraine involves yogic postures, breathing exercises, and

meditation, all of which can be practiced easily within 20 min and thus followed in the modern fast-paced life. In a study of the effect of IAM in normal healthy individuals, it was seen that its practice induces significant changes in an individual's attitude toward stress and also lowers blood levels of adrenaline and cortisol [9-11]. Significant changes were also seen in the heart rate and blood pressure of diabetic patients who practiced IAM [9-11]. IAM practice is also helpful in lowering anxiety and depression in young individuals. Given the potential role of the IAM technique in stress management; we sought to determine the effect of IAM in reducing the severity of headache in patients with migraine.

The mechanism of pain and vascular changes in migraine is unknown. Electrophysiological, clinical, and pharmacological studies suggest central and peripheral sympathetic hypofunction in migraine. Altered plasma and platelet levels of glutamate, serotonin, vascular intestinal polypeptide, and NO have been reported in patients with migraine. Glutamate is an excitatory neurotransmitter in the central nervous system and is speculated to be involved in mechanisms of migraine headache. Low serotonin levels dilate blood vessels and initiate migraine and also cause cerebral artery spasm with enhanced release of pain intermediaries [12]. Migraine also involves the release of various vasoactive peptides, which may be involved in the initiation of a migraine attack [13]. Higher NO production, significantly lower serotonin content, and higher levels of intracellular calcium have been reported in patients affected by chronic daily headaches [14]. Interestingly, regular practice of yoga and meditation was found to lead to changes in the blood levels of these neurotransmitters involved in migraine pathogenesis in patients with migraine.

We have found a significant reduction in the intensity and duration of migraine headaches in patients who practiced IAM for 3 months. The effect sustained for 6 months. Wells *et al.* had hypothesized that mindful meditation may have a greater effect on affective (pain



unpleasantness) and sensory (pain intensity) aspects of pain. According to them, meditation may strengthen cognitive and affective regulation of nociceptive input by mind control training causing decreased nociception [15]. Stress has a direct effect on patients with migraine and acts as a triggering factor as well. Stress prevention can reduce the frequency of migraine headaches [15]. We have observed that the frequency of migraine attacks can be reduced after IAM practice.

Kakigi *et al.* reported that the decreased activity in the thalamus during meditation may be because of the inhibitory action of meditation-induced brain activity on spinal nociceptive neurons. Their study indicated that a person well versed in yoga did not feel pain during meditation [4]. We also found a significant reduction in the duration and intensity of migraine headaches after the continuous practice of IAM meditation.

During migraine, serotonin levels are reported to be reduced. The practice of yoga and meditation can increase serotonin levels [16]. Our study indicates that IAM helps to increase blood levels of serotonin and thus in the control of migraine. Increased serotonin production is considered to aid the treatment of depression as well (Journal of Psychiatry and Neuroscience).

Glutamate levels are higher in the brain and blood circulation in patients with migraine, especially during migraine attacks [12]. We observed a decrease in glutamate levels after regular practice of IAM. Since the practice of IAM decreases glutamate levels, the technique could regulate migraine symptoms as well. An earlier study indicated that the practice of yoga postures is associated with increased brain gamma aminobutyric acid (GABA) levels and that increased thalamic GABA levels are associated with improved mood and decreased anxiety [17]. Another study revealed that GABA levels were increased in long-term practitioners of IAM [5].

Vasoactive peptides activate receptors that are expressed on smooth muscle cells and have a crucial role in the increase of intracellular cAMP, leading to the opening of potassium channels, and vasodilatation in patients with migraine [14]. The reduction in the levels of plasma VIP after IAM practice as observed in our participants reveal that IAM may modulate vasodilatation of cranial arteries during migraine attacks. The changes in VIP levels in plasma before and after meditation practice have not been evaluated earlier.

NO is involved in initiating as well as maintaining migraine and hence NOS inhibition is proposed as a treatment for chronic tension-type headache and for migraine [10]. IAM practice is found to reduce NO levels in patients with migraine. Despite the limitation that our study involved a small number of patients, our findings indicate the beneficial role of IAM in reducing the severity and duration of migraine headaches and also the possible mechanisms involving neurotransmitters.

## CONCLUSION

Our study reveals that regular practice of an IAM Technique can reduce the intensity and duration of migraine attacks is associated with beneficial alterations in plasma levels of neurotransmitters. We recommend a regular practice of IAM as a complementary management strategy for patients with migraine.

## ACKNOWLEDGMENTS

We acknowledge Dr. CC Kartha, Adjunct Professor, Amrita School of Medicine for his support and valuable suggestions.

## AUTHORS' CONTRIBUTIONS

Vandana Balakrishnan is the Principal investigator of the project. The idea of the research topic and manuscript draft and conduct of the study are her contributions; Anand Kumar contributed patient support; and

Aryalakshmi contributed towards conduct of the study, manuscript writing and literature search; Mridula and Renju Rajan contributed to data collection and Greeshma CR contributed to data analysis.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest.

## AUTHORS FUNDING

The authors acknowledge the financial support received from the Ministry of AYUSH, the Government of India for their support and encouragement in carrying out this research work.

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