Research Article

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Magnesium Levels in Migraine and Combination of Folic Acid and Magnesium in Migraine

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Abstract

Background: *Migraine is a functional disorder of the brain. Different mechanisms including modulation of central and peripheral pain structures have been described. Few studies have revealed decreased levels of the micronutrients riboflavin, magnesium and coenzyme in plasma and in the brain of migraine patients. Nutritional deficiency could play a role in the pathophysiology of migraine. Patient not able to tolerate chemical drugs can have beneficial effect by nutritional supplementation.*

Keywords: Migraine, Magnesium, Folic Acid, HIT

List of Abbreviations

CGRP - Calcitonin gene-related peptide
FA Folic acid
HA - Headache
HIT - Headache Impact test
NSAIDS - Nonsteroidal anti-inflammatory drugs
NMDA - N-methyl-D-aspartate glutamate receptors
MG - Magnesium

Introduction

Migraine is a functional disorder of the brain. Different mechanisms including modulation of central and peripheral pain structures have been described .Patients typically experience episodes of unilateral throbbing headaches with varying intensities. Frequently accompanied symptoms are nausea, vomiting phonophobia and/or photophobia [1].

Acute attacks are treated with different analgesics or trip tans. Preventive medications are taken by minority of patients. It should be considered when the quality of life is severely impaired, when two or more attacks occur per month, when migraine attacks do not respond to acute drug treatment or in case of intolerance or side effects of acute treatment [2]. It is mainly used to decrease the frequency, duration and severity of migraine attacks.

The guidelines recommend primarily beta-blockers, flunarizine, antiepileptic's (topiramate or valproic acid), and antidepressants (e.g. amitriptyline) for migraine prevention [3,4]. Vitamin B2 (riboflavin), magnesium and coenzyme Q10 are alternatives to drugs and appeal to patients with a desire for more natural treatment. In addition, micronutrients are seen by the patients as a "mild" form of treatment with no or minor side effects [5,6].

Few studies have revealed decreased levels of the micronutrients riboflavin, magnesium and coenzyme in plasma and in the brain of migraine patients [7-9]. A deficit of these nutrients could play a role in the pathophysiology of migraine. Mitochondrial dysfunction is considered as one of theories causing migraine [10,11]. Riboflavin, magnesium and coenzyme Q10 play an important role in the mitochondrial energy production [12]. Magnesium is needed in various physiological processes like vasoconstriction, platelet inhibition, secretion of serotonin which might influence in pathophysiology of migraine. It acts as co factor for ATP production and is NMDA-channel antagonist which is involved in the regulation of neuronal excitability. Folic acid is also required in the transport and functioning of the system. Concurrent Folic acid and magnesium work in tandem to promote normal function of the nervous system and normal psychological function , contribute to energy yielding metabolism leading reduce tiredness and fatigue .Other nutrients like riboflavin is also essential for electron-transport in the mitochondrial membrane. Based on these observations, it seems plausible that a substitution of these micronutrients in migraine patients might be able to prevent or reduce the intensity of migraine attacks.

The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on ability to function on the job, at school, at home and in social situations. The score shows effect that headaches have on normal daily life and ability to function. Thus pre and post HIT score was evaluated and treatment efficacy was seen.

Thus in this study initially serum magnesium level were studied on presentation and then efficacy of combination of folic acid and magnesium in treatment of migraine and response was compared with flunarizine.

Objectives

1. To study serum magnesium level in patients with Migraine.
2. To compare the efficacy of combination of folic acid and magnesium with Flunarizine in patients with Migraine.

Methods

In this cross sectional analytical observational study, total 56 patients were studied. Serum magnesium levels were monitored in all patients. Then they were recruited into 2 groups with one being combination of folic acid and magnesium and other Flunarizine. Headache impact test score was evaluated pre and post treatment after 3 months. Concomitant medication and occurrence of adverse events were checked at follow-up visit.

Materials and Methods

Study Design

Cross sectional Analytical observational study

Study Setting

All Patients presenting to Neurology Out Patient Department at a tertiary care teaching hospital which caters to urban as well as rural population in Southern coastal part of India.

Duration of Study

Commenced in June 2017 and was completed in November 2017.

Ethical Approval

Institutional ethics committee approved protocol of the study. After obtaining ethical approval, patients were recruited into the study.

Description

1. In this study, all participants were recruited from Neurology Clinic
2. Here patients were not randomly distributed as it is a comparative analytical observational study of 2 different treatment groups
3. As it is a pilot study, 56 patient were recruited according to the criteria of International Headache Society
4. Serum magnesium levels were measured in all cases
5. Eligible patients were then recruited into 2 groups
   a.Folic acid 5mg + magnesium hydroxide 400mg once a day
   b.Flunarizine 10 mg once a day
6. Pre and Post treatment HIT was compared after 3 months
7. Improvement was considered it reduces migraine attack frequency or days by at least 50% within 3 months
8. Concomitant medication and occurrence of adverse events was checked at follow-up visit

Inclusion Criteria

1. Healthy adults aged 18 to 65 years of either sex
2. Migraine criteria as mentioned

Diagnostic Criteria

According to diagnostic criteria established by the International Headache Society, patients must have had at least 5 headache attacks that lasted 4–72 hours (untreated or unsuccessfully treated) and the headache must have had at least 2 of the following characteristics [13].

a. Unilateral location
b. Pulsating quality
c. Moderate or severe pain intensity
d. Aggravation by or causing avoidance of routine physical activity (eg, walking, climbing stairs)

In addition, during the headache the patient must have had at least 1 of the following:

a. Nausea and/or vomiting
b. Photophobia and phonophobia

Exclusion Criteria

1. Migraine prevention (drugs, nutritional supplements or psychotherapy) as well as antipsychotic or antidepressant medication during the last 3 months prior to study entry and throughout the study
2. Medication overuse was excluded
3. Patients who had failed to respond to more than 2 different prophylactic agents in the past
4. Resistant to all acute migraine drugs were not included

Headache Impact Test (HIT)

It is a tool used to measure the impact headaches have on ability to function on the job, at school, at home and in social situations. The score shows effect that headaches have on normal daily life and ability to function. Score is from 36-78.

a. If Scored 60 or More — Headaches are having a very severe impact on your life.
b. If Scored 56 – 59 — Headaches are having a substantial impact on your life.
c. If Scored 50 – 55 — Headaches seem to be having some impact on your life.
d. If Scored 49 or Less — Headaches seem to be having little to no impact on your life at this time.

Statistical Details

1. Analysis was done using IBM SPSS statistics 20
2. All the measurable variables were presented as mean +- SD and all categorical variables were presented as frequency and percentage
3. Mean Pre HIT and Post HIT were compared between 2 groups using independent sample t test
4. Paired sample t test were applied for comparing the mean HIT between pre and post
5. Pearson Chi square was applied for comparing improvement and Sid effects variables between groups
6. If p value <0.05 , considered as statistical significant

Results

Mean magnesium levels was 1.9877 ± 0.1355 mg with range between 1.65-2.34mg. About 21.4 % had low magnesium levels. Mean value of magnesium was found in lower normal range with normal value between 1.9-2.6mg.

In FA+MG, total 27 patients were recruited with Pre HIT mean score of 64.93 ± 5.196. In Flunarizine group , total 29 patients were recruited with Pre HIT mean score of 67.59 ± 4.524.Post HIT mean score in FA+MG group was 53.81 ± 10.340 and Flunarizine group was 54.55 ± 8.919. Comparing post HIT score of both groups showed no statistical significance with p value of 0.776. Comparing the percentage difference between groups showed no statistical significant differences with p value of 0.674. Response to treatment was seen in the form of improvement in 73.2 % of patients with individual groups showing 74.1% and 72.4% respectively.

Demographics and Baseline Data

Total 56 patients were recruited with 48 female and 8 male. Mean age group was found to be 35.80 years. Headache was main symptoms in all patients with about 92% having nausea and photophobia with few patients reporting vomiting, photophobia and osmophobia.

Magnesium Levels

Serum magnesium levels were studied in all patients. In this study mean value of serum magnesium was 1.9877 ± 0.13 with range between 1.65-2.34mg. Mean value of magnesium was found in lower normal range (1.9-2.5 mg/dl).About 21.4 % had low serum magnesium levels.

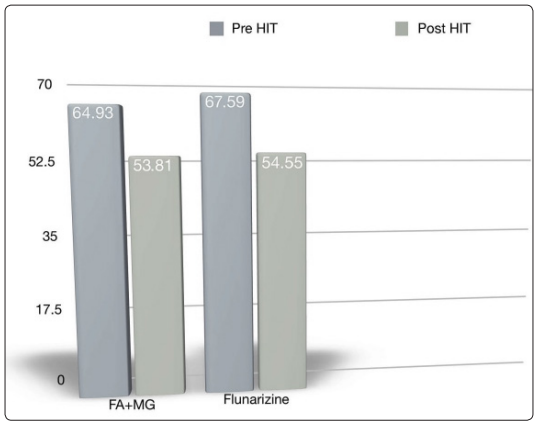
Comparison between Groups

Headache impact test (HIT) - 6 was studied in all patient pre and post treatment. Mean pre HIT score was around 66.30. Patients were then divided into 2 groups (Folic acid + magnesium (FA+MG) and Flunarizine). In FA+MG , total 27 patients were recruited with Pre HIT mean score of 64.93 ± 5.196 .In flunarizine group , total 29 patients were recruited with Pre HIT mean score of 67.59 ± 4.524. Post HIT mean score in FA+MG group was 53.81 ± 10.340 and Flunarizine group was 54.55 ± 8.919. Comparing post HIT score of both groups showed no statistical significance with P value of 0.776. Comparing the percentage difference in score of both groups, we found FA+MG group having 17.08 ± 14.79 % and flunarizine having 18.79± 15.33% with no statistical significant differences with p value of 0.674.

Table 1: Headache impact test

	PRE HIT (Mean ± SD)	POST HIT (Mean ± SD)	P value
Folic acid + magnesium	64.93± 5.196	53.81±10.34	<0.001
Flunarizine	67.59± 4.52	54.55± 8.91	<0.001
P value	0.046	0.776	

PERCENTAGE	DIFFERENCE	POST HIT (Mean ± SD)	P value
	FA + MG	Flunarzine	P value
	(Mean ± SD)	(Mean ± SD)	
HIT	17.08± 14.79	18.79±15.30	O.674



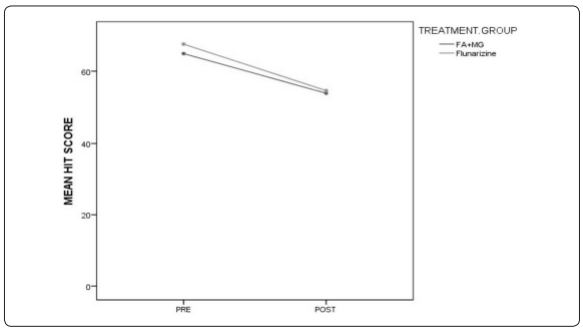


Figure 1: Headache impact test score

Improvement (Table and Figure 2) and side effects

Response to treatment was seen in the form of improvement in 73.2 % of patients with individual groups showing 74.1% and 72.4% respectively.

Side effects were seen in 24.5 % (FA+MG) and 34.9% (Flunarizine) respectively with no statistical significant difference between the 2 groups with p value 0.685.

	BETTER (%)	SAME (%) P	P value
FA+MG	74.1	25.9	0.981
	72.4	27.6	

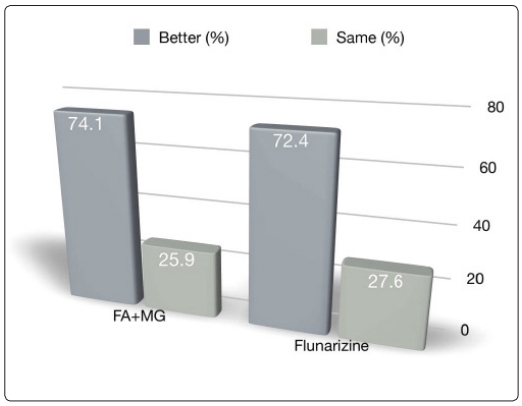


Figure and Table 2: Improvement

Discussion

Migraine is a common disorder that affects up to 12 percent of the general population [14]. It is more frequent in women than in men, with attacks occurring in up to 17 percent of women and 6 percent of men each year [15]. It is and presents with headache associated with nausea, vomiting and photophonophobia.

Initially it was considered that migraine headache was caused by the dilatation of blood vessels, while the aura of migraine resulted from vasoconstriction but this theory longer viable [16]. Vasodilatation is probably an epiphenomenon resulting from instability in the central neurovascular control mechanism [17]. Multiple theories have been hypothesized which includes cortical spreading dissociation, trigeminovascular system, sensitization, role of CGRP and serotonin [16, 18-20]. Primary neuronal dysfunction leads to frequent changes leading to multiple phases of migraine [21].

First part of study included serum magnesium levels in all patients during first presentation with migraine. Mean value was 1.9877 ± 0.13 which was in lower normal range of 1.9-2.5 mg. About 21.4 % had low serum magnesium levels. Showed low magnesium levels in 20 migraine patients [22]. Both reported low levels of magnesium in migraine patients measured serum magnesium in 116 migraine patients, and the results showed low serum magnesium in a considerable number of these patients [23-25]. Thus in this study 21% patients had low magnesium levels. Serum levels are only useful when the value is below normal. Red blood cell magnesium level is a more accurate, and if the value of serum is at the lower end of the normal range, a magnesium deficiency might be present. Thus in this study mean serum magnesium levels was in lower normal range. Thus if ionized or RBC magnesium levels are done there will be considerable amount of hypomagnesaemia in patients with migraine.

Approach to management of migraine includes acute treatment during attack and preventive drugs to decrease frequency and severity of further attacks. A preventive migraine drug is considered successful if it reduces migraine attack frequency or days by at least 50% within 3 months. Multiple class of medications are used like anti-epileptic, antidepressants, beta- blockers, calcium channel antagonists, serotonin antagonists, botulinum neurotoxins [26]. All of these drugs have potential side effects, sometimes of severe nature. For this reason many patients look for a natural preventive treatment of migraine. Recently nutritional therapy for prevention has been used with good therapeutic response. Supplementation with CoQ10 significantly reduced disability and headache frequency [27]. A single DBPC study was conducted in 55 patients using 400 mg of riboflavin daily for 3 months. While the results were positive, a significant difference between riboflavin and placebo was noted only in the third month [28]. Studies have shown improvement with folic acid and magnesium. Folic acid and magnesium work in tandem to promote normal function of the nervous system and normal psychological function, contribute to energy yielding metabolism and reduce tiredness and fatigue. Researchers published a report recommending that all migraine patients should be administered magnesium [29]. Folic acid (FA), vitamin B6, and B12 supplementation has been previously shown to reduce increased levels of homocysteine and decrease migraine symptoms. Lea et al. (2009) reported that vitamin supplementation in MA patients reduced homocysteine levels by 39% when compared to baseline, and the effect was significantly greater than with placebo [30]. Has provided evidence that the folic acid dosage in the proposed vitamin supplementation for migraine treatment plays a pertinent part in reducing homocysteine levels and migraine associated symptoms [31].

Results of magnesium and folic acid trials for migraine prevention are mixed.

Thus we thought of combination drug of folic acid and magnesium in prevention of migraine. In our study, we used 2 different treatment groups (Folic acid + magnesium (FA+MG) and Flunarizine). In FA+MG, total 27 patients were recruited with Pre HIT mean score of 64.93 ± 5.196. In flunarizine group , total 29 patients were recruited with Pre HIT mean score of 67.59 ± 4.524.Comparing Pre HIT score of both groups had significant P value difference of 0.046. Posts HIT mean score in FA+MG group was 53.81 ± 10.340 and Flunarizine group was 54.55 ± 8.919. Comparing post HIT score of both groups showed no statistical significance with P value of 0.776.Comparing the percentage difference in score of both groups, we found FA+MG group having 17.08 ± 14.79 % and flunarizine having 18.79± 15.33% with no statistical significant differences with p value of 0.674.Response to treatment was seen in the form of improvement in 73.2 % of patients with individual groups showing 74.1% and 72.4% respectively.

Flunarizine is a calcium channel blocker that reduces smooth muscle spasm. Compared flunarizine 10 mg daily with propranolol 40 mg 3 times a day over a 16-week period .Frequency of migraine attacks was reduced in 54.5% of people in the flunarizine group which is 72.4% in our study group [32]. an RCT conducted in China, compared flunarizine with topiramate The proportion of people who had at least a 50% reduction in their mean monthly migraine frequency compared with baseline (the primary outcome) was 66.7% (26/39) in the flunarizine group, 72.7% (32/44) in the topiramate group and 76.7% (33/43) in the combined group [33].

Side effects were seen in 24.5 % (FA+MG) and 34.9% (Flunarizine) respectively with no statistical significant difference between the 2 groups with p value 0.685. Side effects were found more with Flunarizine (weight gain and drowsiness) compared to FA+MG (diarrhea).

Thus there was significant improvement in both groups clinically and also as per the HIT score. However no statistical significance was found and none of the groups showed superiority over the other. This shows that both are equally effective.

While many migraine patients will find magnesium beneficial as a prophylactic therapy, or to reduce severity of symptoms – some may have no effect. It is necessary to acknowledge that some migraine patients derive minimal or zero therapeutic benefit from magnesium supplementation. The patients that are least likely to benefit from magnesium as an ant migraine intervention tend to be those without underlying deficiencies. So in that patient trial of combination of multiple vitamins can be useful like giving folic acid, riboflavin, Coq. Usually in common medical practice, patients with vascular headache are always started on symptomatic treatment and commonly used drug for prevention is flunarizine. But recent studies have shown effect if vitamins in prevention of migraine attacks. In our study we have shown that the combination of folic acid and magnesium has the same safety and efficacy as compared to flunarizine and hence can be used as first line therapy for patients with migraine. As the final result shows no statistical difference between both groups and thus comparing between both groups with age match, sex match or symptom distribution is not important.

Limitations

This study is observational study with Small sample size. There was no control group for comparison of magnesium levels. It was taken as combination and individual effect can't be predicted.

Conclusions

Hypomagnesemia can be one of the causative factors causing migraine. Initial treatment with combination of FA+ MG can be useful. Studies with rigorous methodologies and larger sample sizes are needed to further support the safe and effective use of these treatment.

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