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Original Research Article.

Role of Magnesium in Prophylaxis of Migraine

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ABSTRACT

Background: Circumstantial evidence points to be possible role of magnesium (Mg^{+2}) deficiency in the pathogenesis of migraine and has raised questions about the clinical utility of magnesium as a therapeutic regimen in migraine. This was a prospective, randomized, double blind, placebo controlled trial comparing the efficacy and tolerability of 400mg magnesium hydroxide once daily (23 patients), 10 mg Propranolol 3 times daily (22 patients), 200 mg Na-valproate twice daily (20 patients), and placebo (22 patients) in the prophylaxis of migraine diagnosed according to the criteria of the International Headache Society. Patients were evaluated for attack frequency, severity, drug side effects monthly for 3 months. Magnesium, Propranolol and Na-valproate were all superior to placebo ($p<0.001$) in reducing both attack frequency and severity after the first month. There was no significant difference between the three active drugs in reduction of attack frequency and severity. No serious side effects were observed and the frequency of side effects was not significantly different in all treatment groups. Our results show that oral magnesium is an effective and well tolerated drug in the prophylaxis of migraine and compares well to established drugs like Propranolol and Na-valproate both in effectiveness and occurrence of side effects. Magnesium may be an alternative drug in migraine prophylaxis, but more larger comparative trials are needed to confirm these results.

Aim: To find out the role of magnesium in migraine prophylaxis and compare it with two established drug Propranolol and Na-valproate on some diagnosed case of migraine.

Method: This was a prospective, randomized, double blind, placebo controlled trial conducted in the outpatient department of Neurology, Dhaka medical college & Hospital from July 2015 to June 2016. Sample size was 87.

Results: There was no statistically significant difference between the Magnesium, Propranolol and Na-valproate in reduction of migraine attack frequency and severity with (P-value >0.05; which is not significant). Our result shows that magnesium significantly reduced the frequency of migraine attack and severity with no serious side effects compares well to established drugs like Propranolol and Na-valproate.

Conclusion: The study was conducted to find out the role of magnesium in migraine prophylaxis. The present study found that magnesium significantly lowers the frequency of attack & severity of migraine. So magnesium can be used as an alternative agent for migraine prophylaxis for its effectiveness, well tolerability and less side effects.

Keywords: Migraine Prophylaxis, Propranolol, Na-Valproate, Magnesium.

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INTRODUCTION

Migraine is a common chronic disorder often incapacitating its sufferers; approximately 15% of migraineurs suffer from more than two attacks per month and require prophylactic medication.[1] Many drugs of different categories have been used in migraine prophylaxis so far. As they have to be used for a long time, their efficiency is frequently shadowed by their side effects, sometimes resulting in discontinuance of the drug.[2-7]

The most commonly used drugs for migraine prophylaxis are beta-blockers, calcium channel blockers, especially flunarizine, and tricyclic antidepressents, especially amitriptyline.[5-15] Circumstantial evidence points to be possible role of magnesium (Mg^{+2}) deficiency in the pathogenesis of migraine and has raised questions about the clinical utility of magnesium as a therapeutic regimen in migraine.[16-18]

Studies using magnesium for the prophylactic use of migraine have gained interest lately.[19-22] Most of them showing a good prophylactic effect of magnesium versus placebo and a good tolerability of drug.[19,21,22] Although there have been placebo controlled trial investigating magnesium in migraine prophylaxis, no study has compared magnesium to other drugs commonly used in migraine prophylaxis. We compare the efficacy and tolerability of Magnesium with that of Propranolol, Na-valproate and placebo in the prophylaxis of migraine.

METHODS

This was a prospective, randomized, double blind, and placebo controlled study conducted in the outpatient department of Neurology, Dhaka medical college & Hospital from July 2015 to June 2016. 92 patients (68 women and 24 men) suffering from migraine with or without aura and diagnosed according to the criteria of International Headache Society (HIS)[23] were randomized. Their age ranged from 20 to 54 years (mean 31.2 years). All patients were informed of, consented to and underwent a complete physical and neurological assessment. Hematological and biochemical parameters and electrocardiograms were obtained before entering the trial. Our inclusion criteria were a normal systemic and neurological examination, 3 or more migraine attacks per month, not having taken any prophylactic medications for the last 4 months and no regular usage of any medication except for oral contraceptives. Our exclusion criteria were suffering from heart, liver and renal diseases, a blood pressure over 180/95 mm of Hg, pregnancy or lactation, usage of alcohol and having more than 10 attacks of migraine per month. Patients matching our criteria were followed for one month, and were told to keep a diary of the number and intensity of their migraine attacks during this month and not to use any analgesic antimigraine medication except for oral ergotamine - caffeine combination during the attacks. All patients were strictly advised and did not use ergotamine preparation more often than twice a week and in a greater dose than 4 mg /day when needed. At the end of the one month period, patients were reassessed, and those with marked differences in attack frequency, duration and intensity compared to the last 4 months as well as those whom we thought to be unable to comply were excluded.

Patients entering the trial were divided into 4 groups. Initially there were 100 patients, 25 in each group, but 1 patient in the magnesium group, 2 in the Propranolol group, 3 in the Na-valproate group and 2 on placebo failed to show up after initiation of the study. These patients were excluded and all analyses were done on the remaining 92 patients. The first group comprises 24 patients, was given 400mg magnesium hydroxide once daily ,the second group comprising 23 patients, was given 10 mg Propranolol 3 times daily, and 22 patients in third group was given 200 mg Na-valproate twice daily and last group our control group comprising 23 patients, received placebo three times a day. All patients were followed monthly for 3 months, and attack frequency, intensity and drug side effects were noted. Evaluations were done by a neurologist blind to the treatment given. Attack frequency was counted from the last follow up. Pain intensity was graded in 4 categories: 0, no pain; 1, mild pain not interfering with daily activities; 2, medium pain, the pain affects daily activities but does not hinder them; and 3, severe pain, hindering almost all daily activities.

All values were displayed as mean ±SD. Categorical variable s were compared by chi-square test. One way ANOVA and posthoc Turkey's b test and ANOVA for repeated measures were used to compare the numeric variables among drug groups and within each group respectively. For correlations, two-tailed Person's test was used. Significance level was set at 0.05. All analyses were performed using SPSS 8.0 software program.

Table 1: Demographic and migraine characteristics of the 87 patients completing the study

Parameters		Placebo	Magnesium	Propranolol	Na Valproate
		n=22	n=23	n=22	n=20
Mean age, years		32.4±6.7	32.6±6.4	35.1±8.0	30.4±7.0
Women, n		16	17	17	15
Aura, no. of patients		8	9	5	10
Mean attack frequency per month		4.32±0.46	4.22±1.31	4.14±1.25	4.30±1.26
Mean attack severity		2.73±0.46	2.74±0.45	2.86±0.35	2.65±0.49
Attack, no. of patients	**Severe**	16	17	19	13
	Moderate	6	6	3	7

Table 2: Comparative efficacy of medications

Parameters		Placebo	Magnesium	Propranolol	Na Valproate
Frequency	**Baseline**	4.32±1.13	4.22±1.31	4.14±1.25	4.30±1.26
	Month 1	4.05±1.05	3.52±1.38	3.55±1.26	3.70±1.13
	Month 2	4.00±1.27	2.22±1.91	2.59±1.01	2.70±0.92
	Month 3	3.81±1.14	1.52±1.34	1.73±1.42	1.90±0.97
Severity	**Baseline**	2.73±0.46	2.74±0.45	2.86±0.35	2.65±0.49
	Month 1	2.59±0.50	2.39±0.84	2.55±0.51	2.61±0.49
	Month 2	2.50±0.51	1.65±0.98	1.55±0.67	1.70±0.57
	Month 3	2.55±0.59	1.13±0.81	1.05±0.65	1.70±0.57

*Higher with placebo than with other medications, one way ANOVA with post-hoc multiple comparisons by Turkey's b method *(p<0.001)*

RESULTS

During the study there were 5 dropouts from the 92 patients participating. In the placebo group, patient discontinued the medication because of ineffectiveness at the end of the first month. The other four patients retarded from the study due to drug side effects (severe diarrhea in one taking magnesium, decrease libido in one taking propranolol and drug rash due to Na-valproate). The remaining 87 patients completing the study were taken into the analysis. Their ages ranged from 20-54 years (mean 32.6±7.1 years) and 65 were women and 22 were men. Migraine with aura was diagnosed in 32 (36.7%) patients, 65 (74.7%) of enrolled patients had severe attacks, whereas 22 (25.3%) had only moderate attacks. 42 patients also complained of episodic attacks of tension type headache, but the frequency of this attacks was not more than 5 per month and no patient had more than 15 days with headache per month. The patients were advised not to take any medication for these attacks as well. All patients were strictly advised and did not use ergotamine preparations more often than twice a week and in a greater dose than 4 mg per/day when needed. None of them used ergotamine preparations for all of their migraine attacks and none of them fulfilled the HIS criteria for ergotamine induced headache. The patients with highest attack frequency, complaining of 8 migraine attacks per month, only used ergotamine in 5 of them; two of the three attacks not necessitating medications were at the end of follow-up month. This knowledge was helpful in excluding the possibility of headaches due to ergotamine abuse. The demographic characteristics and migraine history details of all patients were similar across the treatment group as were the accompanying symptoms observed during migraine attacks (Table: 1).

The comparative effects of the study drugs and placebo on the monthly frequency of migraine attacks are given in Table 2. Treatment with any of drugs significantly reduced the number of attacks compared to placebo after the first month. Moreover, a significant reduction in attacks frequently appeared with each active drug regimen at the end of the first month when comparisons were performed with their pre-treatment values. But when the effects of 3 active drugs, magnesium, Propranolol, Na-valproate, were compared with each other there was no significant difference between them in reducing attacks frequency. The preventive effect of magnesium tended to appear earlier than the other drugs.

Severity of migraine attacks was also significantly reduced in comparison to placebo after the first month. By intrasubject analysis, both magnesium and propranolol provided a significant benefit by reducing attack severity at this time but this was not the fact for Na-valproate. After the end of the second month, neither drug was superior to the other in this respect.

Attack frequency and attack severity showed no significant correlation. Attack severity was diminished in all patients using propranolol and in 95%, 91.3% and 37.3% of patient using magnesium, Na-valproate and placebo, respectively. The efficacy of the study drugs on severe attacks. All drugs were found to be equally preventive on severe attacks. Effects on moderate attacks were not separately analysed from the sample size. 18 patients became pain free at the end of 3 months: 7 (29.1%) in the magnesium group, 6 (26%) taking propranolol, 4 (18.1%) taking Na-valproate and 1 (4.3%) in the placebo group. There was no significant difference among the pain free rates of the treatment drugs.

No serious side effects were observed in the patients during the study. Drugs were discontinued in 4 patients because of side effects during the study. Frequency of side effects in patients completing the study were 47.8%, 72.7%, 70% and 41% in those using magnesium, propranolol, Na-valproate and placebo, respectively. Reported side effects with magnesium, sometimes in combination, were stool softening (n= 11), one of whom reported severe diarrhea, appetite gain (n= 1), drowsiness (n= 2), asthenia (n= 3), nausea and /or dyspepsia (n= 4) and dry mouth (n= 5).

During propranolol therapy, side effects were bradycardia (n=14), cold extremity (n=1), bronchoconstriction (n=3), hypoglycaemia (n=1), dyslipidemia (n=6), sexual dysfunction (n=1), insomnia (n=6), hypotension (n=4).

The adverse effects reported by patients taking Na-valproate were weight gain (n=13), impaired glucose tolerance test (n=7), nausea (n=5), dyspepsia (n=8), polycystic ovarian syndrome (n=2), elevated liver enzyme (n=2), pancreatitis (n=1), coagulation disorder (n=1)

2 patients in placebo group complained of appetite gain. The other side effects in placebo patients were drowsiness (n= 1), asthenia (n= 4), dyspepsia (n= 6) and dry mouth (n= 6) and constipation (n= 2).

DISCUSSION

Magnesium deficiency has been shown to play a possible role in the pathogenesis of migraine during the past two decades.[16-18] This has led to trials questioning the utility of magnesium as a therapeutic choice in the prophylaxis of migraine. [19-22] In most of this trial oral magnesium therapy has been shown to reduce attack frequency significantly when compared to placebo. [19,21,22] But none of them has compared to magnesium to any other drug commonly used in migraine prophylaxis. In this study we compared magnesium in a higher dose than used in other trials to propranolol & Na-valproate. Although this two drugs are not first choice drugs for migraine prophylaxis, they are commonly used & have been shown to be effective. [5-7,9-11,13,15]

We showed that 400 mg/day oral magnesium reduced mean attack frequency by 64% compared to placebo 12% after 3 months of treatment. This is somewhat higher than the result of Peikert et al. who found that magnesium reduced the mean attack frequency by 41.6%[21] and Taubert who achieved a reduction of 33%[19], both using a magnesium dosage of 600 mg/day. Our success rates may be the higher dose of magnesiumwe used. Peikert et al.[21] reported that magnesium was been significantly superior to placebo at the end of second month, which was also the fact of our study. Pfaffenrath et al.[20], on the contrary, found no benefit of magnesium compared to placebo during an interium analysis & decided to discontinue their trial.

Mean attack severity was reduced by 59% with magnesium compared to 7% with placebo in our study, leading us to the conclusion that magnesium was also superior to placebo in reducing attack severity. Similar results have been reported in other studies. Peikert et al.[21] also reported that magnesium was more effective in reducing attack severity than placebo (34% vs. 20%) but their results did not reach statistical significance. This was also the fact in the study of Taubert where there was no

significant difference between magnesium (44%) & placebo (24%) in reducing attack severity[19], though the results were in favor of magnesium. In another study, 300mg oral magnesium pyrrolidone carboxylic acid reduced both attack frequency & intensity in the patient with menstrual migraine.[22]

We found that all three drug regiments, magnesium, propranolol & Na-valproate are superior in reducing attack frequency & severity when compared to placebo. The reduction in frequency & severity of migraine attack for magnesium (64% & 59% respectively), propranolol (58% & 63% respectively), & Na-valproate (56% & 59% respectively), and the pain free rates did not reach significance when compared to each other.

Other studies have also confirmed the efficacy of propranolol & Na-valproate respectively. Propranolol was found to be superior to placebo in reducing attack frequency[5-7,15] & severity.[6] Na-valproate has been compared to placebo & found superior in its effects on attack frequency[9-11,13] but not on attack severity.[9,10] This lack of effectiveness of Propranolol on attack severity stands in contrary to our results where the difference was highly significant. Propranolol has also been shown to have an increased effect in reduction of attack frequency after continuation of treatment after 3 months.[10,11] This may mean that there could have been a difference between the treatments if they had been continued for longer. But because of the higher occurrence of side effects like depression reported with longer continuance of Propranolol, we preferred to stop the trial at the end of 3 months.[24]

Our high success rates with all medications in our study are an interesting finding, though we do not think that the rates are tremendously high. Pooled data from studies with Propranolol reveal a success rate of 42%[25], while the only placebo controlled double blind study with Propranolol[5], also gave a success rate of 42%. Although our success rates are higher than this we do not think that they are unacceptably high. This seems to be a problem common to many studies involving only a small group of patients[22-24] [in our study for all groups] and we think that only cumulative data from many studies or larger studies could reveal the true success rate of drug.

Furthermore our more success rates with magnesium could probably result from the much higher dose of magnesium we used compared to other trials. Further trial comparing our dose with lower dose of magnesium could clarify this. The very high therapeutic gain in our study probably resulted from our low placebo rates rather than high success rates. We are unable to explain the low placebo efficiency (i. e .12% for attack frequency & 7% for attack severity) in our study. Usually the placebo success rate would be expected to be lie between 15% & 25%, but interestingly it was much lower in our study. It is possible that the patient noted that placebo was not effective, but there was only one dropout due to ineffectiveness in the placebo group and all remaining patients continued on their drug.

Magnesium has been proposed to play a role in many theories about migraine. Magnesium has a modulatory role on the sensitivity of NMDA receptor to glutamate[26], which plays an important role in the initiation and spreading of cortical depression.[27] Experimental studies have shown that magnesium can block the spreading cortical depression induced by glutamate and that spreading cortical depression is more easily initiated with low levels of magnesium in the cerebral cortex.[28] Magnesium also plays an important role in the regulation of the cerebral and peripheral vascular tone[29] by acting like a physiological calcium – channel blocker.[16,30]

Serotonin receptor activity is altered by change in level of ionized magnesium[31,32] and vasoconstriction induced by serotonin can be effectively blocked by pretreatment with magnesium.[33] Experimental magnesium deficiency leads to generation & release of substance P[34] which is thought to act on sensory fibers and cause the pain in headache.[35]

Because of these effects magnesium has been supposed to play a role in neuronal and vascular theories for migraine pathogenesis[16] and during the last years many studies have investigated the relation between migraine & magnesium. Ramadan et al reported lower intracellular magnesium concentrations in migraine patients versus controls either during or between attacks & suggested that there may be a relation between magnesium & the triggering of migraine attack.[18] Later studies have shown that migraine sufferers have low magnesium level in serum & or saliva[36,37], erythrocytes[37-40], monocytes & lymphocytes.[22,40,41] Mauskop et al. reported that 42% of patients have low ionized magnesium levels during a migraine attack.[17] It has been proposed that as a result of stress, migraine sufferers excrete magnesium in increased amounts leading to transient hypomagnesemia & or magnesium wasting.[16] Chocholates & cheeses which provoke migraine contain tryptamine like substances which in the presence of lowered cerebrovascular magnesium would result in cerebrovasospasm.[16] A fall in serum ionized magnesium levels may be triggering factor in the migraine attack & the following clinical syndrome may be the result of a combination of various pathophysiological mechanisms induced or facilitated by hypomagnesemia. Oral magnesium supplementation might help migraine sufferers to keep a normal serum magnesium concentration, thus preventing low serum magnesium levels from initiating migraine attacks by the mechanisms previously mentioned.

The occurrence of side effects of magnesium in our study was comparable with placebo (47.8% and 41% respectively). One patient in the magnesium group had to discontinue treatment because of severe diarrhea, which ceased after drug withdrawal, one in the Propranolol group, because of excessive daytime sedation & two patients on Na-valproate had to stop treatment due to remarkable drowsiness. The most common side effect with the magnesium was a softened stool in 47.8%. Diarrhea was only seen in 1 patient 4%. This number is somewhat higher than in the studies of Pfaffenrath et al.[20] (28.6%) & Peikert et al.[21] (18.6%), but in the latter study 2 patients 5% had to discontinue treatment because of diarrhea.[21] This side effect seems to occur only with oral intake of magnesium, as we did not encounter any gastrointestinal side effects in our study with intravenous magnesium sulphate[43], nor did Mauskop et al. in a similar study.[44] Our total frequency of side effects with magnesium (47.8%) is comparable to that in other studies which reported frequencies of 37.2%[21] and 45.7%.[20] Our higher rate of side effects might result from the higher dose of magnesium we used.

There were higher frequencies of side effects with Propranolol (72.7%) and Na-valproate (70%) although none of them were serious. Comparison between the side effect frequencies in the treatment groups failed to show any significant difference. Also the dropout rates were not significantly different in three treatment groups. Although not significant there seem to be fewer side

effects with magnesium. Magnesium, which is also used frequently, parenterally for the treatment of eclampsia, has not be shown to have adverse effects on the human fetus.[45] Although we have not taken this into consideration in this trial, there is the possibility that magnesium could be used for migraine prophylaxis in pregnancy safely and effectively, where many other current drugs are contraindicated or can only be used cautiously.

Our patients with 400 mg oral magnesium seem to be more effective on attack frequency and intensity and in side effect occurrence when compared to trials using 600 mg oral magnesium. Our dose of magnesium was well tolerated and did not produce more unacceptable side effects & did not lead to a higher dropout rate when compared to trials using higher dose. Dose comparative trials are needed to find the best effective dose for magnesium in the prophylaxis of migraine.

Finally, although this trial was designed as a double blind study there was no correct blinding in regard to the medications given as the 4 different medications were used in different frequencies per day. But it was inevitable to design the study this way as we were comparing 2 drugs which are recommendedly taken at a single dose/day with magnesium which has to be given in multiple doses. As our primary aim was to show whether magnesium was effective or not, we chose to give the placebo group the same frequency of doses as the magnesium group. We still think that there was enough blinding as none of the patients knew what medication they or the patients were receiving. This trial shows that magnesium is equally effective & as well tolerated as propranolol, Na-valproate in migraine prophylaxis. It could be new treatment option, especially for patients in whom other established drugs are contraindicated, not tolerated & ineffective. As this is the only comparative trial of magnesium in migraine prophylaxis so far & our numbers are small, more & larger comparative trials with magnesium, also comparing first choice drugs like flunarizine, are needed. The ideal drug for migraine prophylaxis however, a drug that is highly effective in reducing attack frequency but has few side effects, is yet to be found.

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