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Original Article

Comparative Study of Flunarizine versus Propranolol in the Prophylaxis of Migraine

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Abstract

Background: *Propranolol and flunarizine are the most used first-line drugs in the treatment of migraine. There are limited data regarding the use of prophylactic agents available in Bangladesh. This study aimed to compare the efficacy and tolerability of propranolol and flunarizine in prophylactic management.*

Materials and methods: *This was a open label randomized clinical trial. One hundred and fifty migraine patients were recruited from the Outpatient Department of Neurology and Medicine of Chittagong Medical College Hospital from October, 2017 to September, 2018. They were randomized in a 1:1 ratio to receive either flunarizine (n=75) or propranolol (n=75) once daily. Patients were evaluated for attack frequency, pain severity, duration of headache, disability and drug side effects at 6 weeks and 12 weeks.*

Results: *The Flunarizine group showed a reduction in the mean (±SD) frequency of migraine attacks from 10.58±4.11 to 3.25±2.90 per month, intensity of headache per attack from 8.00±1.33 to 3.63±1.87, number of headache days per month from 11.93±4.12 to 3.25±2.90, duration of headache per episode from 21.18±16.15 to 3.13±3.26 and MIDAS (Migraine Disability Assessment Test) score from 23.15±8.77 to 4.70±4.80. In patients treated with propranolol, a reduction in the mean (±SD) of monthly frequency of migraine attacks from 9.64±3.81 to 4.67±3.15, the intensity of headache per attack from 7.99±1.27 to 4.57±1.48, number of headache days per month from 11.66±4.49 to 4.67±3.15, duration of headache per episode from 24.19±19.33 to 4.85±4.31 and MIDAS score from 23.78±10.48 to 6.51±5.36. The percentage of responders at the study endpoint was 58.2% for propranolol and 80.3% for flunarizine. Both the drugs were well tolerated but adverse effects were more in the propranolol group.*

Conclusion: *Flunarizine was more effective and better tolerable than propranolol in prophylaxis of migraine.*

Key words: Flunarizine; Migraine; Migraine prophylaxis; Propranolol.

INTRODUCTION

Migraine is one of the most common causes of headache and neurologic causes of frequent disability in the world, affects approximately 15% of women and 6% of men.[1] Migraine imposes a substantial economic burden on society result from missed working hours and lost work productivity.[2,3] Thus treatment of migraine should be optimized to improve productivity and mitigate the staggering costs of this disease.

Prophylactic migraine treatment should be given in patients who have more than four migraine headaches per month or at least eight headache days in one month and patients with severe debilitating headaches despite appropriate acute treatment, or those who are intolerant or have contraindications to acute therapy.[4] The goal of prophylaxis is to prevent or reduce the frequency of migraine attacks, shorten the duration of headaches, reduce their severity, improve response to acute medications, maintain wellbeing and reduce disability.[5]

Drugs that are most commonly used for migraine prophylaxis with good efficacy and tolerability are beta-blockers, calcium channel blockers, antidepressants, anti-epileptics. The non-specific calcium channel blocker flunarizine and propranolol are the two most commonly used drugs for migraine prevention.[6]

Propranolol is a beta-blocker, one of the established therapies for the prevention of migraine attacks.[7] Adverse events commonly reported with beta-blocker are fatigue, depression, nausea, dizziness, bradycardia, hypotension, impotence and insomnia.[7,8] It is contraindicated in patients with specific cardiovascular disorders or patients with asthma or uncontrolled diabetes mellitus.[9] An alternative first line drug for migraine prophylaxis is therefore often needed.[9]

Recent meta-analyses suggested that 10-mg flunarizine per day is effective and well-tolerated in treating migraine and has a manageable safety profile with weight gain and drowsiness being commonly reported.[10,11] However, few clinical trials are available in which these two drugs, propranolol and Flunarizine, are compared directly.[9,12] It was confirmed that both drugs effectively prevent migraine, with a significant reduction in the number of episodes and severity of headaches from baseline to end of treatment. However, studies were not consistent about the superiority of one drug over another.[9,12]

These drugs are easily available and have the advantage of lower cost. But the reference of comparative study between these two drugs in Bangladesh was scarce, which is imperative for the clinicians to choose the more convenient drug between flunarizine and propranolol as preventive therapy for migraine in our setting. Considering the routine use of both drugs in clinical practice in Bangladesh, this study was designed to compare the effectiveness and tolerability between flunarizine and propranolol in migraine prophylaxis.

MATERIALS AND METHODS

This open label randomized clinical trial was conducted at the Outpatient Department of Neurology and Medicine, Chittagong Medical College Hospital, Chattogram, Bangladesh from October, 2017 to September, 2018. Study protocol was approved by the Ethical Review Committee of Chittagong Medical College and written informed consent were obtained from each participants. Patients of 18-55 years age irrespective of sex, diagnosed to have migraine with aura or without aura as defined by the International Headache Society were included in the study.[13] Patients with all other primary headaches (Tension type, cluster headache etc) and secondary headaches, pregnant and lactating women; patients allergic to study medication; patients who had previously failed an adequate trial (A trial of at least 3 months) of flunarizine or propranolol because of lack of efficacy or adverse events; used prophylactic medication within last 3 months; had any significant cardiovascular diseases (Heart failure, sinus bradycardia (<45 bpm), 2nd degree AV block, hypotension, peripheral vascular disease) Chronic obstructive airway disease, bronchial asthma, hepatic or renal dysfunction were excluded.

A power analysis reveals that a sample size of 64 participants was required in each treatment arm to identify a significant difference given an effect size of 0.5 and a power of 0.8 at the 0.05 significance level.[14] Considering the drop out final sample size was increased to 75 patients in each group making a total of 150 patients.

At the start of trial, a complete medical history and specific migraine history were recorded. A general physical examination (e.g. pulse, blood pressure), ophthalmological and neurological examination were performed. Patients' baseline characteristics such as age, sex, co-morbidities, current medication and type of migraine were recorded.

The eligible patients were randomly selected in two groups by simple lottery method. For Flunarizine Group: tablet Flunarizine was given 5 mg once daily at night for 7 days then 10 mg once daily at night for a duration of three months and for Propranolol Group: tablet propranolol were titrated as follows: 20 mg bid for 7 days and from day 8 (40 mg bid) (Maintenance dose).

Use of acute headache medications, including over-the-counter analgesics, NSAIDs, triptans, ergot derivatives, were permitted for symptomatic relief of headaches throughout the study. Subjects were instructed to adhere as closely as possible to the type and timing of acute therapy used before enrollment. Use of preventive migraine treatments other than the study medication were prohibited for the duration of the trial.

Patients were educated to maintain their headache character in a headache diary supplied to them. It included the frequency of migraine per month, number of days with migraine, the pain severity on a scale of 1 (Mild) to 10 (Excruciating) the duration of each attack (Hours), presence or absence of aura, associated symptoms like nausea, vomiting, photophobia, phonophobia, osmophobia, intake of rescue medicine.

Patients were followed-up at the end of 6 week and 12 weeks after starting the prophylaxis. During the follow up the migraine diary was checked to examine the change in the migraine frequency and pain intensity. Weight was measured and recorded at baseline, at the end of 6 week and at the end of 12 weeks of follow-up. MIDAS scores were assessed and recorded at baseline and at the end of 3rd month of follow-up. Tolerability of the drugs were assessed based on adverse drug reactions. The number of patients withdrawn from the trial due to adverse events and poor drug compliance were considered as the primary outcome of tolerability. Brief physical examinations were done at baseline, 6 week and 12 weeks and brief neurologic examinations were performed at each visit. Vital signs were measured at each visit; body weight and height were recorded at first and last visit as well as an electrocardiogram was performed at each visit.

Continuous variables were reported as the means ±SD or median and Interquartile Range (IQR) and compared by either the Independent sample t test or Mann-Whitney-U test. Categorical variables were expressed as frequency and percentages and were compared by either the Chi-square test or

Fisher's exact test. Data were analyzed per protocol principle. Data analysis was conducted using SPSS version 23.0. Statistical significance was defined as $p < 0.05$.

RESULTS

Out of 150 patients 12 (8%) were excluded (4 from flunarizine group and 8 from propranolol group) from the analysis as they failed to complete the study per protocol. Rest of the patients (67 in propranolol group and 71 in flunarizine group) were included in final efficacy analysis. Overall the median age of the studied patients was around 27 years with a female to male ratio of 2.3:1. Table I displayed that both the groups were similar in terms of their baseline demographic and clinical characteristics.

Table I Baseline demographic and clinical characteristics

Variavles	Propranolol (n=67)	Flunarizine (n=71)	p value
Age, in years	27 (22-33)	26 (16-32)	0.059#
Female sex	49 (73.1%)	47 (66.2%)	0.734*
Family history of migraine	56 (83.2%)	59 (83.1%)	0.562*
Duration of disease, in years	4.5 (2.0-10.0)	4.1 (2.0-11.0)	0.289#

Data are expressed as frequency (%) or Median (Interquartile range), #Mann-Whitney-U test,*Chi-square test.

The mean frequency of migraine attacks per month were significantly lower in Flunarizine group than the propranolol group after 12 weeks of treatment. Percentage reduction in attack frequency was higher in the Flunarizine group than the propranolol group both at 6 weeks and 12 weeks. Mean intensity of migraine attacks in the previous month was significantly lower in flunarizine group than propranolol group, both at 6 weeks and 12 weeks. Mean number of headache days per month at baseline in both the groups are comparable, but number of headache days reduced gradually over time and at 12 weeks it was significantly lower in the Flunarizine group. Similar trend was observed regarding average duration of headache per episode (Table II).

Table II Comparison of the outcome parameters in different visits between the study groups

Variables	Propranolol (n=67)	Flunarizine (n=71)	p value†
Frequency of attack in last month			
Baseline	9.64±3.81	10.58±4.11	0.168
After 6 weeks	5.88±3.25	4.85±2.63	0.041
After 12 weeks	4.67±3.15	3.25±2.90	0.007
Percentage reduction of attack frequency			
After 6 weeks	38.37±22.71	52.81±18.90	0.001
After 12 weeks	52.55±23.28	70.07±22.89	0.007
Intensity of headache			
Baseline	7.99±1.27	8.00±1.33	0.946
After 6 weeks	5.30±1.23	5.18±1.26	0.566
After 12 weeks	4.51±1.48	3.63±1.87	0.003
No. of headache days			
Baseline (IQR)	11.66±4.49	11.93±4.12	0.711
After 4 weeks	5.88±3.25	4.85±2.63	0.042
After 12 weeks	4.67±3.15	3.25±2.90	0.007
Duration of headache per episode			
Baseline	24.19±19.33	21.18±16.15	0.321
After 6 weeks	7.89±7.06	4.96±4.09	0.004
After 12 weeks	4.85±4.31	3.13±3.26	0.009

Data are expressed as Mean (±SD) †Independent sample t test.

Figure 1 shows that, the percentage of responders at study endpoint was 80.3%% and 58.2% respectively in the flunarizine and propranolol group. The extent of reduction with flunarizine was greater than that with propranolol but the difference failed to reach statistical significance (p=0.060).

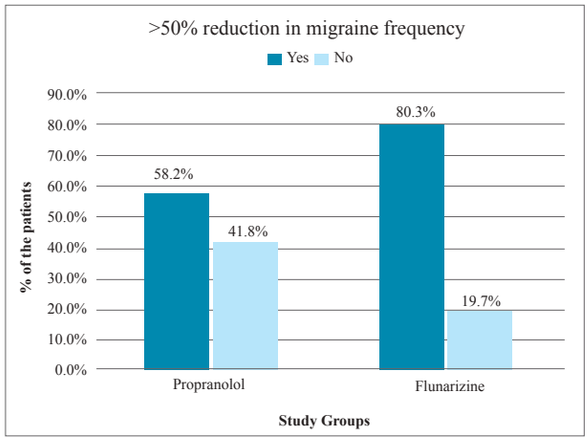

Figure 1 Percentage of responder (≥50% reduction in migraine frequency in comparison to baseline) at study end point among the study groups

After 12 weeks of treatment 41.8% patients in the flunarizine group evaluated the treatment as good compared to 22.4% in the propranolol group. This difference was significant statistically (p=0.008) (Figure 2).

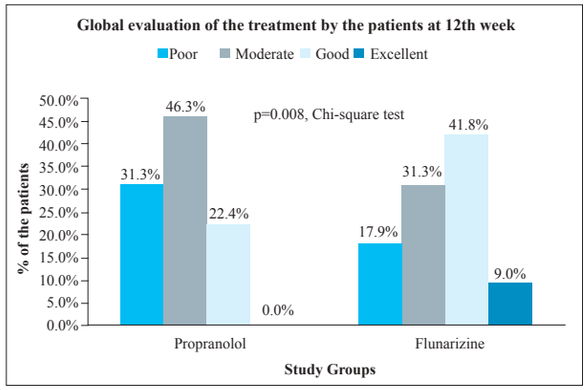

Figure 2 Global evaluation of the treatment by the subjects at the 12th week of treatment in both groups

Table III shows that, at baseline both the groups are comparable with respect to mean MIDAS score. Paired sample t test within groups between baseline and 6th week and between 6th and 12th week of treatment revealed that, in both treatment group MIDAS score decreases significantly at 6th week from baseline and at 12th week from 6th week (p<0.001, not shown in result).

Table III MIDAS score of the patients in course of time among the study groups

Time	Propranolol group (n=67)	Flunarizine group (n=71)	p value
At baseline	23.78±10.48	23.15±8.77	0.707
After 6 weeks	15.40±6.97	14.14±5.89	0.252
After 12 weeks	6.51±5.36	4.70±4.80	0.041

Data are presented as mean ± SD of average duration of headache, *Independent sample t test.

In this study, treatment related adverse events occurred in patients treated with propranolol were mainly tiredness (17.91%), dizziness (13.43%) and adverse events occurred in patients treated with flunarizine were mainly drowsiness (19.72%), weight gain (12.67%).

DISCUSSION

Flunarizine and propranolol have been used for more than three decades for the prophylactic management of migraine.[6] The present study demonstrated that in our setting, flunarizine was more effective in reducing the frequency and severity of migraine headaches than propranolol. According to our study results, flunarizine may be more effective and better tolerable in migraine prophylaxis in comparison to propranolol.

Reduction of frequency of headache was significant in both groups, but percentage reduction in attack frequency after 6 weeks and 12 weeks were significantly more in flunarizine group than propranolol group. The secondary efficacy parameters namely mean duration of migraine attacks, mean numbers of headache days per month, and severity of migraine attacks reduced gradually over time in both group and at 12 weeks it was significantly lower in flunarizine group than propranolol. In the study of Bhat et al. propranolol and flunarazine have shown a high degree of effectiveness and a slight advantage of flunarazine in reducing the frequency and duration of migraine, while as propranolol was more effective in reducing the severity of attacks, but none among these has reached the level of statistical significance.[15] A systematic review by Linde et al. propranolol was found to be more effective than placebo and no clear differences were found between propranolol and other migraine-preventing drugs like, amitriptyline, flunarizine, cyclandelate etc.[7] Differences in our study may be due to observer variation, small sample size, short duration of study, single center study and different dose of propranolol.

Both the drugs contributed in reducing migraine related disability although pre and post treatment MIDAS score were significantly different for individual group. Percentage of responders at study end point by propranolol group was 58.2% and 80.3% by flunarizine group which is statistically significant whereas Gawel et al. also showed that the responders were greater (67%) in the patient taking flunarizine than that of the patients who were treated with propranolol (51%), but not statistically significant.[12] Diener et al. showed that percentage of responders were equal (44%) in both group which is less than our study.[9]

During the follow up, patients complained of tiredness, dizziness, insomnia, nausea in propranolol group. In flunarizine group, the frequent adverse events were drowsiness and weight gain. Drug induced extrapyramidal effects which have been described for flunarizine were not observed in this study. None of these adverse events caused withdrawal of medication. However, regarding global treatment evaluation by the patients, better patient satisfaction were observed in the flunarizine group than that of the propranolol group.

LIMITATIONS

Present study had some limitations. It was an open label study and the length of the treatment was only 12 weeks. In most cases, patients with migraine have medical comorbidities, most of which were excluded from the study.

CONCLUSION

In migraine prophylaxis, flunarizine showed better efficacy in reducing frequency of migraine attacks, number of headache days, duration and severity of headache and MIDAS score in comparison to propranolol in Bangladeshi population. Though both the drugs were well tolerated, adverse effects developed less frequently in the flunarizine group than propranolol group. Flunarizine may be considered as a better treatment option than propranolol in migraine prophylaxis for our population. However, large-scale, multi-center, double blind placebo-controlled trial is warranted for robust conclusions to be drawn.

DISCLOSURE

All the authors declared no competing interest.

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