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Efficacy and Safety of Flunarizine to Propranolol in the Prophylaxis of Migraine: A Comparative Study in a Tertiary Level Hospital

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Abstract:
Introduction: *Migraine is a chronic episodic disease and attack frequency of migraine varies throughout the life of an individual. Prophylactic pharmacotherapy of migraine is indicated in patients in whom the frequency and/or severity of migraine attacks persistently disrupt the patient's daily functioning despite use of effective treatment in acute attacks and the institution of appropriate nonpharmacological approaches.*
Objective: *The aim of this study was to compare the efficacy and safety of flunarizine to propranolol in the Prophylaxis of Migraine in outpatients of a tertiary level hospital.*
Methods: *This observational comparative study was conducted at the Department of Neurology in Cox's Bazar Medical College and Hospital, Cox's Bazar, Bangladeshi from January 2020 to January 2021. A total of 188 outpatients aged above 18 years with a documented history of migraine attacks were enrolled in this study. Of them, 94 were enrolled in Flunarizine Group and 94 were enrolled in Propranolol Group. The collected data were analyzed using Statistical Package for Social Sciences (SPSS), version-23.0. The ethical clearance of this study was obtained from the Institutional Review Board of Cox's Bazar Medical College, Cox;s Baxar, Chattogram, Bangladesh.*
Results: *The most frequent age group of the patients in flunarizine-group was (18-28) years which includes 42(44.68%) patients while the most frequent age group in Propranolol group was (18-28) years which includes 39(41.41%). The mean age of Flunarizine-group was 39.7±7.3 years and the mean age of Propranolol group was 38.3±8.2 years (p=0.217). The majority of the patients of Flunarizine-group were females 58(61.70% while 55(58.51%) patients of Propranolol group were females. The most frequent 84(89.36%) patients completed the four month active treatment phase in flunarizine group and 86(91.98 %) patients in propranolol group. Both treatments resulted in a significant reduction in the primary endpoint of migraine frequency. The flunarizine group had fewer migraine attacks than propranolol group (p=0.001). The mean weighted duration of last evaluable was 0.21±8.25 hours in flunarizine group and 0.58±9.17 hours in propranolol group which was not statistically significant (p>0.05). The mean weighted duration of migraine attack severity of last evaluable in flunarizine group was -0.01± 2.49 hours and 0.10±2.76 hours in propranolol group which was not statistically significant (P>0.05). In flunarizine group, 3 (3.19%) patients reported depression followed 1(1.06%) weight gain and 1 (1.06%) patients fatigue whereas in Propranolol group, 4(4.25%) patients reported depression followed 3(3.19%) weight gain, 2(2.12%) fatigue, 1(1.12%) rash, and 1(1.06%) increase headache(P=0.001).*
Conclusion: *This study investigated that that flunarizine and propranolol are each effective and well-tolerated medications for the prophylactic treatment of migraine headache. Flunarizine is at least an effective and may be better tolerated than propranolol*
Key words: *Efficacy, Safety, Flunarizine, Propranolol, Prophylaxis, Migraine, Comparative*

I. INTRODUCTION

Migraine is a chronic episodic disease and attack frequency of migraine varies throughout the life of an individual. Prophylactic pharmacotherapy of migraine is indicated in patients in whom the frequency and/or severity of migraine attacks persistently disrupt the patient's daily functioning despite use of effective treatment

in acute attacks and the institution of appropriate nonpharmacological approaches [1]. Although this migraine profile describes approximately one-third or less of migraineurs. This type of headache sufferer may represent a large proportion of the headache practice of a neurologist [2]. If migrainous headaches are recurring twice a month or more, a prophylactic treatment is required [3]. There is a variety of medication usually employed in the migraine prophylaxis, a hint that none is entirely effective. Moreover, usually there are patients who do not respond to one or more prophylactic drugs. Besides, there are individual differences in the responsiveness to different prophylactic agents and even sometimes, an inability to sustain an initial good response to a particular agent [4]. Research continues in this area to identify an agent with maximal efficacy and a minimal side effect. Currently in North America, propranolol is the most commonly prescribed medication for this indication [5]. The prophylactic utility of propranolol is limited, however, by its con traindications (asthma, insulin-dependent diabetes) and its side effect profile, which includes potentially dangerous cardiovascular effects [6].Recently, calcium channel antagonists have received increasing attention as alternative medications for migraine prophylaxis [7]. In Canada, several such agents are commercially available and have been investigated for the prophylaxis of migraines, however, only flunarizine has been approved for this indication. Flunarizine is a difluorinated piperazine derivative designated as a class IV calcium antagonist according to the WHO classification system [8].It is structurally and pharmacodynamically similar to cinnarizine. Flunarizine does not interact with cardiovascular slow calcium channels and consequently does not affect cardiovascular function. By virtue of its ability to cross the blood-brain barrier, flunarizine's activity is selective for central nervous system calcium channels. Pharmacological studies have generated several hypotheses for the mechanism of flunarizine's possible beneficial effect in the treatment of migraine: inhibition of vasospasm in cerebral blood vessels, direct cellular inhibition of hypoxia, and prevention of vasoconstriction, normalisation of abnormal central serotoninergic nerve activity, and improved blood viscosity and erythrocyte deformability [9, 10]. Several well-controlled, double-blind, randomized clinical trials against placebo and active agents have demonstrated flunarizine's activity in this patient population[11].However, There are very few studies and limited data regarding the efficacy and safety of Flunarizine to Propranolol in the Prophylaxis of Migraine in Bangladesh. Therefore, the aim of this study was to determine the efficacy and safety of Flunarizine to Propranolol in the Prophylaxis of Migraine of the patients attending in a tertiary level hospital in Southeastern Bangladesh.

II. OBJECTIVE

To compare the efficacy and safety of Flunarizine to Propranolol in the Prophylaxis of Migraine in outpatients of a tertiary level hospital.

III. METHODS

This observational comparative study was conducted at the Department of Neurology in Cox's Bazar Medical College and Hospital, Cox's Bazar, Bangladeshi from January 2020 to January 2021. Purpose and benefit of this study was disclosed to the patients and written informed consent was obtained. Then, purposive sampling technique was used and a total of 188 outpatients aged above 18 years with a documented history of migraine attacks were enrolled in this study. Of them, 94 were enrolled in Flunarizine Group and 94 were enrolled in Propranolol Group. Treatment Plan Patients were initially randomized to one of two parallel double-blind active treatment groups: flunarizine or propranolol. A one month single-blind placebo washout and baseline period preceded the four month active treatment phase. The dosage of double-blind study medication was initially titrated in fixed increments to the maintenance dose. Patients assigned to propranolol were titrated as follows: day 1 (40 mg qhs), day 3 (40 mg bid), day 5 (40 mg qam + 80 mg qhs), day 8 (80 mg bid) (maintenance dose). Patients randomized to flunarizine received 5 mg qhs for the first 6 days followed by 10 mg qhs thereafter (maintenance dose). The double-dummy technique was employed to maintain the blind with twice and once daily dosing regimens; patients assigned to flunarizine received a placebo capsule qam. Patients were assessed monthly. Daily diaries were used by patients to record the number of migraine attacks, the pain severity on a scale of 1 (mild) to 10 (excruciating) and the duration of attack (hours). Patients also recorded any rescue medication (analgesic) use as well as the occurrence of any adverse experience(s) on a daily basis. Diary data were summarized monthly. The "headache unit index", defined as the average number of attacks per day, was calculated from diary data. In the clinic, patients were questioned with respect to changes in alcohol and tobacco consumption as well as diet and lifestyle changes. A global evaluation of study medication efficacy on a 6-point categorical scale was conducted at the end of the study period by both physician and patient. Safety assessments included routine biochemistry, haematology and urinalysis at baseline and after 2 and 4 months of active treatment. Vital signs (blood pressure, heart rate and weight) were obtained at each visit. Blood pressure and heart rate were recorded by an independent third party, uninvolved in patient management or in the assessment of symptoms, in order to prevent unblinding due to the known cardiovascular effects of propranolol. Adverse experiences reported were recorded at each visit. The comparability of treatment groups for demographic and baseline parameters was assessed with the unpaired t-test for continuous parameters and Pearson's Chi Square

test as appropriate for categorical variables where $p<0.05$ considered as the level of significance. Analysis of efficacy data and vital signs was conducted on eligible patients. Availability of baseline data plus one postwashout on-treatment evaluation was set as the criterion for efficacy evaluability. Analysis of laboratory parameters and adverse experiences was by the intention-to-treat method. Two efficacy parameters were designated as primary: migraine attack frequency (days with headache and number of attacks) and average attack intensity. All other parameters were considered secondary: headache unit index (number of attacks per day), attack duration, end-of-treatment patient global evaluation, and analgesic use. The ethical clearance of this study was obtained from the Institutional Review Board of Cox's Bazar Medical College, Cox;s Baxar, Chattogram, Bangladesh

IV. RESULTS

Table-1: Baseline characteristics of the study Patients (n=188).

Age(years)	Flunarizine(n=94) N(%)	Propranolol(n=94) N(%)	Total N(%)	P-value
18-28	42(44.68)	39(41.41)	81(43.08)	
29-39	38(40.42)	37(39.36)	75(39.89)	
40-50	8(8.51)	9(9.57)	17(9.04)	
51-60	4(4.25)	6(6.38)	10(5.31)	
>61	2(2.12)	3(3.19)	5(2.69)	
Total	94	94	188(100)	
Mean age(years)	39.7±7.3	38.3±8.2		0.217
Sex				
Male	36(38.29)	39(41.48)	75(39.89)	
Female	58(61.70)	55(58.51)	113(60.10)	
Total	94	94	188(100)	
Residence				
Urban	66(70.21)	65(69.14)	131(69.68)	
Rural	28(29.78)	29(30.85)	57(30.13)	
Total	94	94	188(100)	
Socio-economic Condition				
Upper	20(21.27)	19(20..21)	38(20.21)	
Middle	39(41.48)	38(40.42)	77(40.95)	
Lower	35(37.23)	37(39.36)	72(38.29)	
Total	94	94	188(100)	
Diagnosis				
Classic	41(43.61)	44(46.80)	85(45.21)	
Common	53(56.38)	50(53.19)	103(54.78)	
Total	94	94	188(100)	
Mean attack frequency(Last 3 months)	4.5±1.6	4.6±1.7		0.678
Mean attack severity(Last 3 months)	7.6 ±1.9	7.6 ±1.8		1.000

Table-1 shows the baseline characteristics of the study patients. The most frequent age group of the patients in Flunarizine-group was (918-28) years which includes 42(44.68%) patients followed by 38(40.42%) (29-39) years.,8(8.51%) (40-50) years 4(4.25%) (51-60) years and 2(2.12%) (>60) years while the most frequent age group in Propranolol group was (18-28) years which includes 39(41.41%) followed by 37(39.36%) (29-39) years, 9(9.57%) (40-50) years, 6(6.38%) (51-60) years and 3(3.19%) (>61) years. The mean age of Flunarizine-group was 39.7±7.3 years and the mean age of Propranolol group was 38.3±8.2 years (p=0.217). The majority of the patients of Flunarizine-group were females 58(61.70% while 55(58.51%) patients of Propranolol group were females. The socio-economic condition of maximum patients of Flunarizine group was middle class 39(41.48%) whereas the socio-economic condition of maximum patients of Propranolol group was also middle class 38(40.42%). In Flunarizine group the most frequent diagnosis was observed Common 53(56.38%) while the most frequent diagnosis was observed 50(53.19%) in Propranolol group. Mean attack frequency (Last 3 months) was observed in Flunarizine group 4.5±1.6 while the Mean attack frequency (Last 3 months) was observed in

Propranolol group 4.6±1.7 (p=0.678). Mean attack severity (Last 3 months) in Flunarizine group was observed 7.6 ±1.9 whereas Mean attack severity (Last 3 months) in Propranolol group was found 7.6 ±1.8 (p=1.000).

Table-2: Distribution of patients attrition according to time in trial (n=188).

Time in trial	Flunarizine (n=94) N(%)	Propranolol(n=94) N(%)	P-value
Enrolment	94(100)	94(100)	0.001
Baseline	90(95.74)	88(93.61)	
Month 1	90(95.74)	88(93.61)	
Month 2	90(95.74)	88(93.61)	
Month 3	87(92.55)	87(92.55)	
Month 4	84(89.36)	86(91.98)	

Table-2shows the distribution of patients according to time in trial. A total of 94(100 %%) patients were enrolled in each group to justify the efficacy of flunarizine and propranolol. The most frequent 84(89.36%) patients completed the four month active treatment phase in flunarizine group and 86(91.98 %) patients in propranolol group. Both treatments resulted in a significant reduction in the primary endpoint of migraine frequency. The flunarizine group had fewer migraine attacks than propranolol group (p=0.001).

Table-3: Mean weighted duration of migraine attack and difference from baseline scores (n=188).

Visit	Flunarizine Weighted duration of migraine attack(hours) Mean± SD	N (%)	Propranolol Weighted duration of migraine attack(hours) Mean± SD	N (%)	P-value
Baseline	12.0±4.1	90(95.74)	11.6±5.2	88(93.61)	0.527
Month 1	12.6±6.1	90(95.74)	9.7 ± 5.9	88(93.61)	0.527
Month 2	12.8±6.3	90(95.74)	10.1±6.6	88(93.61)	0.527
Month 3	12.2±5.2	87(92.55)	8.8 ± 7.3	87(92.55)	1.000
Month 4	12.3±7.5	84(89.36)	10.4 ±7.5	86(89.36)	1.000
Difference Scores					
Final(Completers)	0.33±8.61	90(95.74)	-1.01±8.51	88(93.61)	1.000
Last evaluable	0.21±8.25	84(89.36)	0.58±9.17	86(91.98)	

*midpoint weight for categorical duration groups) x (number of attacks of that duration)] / (total number of attacks)

Table-3 shows the mean weighted duration of migraine attack and difference from baseline scores. The mean weighted duration of last evaluable was 0.21±8.25 hours in flunarizine group and 0.58±9.17 hours in propranolol group which was not statistically significant (p>0.05).

Table-4: Mean migraine attack severity and difference from baseline scores (n=188).

Visit	Flunarizine Weighted duration of migraine attack severity(hours) Mean± SD	N(%)	Propranolol Weighted duration of migraine attack severity (hours) Mean± SD	N(5%)	P-value
Baseline	5.1±1.5	90(95.74)	5.1±1.4	88(93.61)	0.527
Month 1	5.0±2.0	90(95.74)	4.5 ± 2.0	88(93.61)	0.527
Month 2	5.5±2.1	90(95.74)	4.2±2.2	88(93.61)	0.527
Month 3	4.7±2.0	87(92.55)	4.2 ± 2.6	87(92.55)	1.000
Month 4	5.3±2.6	84(89.36)	4.6 ±2.5	86(91.98)	1.000
Difference Scores					
Final (Completers)	0.00 ± 2.49		-0.51±2.48		0.161
Last evaluable	-0.01± 2.49		-0.10±2.76		0.814

*severity grading scale of 1 (mild) - 10 (excruciating).

Table-4: shows the mean migraine attack severity and difference from baseline scores. The mean weighted duration of migraine attack severity of last evaluable in flunarizine group was -0.01± 2.49 hours and 0.10±2.76 hours in propranolol group which was not statistically significant (P>0.05).

Table-5: Adverse effects associated with premature discontinuation (n=188).

Adverse Effects	Flunarizine{n=94) N(%)	Propranolol(n=94) N(%)	P-value
Depression	3(3.19)	4(4.25)	0.001
Weight gain	1(1.06)	3(3.19)	
Fatigue	1(1.06)	2(2.12)	
Rash	0(0)	1(1.06)	
Increased headache	0(0)	1(1.06)	

Table-5: Adverse effects associated with premature discontinuation. In flunarizine group, 3 (3.19%) patients reported depression followed 1(1.06%) weight gain and 1 (1.06%) patients fatigue whereas in Propranolol group, 4(4.25%) patients reported depression followed 3(3.19%) weight gain, 2(2.12%) fatigue, 1(1.12%) rash, and 1(1.06%) increase headache(P=0.001).

V. DISCUSSION

This comparative study was designed to detect differences in the efficacy and safety profiles of two drugs commercially available in Bangladesh for the prophylaxis of migraine headache: flunarizine and propranolol. A comprehensive and conservative between-treatment (across-time and endpoint) as well as a within-treatment (endpoint) approach to the statistical analysis was taken in order to validate and strengthen the credibility of clinical conclusions drawn from this active control trial. The results of this study confirm the efficacy of both flunarizine and propranolol in the prophylactic management of migraine has been established in previous controlled investigations.[12,13]The onset and maintenance of ant migraine activity as well as the magnitude of response obtained with flunarizine treatment were at least comparable to propranolol, the current standard of therapy. On several key efficacy measures, the response to flunarizine clinically surpassed that to propranolol. Statistically, flunarizine was favored in the between-treatment comparisons. However, statistical separation of treatment groups was not found frequently; this inability to detect consistent differences is likely a reflection of the small sample size and high degree of variability associated with many of the subjective efficacy assessments. The most frequent 86(89.36%) patients completed the four month active treatment phase in Propranolol group and 86(91.98 %) patients in Propranolol group. Both treatments resulted in a significant reduction in the primary endpoint of migraine frequency. The Flunarizine group had fewer migraine attacks than Propranolol group (p=0.001). This current study observed that the mean weighted duration of last evaluable was 0.21±8.25 hours in flunarizine group and 0.58±9.17 hours in Propranolol group which was not statistically significant (p>0.05) and The mean weighted duration of migraine attack severity of last evaluable in flunarizine group was -0.01± 2.49 hours and 0.10±2.76 hours in Propranolol group which was not statistically significant (P>0.05). Thus, to some extent, the trend to superiority in the flunarizine group was established. Therefore, the safety profiles of flunarizine and propranolol observed in this study were predictable. This study observed weight gain, depression and fatigue are the common adverse effects but comparatively high frequency of adverse effects were observed in Propranolol group than that of flunarizine group. This effect may have been due to improvement in the migraine attack rate or to a pharmacological mechanism.[14,15]Drug-induced extrapyramidal effects which have been described for flunarizine were not observed in this study.[16-18] It is concluded that flunarizine and propranolol are each effective and well-tolerated medications for the prophylactic treatment of migraine headache. flunarizine is at least as effective and may be better tolerated than propranolol.

VI. CONCLUSION

This study investigated that that flunarizine and propranolol are each effective and well-tolerated medications for the prophylactic treatment of migraine headache. Flunarizine is at least an effective and may be better tolerated than propranolol

VII. LIMITATIONS OF THE STUDY

This s was a single center study with a limited sample size conducted over a short study period. There, the results of this study may not reflect of the whole country.

VIII. RECOMMENDATIONS

A multicenter study with an adequate sample size is recommended to justify the results of this study to predict the study drugs in the treatment of prophylaxis of migraine in Bangladesh context.

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