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Original Research Article

Comparing Efficacy of Propranolol Plus Flunarizine Combination and Valproate Monotherapy in Migraine Prophylaxis at a Tertiary Centre in Bihar: A Randomized Control Trial

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Abstract

Background: Migraine is one type of headache, described as a recurring syndrome of headache associated with certain neurological dysfunctions in varying admixtures. It is the second most common cause of headache, and it is the most common headache-related and indeed neurologic cause of disability in the world, affecting about 15% of women and 6% of men over a period of 1 year.

Aims and Objectives: The present study was conducted to assess the efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in a tertiary care center.

Materials and Methods: The present prospective cross-sectional study comprised 120 patients with migraine. Out of 120 patients, 24 did not meet the inclusion and exclusion criteria. Hence, 96 patients were enrolled. But six patients were lost to follow-up. The final analysis was done on 90 patients. Patients were divided into two groups for this clinical study in a prospective parallel group design. 45 patients were included in each group. Group I patients received valproate monotherapy, and Group II patients were on propranolol and flunarizine combination therapy.

Results: The study was done on 90 patients with migraine. The mean age of Group I patients was 32.69 ±8.05 (mean SD) years, whereas the mean age of Group II patients was 31.82 ±8.74 (mean±SD) years, respectively. Males were 32 (35.56%) and females were 58 (64.44%). The reduction of headache at baseline was 9.86 with valproate monotherapy and 8.42 with propranolol + flunarizine combination therapy, at the 1st visit it was 6.07 and 5.82, and at the 2nd visit it was 2.81 and 2.19, whereas the reduction in MIDAS score at baseline was 19.50 with valproate monotherapy and 19.6 with propranolol + flunarizine combination therapy, at the 1st visit it was 10.23 and 10.6 and at the 2nd visit it was 5.72 and 5.61 in group I and II, respectively The difference was significant ($P < 0.05$).

Conclusion: In the present study, we found that valproate and propranolol plus flunarizine combinations were both highly effective in migraine prophylaxis. Propranolol plus flunarizine combination therapy was proven to have a better outcome than valproate monotherapy in migraine prophylaxis.

Keywords: Migraine, Propranolol, Flunarizine, Valproate.

Introduction

Migraine has a similar distribution in prepubescent boys and girls. Girls are more affected than boys, and the pattern is seen from the time of puberty. Peak migraine prevalence for both sexes occurs in the fourth decade of life, during which time approximately 24% of women and 7% of men have migraines.[1] Quality of life is the most affected parameter in migraine; a feeling of well-being is greatly hampered in migraine patients. Regardless of age, gender, or socioeconomic status, studies carried out in many countries on individuals from the general population or headache clinic patients reveal that migraine is associated with significantly lower scores on a variety of health-related quality-of-life rating scales.[2,3] CDSCO approved Propranolol 40mg (SR Pellets) and Flunarizine 5 mg/10 mg capsules for the prophylaxis of migraine on March 16, 2010.[4] Migraine is one type of headache, described as a recurring syndrome of headache associated with certain neurological dysfunctions in varying admixtures. It affects about 15% of women and 6% of men over the course of a year, therefore being the second most common cause of headache and the most common headache-related, and in general, neurologic, cause of disability worldwide.[5] FDA-approved drugs named valproate products are used to treat seizures, manic or mixed bipolar disorder (manic-depressive disorder) episodes, and migraine headache prophylaxis. In adults, valproate is recommended at 400–600 mg/day for migraine prophylaxis.[6] Most of the patients with migraines require medication for the acute attack. Patients with an increased frequency of attacks (4/month, usually over 4–6 months) or with attacks that are either poorly responsive or unresponsive to acute treatments are preferred candidates for prophylactic therapy, with therapy, with an objective to reduce number of acute migraine episodes.[7] Valproate products are FDA-approved drugs to treat seizures, manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches.[8]

Aims and objectives: The present study was conducted to assess the efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in a tertiary care teaching hospital in eastern India.

Materials and Methods

The present prospective cross-sectional study comprised 120 patients with migraine. Out of 120 patients, 24 did not meet the inclusion and exclusion criteria. Hence, 96 patients were enrolled. But six patients were lost to follow-up. The final analysis was done on 90 patients. It was a hospital-based interventional study of both genders at the Bhagwan Mahavir Institute of Medical Science, Pawapuri, Bihar, India, in the department of pharmacology, in collaboration with the department of medicine. The institutional ethical committee gave its clearance before the study could be carried out. The research was conducted from April 2022 to September 2022. All patients attending the General Medicine OPD were informed regarding the study, and their consent was obtained. Names, ages, genders, and other details about the patient were noted. Patients were divided into two groups for this clinical study in a prospective parallel group design. 45 patients were included in each group. Group I patients received valproate monotherapy, and Group II patients were on propranolol+flunarizine combination therapy. The selection of

patients in each group was done by the randomization method.

Dosage Frequency

Valproate: 500 mg OD. Mode of administration: oral

Propranolol: 40 mg OD. Mode of administration: oral

Flunarizine: 10 mg OD. Mode of administration: oral

Parameters such as a complete blood count, blood sugar, liver function test, urea, creatinine, sodium, potassium estimation, a 12-lead ECG, etc. were performed. A MIDAS score was also recorded.

Statistical analysis

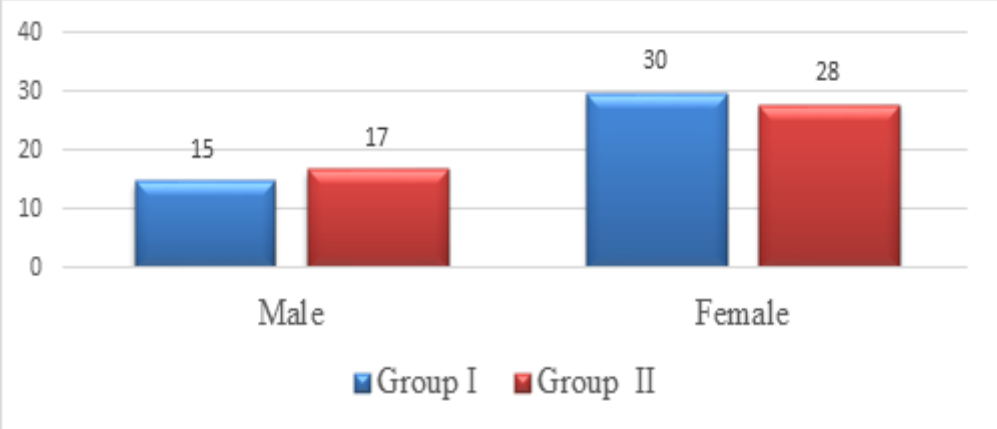
Results thus obtained were subjected to statistical analysis with the help of Microsoft Excel 15 and SPSS Version 22 software. Given that the data were parametric, we ran an unpaired t test for headache frequency to determine whether there was any significant baseline difference between groups that was statistically significant. A P value less than 0.05 was considered significant.

Result

The study was done on 90 patients with migraine. The mean age of Group I patients was 32.69 ±8.05 (mean ±SD) years, whereas the mean age of Group II patients was 31.82 ± 8.74 (mean ±SD) years, respectively. Males were 32 (35.56%) and females were 58 (64.44%).

Table 1: Distribution of Patients

Parameters	Group I	Group II
Male	15	17
Female	30	28
Drug	Valproate	Propranolol +Flunarizine
Mean age (Mean±SD) in years	32.69± 8.05	31.82± 8. 74



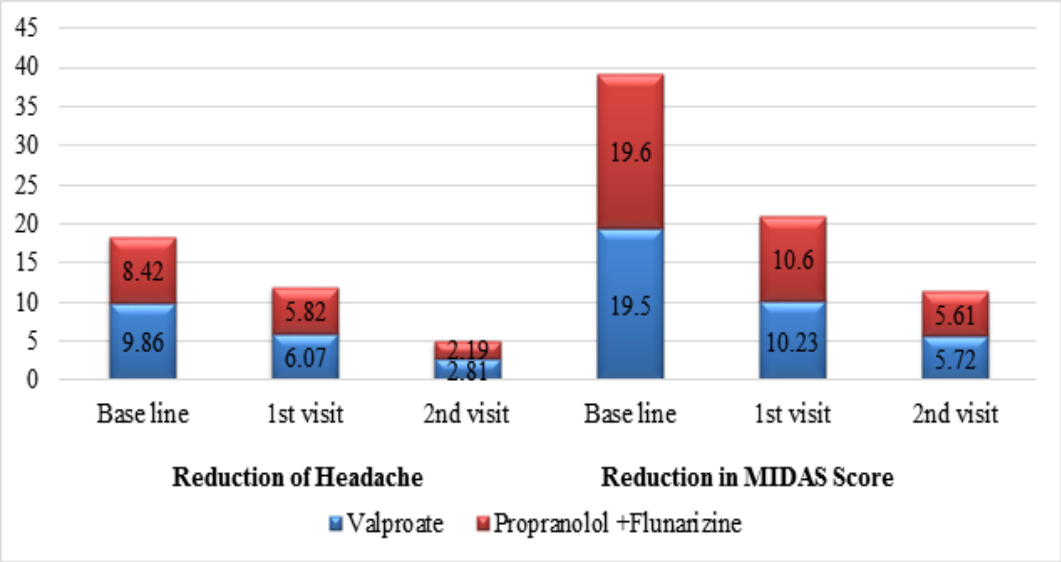
Graph 1: Distribution of Patients

Table I and Graph I shows that group I had 30 males and 15 females and group II had 28 males and 17 females.

Table 2: Comparisons of parameters

Parameters	Variables	Valproate	Propranolol +Flunarizine	P value
Reduction of headache	Baseline	9.86	8.42	0.04
	1st visit	6.07	5.82	
	2nd visit	2.81	2.19	
Reduction in MIDAS Score	Baseline	19.50	19.60	0.15
	1st visit	10.23	10.6	
	2nd visit	5.72	5.61	

Table II and graph II shows that reduction of headache at baseline was 9.86 with valproate monotherapy and 8.42 with Propranolol +Flunarizine combination therapy, at 1st visit was 6.07 and 5.82 and at 2nd visit was 2.81 and 2.19 whereas reduction in MIDAS score at baseline was 19.50 with valproate monotherapy and 19.60 with Propranolol +Flunarizine combination therapy, at 1st visit was 10.23 and 10.6 and at 2nd visit was 5.72 and 5.61 in group I and II respectively. The difference was significant (P< 0.05).



Graph II: Comparisons of parameters

Discussion

Though several treatment options exist, the management of migraine is still a challenge for physicians. Long-term compliance and ADR are the main hindrances to treating migraine. Beside this, the poor quality of life added to the poor outcome. Very often, patients use to live with the headache, and productivity in social life and at work is lost. It is therefore critical to identify the treatment with the best combination of efficacy and safety. We have made an extensive search through published literature but have failed to find any study that includes these drugs with all these parameters for head-to-head comparison for the treatment of migraine in an OPD setting. We have clearly seen a female preponderance, with maximum patients involving the 2nd to 4th decade of life, which was similar to other migraine-related studies. In the study, Evaluation of propranolol, flunarizine, and divalproex sodium in the prophylaxis of migraine by Majid F. Bhat et al. [7], in the case of frequency of migraine attacks per month, a difference was reached as early as the 1st month for all three groups and remained statistically significant throughout the treatment phase. There was a progressive and statistically significant (P <0.001) decrease in the average duration of the migraine attacks in all three treatment groups. A significant reduction in MIDAS scores was noted at the end of the treatment period when compared to the baseline in the treatment group.

A meta-analysis of 10 small trials was done by Adam R. Aluisio et al. [8] and in two studies (one comparing divalproex sodium vs. propranolol and another evaluating sodium valproate vs. flunarizine). There were no significant differences in the proportion of responses.

Chowdhury MI et al. [9] conducted a study at the BSMMU Headache Clinic in the

Department of Neurology from November 2005 to December 2006.There was no significant difference between the groups in terms of headache frequency (no attacks in 3 months) in the propranolol group but not in the valproate group. Reduction in headache days over 3 months had also the same outcome. The reduction in MIDAS score was 47.73 from 16.08 with a p value <0.001 in the propranolol group and 49.62 to 17.41 with a p value <0.001 in the valproate group; there was no significant difference between groups.

Similar results were obtained from our study, but with the combination of propranolol and flunarizine. The reasons behind combining the drugs were dose reduction as well as reduction of ADR. The current study supports the findings of the Dakhale et al.[10] study, which compared the efficacy and safety of low-dose sodium valproate (500 mg/day) and low-dose propranolol sustained release (SR) 40 mg/day in the prophylaxis of common migraine headache in 60 patients with common migraine (≥2attacks/month) treated for 12 weeks. In the course of the study, the participants were assessed at 0, 4, 8, and 12 weeks.

At the end of the treatment, both sodium valproate and propranolol caused a significant (*P* <0.0001) reduction in the frequency, severity, and duration of migraine headache. Propranolol caused a significantly greater reduction in the severity of headache (*P* = 0.0410) than sodium valproate. 60% of respondents in the sodium valproate group and 70% in the propranolol group responded to the survey. Drowsiness was the most common adverse effect noted in both groups.

In our present study, we found that headache, which was 9.86 and 8.42 respectively in Group I and Group II at baseline, was reduced to 6.07 and 5.82 at the 1st visit and further reduced to 2.81 and 2.19 in the 2nd visit, respectively, whereas the reduction in MIDAS score was 19.50 and 19.6 respectively in Group I and Group II at baseline; at the 1st visit, it was 10.23 and 10.6 and at the 2nd visit, it was 5.72 and 5.61 in Group I and II, respectively. The difference was significant (P 0.05), similar to the studies done by Panigrahi, M et al. [11], and Banerjee et al. [12]

Valproate and the propranolol+flunarizine combination were both found to be highly effective in migraine prophylaxis by Panigrahi, M., et al. [11]

Banerjee et al. [12], in their study of 75 patients with migraine, In this open-label, parallel-group, 24-week (first follow-up, 12 weeks; second follow-up, 24 weeks), interventional study, it was found that both Valproate and Propranolol plus Flunarizine were highly effective in migraine prophylaxis. There were no differences between the groups within the first and second follow-up. Migraine frequency and duration were reduced, as well as the migraine-associated disability assessed by the MIDAS score. Quality of life was also significantly improved in those groups from baseline, which may be due to both pain reduction and improvements in usual activity, mobility, and anxiety or depression with those two groups of drugs, but Valproate was proven to have a better outcome than the other group. They found that the mean ±SD was 35.023± 8.476 and 37.27 ±12.44 in Group V and PF, respectively, and the p value was 0.0951 at the baseline. When we studied EQ-VAS, the mean ±SD in the case of headache duration was 11.76± 3.427 and 10.27 ±2.44, and the p value was 0.1105. So, in both occasions, we found non-significant results. Change in headache frequency was done within group V (repeated measure ANOVA) followed by a Wilcoxon match pair posthoc test, and the mean±SD were 9.054 ±2.107, 6.027±1.236, and 2.649±1.317, respectively, from baseline to follow-up, and the p value was very significant.

Limitations of study

The limitations of present study are that the number of the subjects is small and the study duration is short.

Conclusion

In present study we found that Valproate and Propranolol plus Flunarizine combination both were highly effective in migraine prophylaxis. There were no differences between the groups within first and second follow-up. Migraine frequency and duration was reduced, as well as the migraine associated disability assessed by MIDAS score. Quality of life was also improved significantly in those groups from baseline which may be due to both pain reduction and also improve in usual activity, mobility and anxiety/depression with those two groups of drugs, but Propranolol plus Flunarizine combination therapy was proved with better outcome than valproate monotherapy in migraine prophylaxis.

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