

**How to Cite:**

Panigrahi, M., Marndi, G., & Beshra, S. (2022). Efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in a tertiary care teaching hospital in Western Odisha. *International Journal of Health Sciences*, 6(S2), 13350–13354. <https://doi.org/10.53730/ijhs.v6nS2.8588>

## **Efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in a tertiary care teaching hospital in Western Odisha**

**Dr Muralidhar Panigrahi**

MD, Associate Professor. Department of Pharmacology, Bhima Bhoi Medical College & Hospital, Balangir, Odisha

Corresponding author email: [mdpanigrahi@gmail.com](mailto:mdpanigrahi@gmail.com)

**Dr Gujaram Marndi**

MD, Assistant Professor, Department of Pharmacology, Bhima Bhoi Medical College & Hospital, Balangir, Odisha.

Email: [gujaram352@gmail.com](mailto:gujaram352@gmail.com)

**Dr Sabitri Beshra**

MD, Assistant Professor, Department of Pharmacology, Bhima Bhoi Medical College & Hospital, Balangir, Odisha

Email: [sabitri84@gmail.com](mailto:sabitri84@gmail.com)

**Abstract**--Background: Among various types of headaches, Migraine is very common, universal, and disabling neurological disorder. The average prevalence of migraine is about 18% in women and 6% in men. This study was conducted to evaluate efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in a tertiary care teaching hospital in Western Odisha. Materials & Methods: For the present study 58 adult and adolescent (age > 12 years) patients diagnosed with migraine were enrolled equally into 2 groups. Group I patients received Valproate 500 mg once daily dose and group II received Propranolol 40 mg plus Flunarizine 10 mg once daily dose. Parameters such as complete blood count, blood sugar, liver function test, urea, creatinine, sodium, potassium estimation, 12 lead ECG etc. was performed. MIDAS score was also recorded. Results: Group I had 19 males and 10 females and group II had 18 males and 11 females. Reduction of headache at baseline was 9.12 and 8.14, at 1st visit was 6.03 and 5.62 and at 2nd visit was 2.41 and 2.17 and reduction in MIDAS score at baseline was 19.2 and 19.8, at 1st visit was 10.5 and 10.8 and at 2nd visit was 5.2 and 5.4 in group I and II respectively. The difference was significant

( $P < 0.05$ ). Conclusion: Valproate and Propranolol plus Flunarizine combination both were highly effective in migraine prophylaxis.

**Keywords**---flunarizine, propranolol, migraine.

## **Introduction**

Migraine headache is a common, universal, and disabling neurological disorder. The average prevalence of migraine is about 18% in women and 6% in men.<sup>1</sup> Most of the patients with migraine require medication for the acute attack. Patients with an increased frequency of attacks ( $\geq 4$ /month, usually over 4–6 months) or with attacks that are either poorly responsive or unresponsive to acute treatments are preferred candidates for a prophylactic therapy, with an objective to reduce the number of acute migraine episodes.<sup>2</sup> The drugs approved for the prophylactic treatment of migraine headache include flunarizine, propranolol, topiramate, sodium valproate and methysergide. Out of the presently available prophylactic agents, non are universally effective, hence the search continues to identify an agent or combination of items with maximal efficacy and minimal adverse effect.<sup>3</sup> Propranolol is  $\beta$  adrenergic receptor antagonist and is nonselective. Beta blockers were developed primarily for control of cardiac symptoms, but it was found coincidentally that these drugs had a remarkable effect on migraine prevention. Flunarizine is a calcium channel blocker that reduces smooth muscle spasm. Studies suggest that flunarizine is as effective as propranolol or topiramate at reducing the frequency of migraines in adults.<sup>4</sup> Valproate products are FDA-approved drugs to treat seizures, and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches.<sup>5,6</sup> The present study was conducted to assess efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in the study groups.

## **Materials & Methods**

The present study was conducted in Department of Pharmacology, Bhima Bhoi medical college, Balangir. The study consisted of 58 adult and adolescent (age > 12 years) patients of both genders diagnosed with migraine according to the 3rd edition (beta version) of International Classification of Headache Disorders (ICHDIII) criteria of International Headache Society (IHS). All gave their written consent to participate in the study. Data such as name, age, gender etc. was recorded. Patients were divided into 2 groups. Group I patients received Valproate 500 mg once daily dose and group II received Propranolol 40 mg plus Flunarizine 10mg once daily dose. Parameters such as complete blood count, blood sugar, liver function test, urea, creatinine, sodium, potassium estimation, 12 lead ECG etc. was performed. MIDAS score was also recorded. Results thus obtained were subjected to statistical analysis. P value less than 0.05 was considered significant.

## Results

Table I Distribution of patients

Groups	Group I	Group II
Drug	Valproate 500 mg OD	Propranolol 40 mg plus Flunarizine 10 mg OD
Male: Female	19:10	18:11

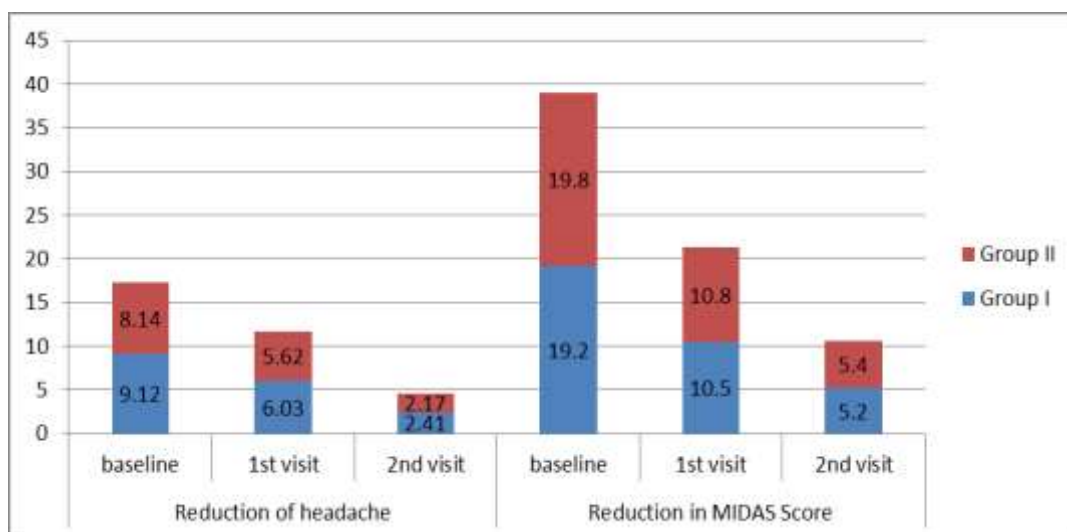
Table I shows that group I had 19 males and 10 females and group II had 18 males and 11 females.

Table II Comparison of parameters

Parameters	Variables	Valproate 500 mg OD	Propranolol 40 mg + Flunarizine 10 mg OD	P value
Reduction of headache	baseline	9.12	8.14	0.04
	1 <sup>st</sup> visit	6.03	5.62	
	2 <sup>nd</sup> visit	2.41	2.17	
Reduction in MIDAS Score	baseline	19.2	19.8	0.15
	1 <sup>st</sup> visit	10.5	10.8	
	2 <sup>nd</sup> visit	5.2	5.4	

Table II, graph I shows that reduction of headache at baseline was 9.12 and 8.14, at 1<sup>st</sup> visit was 6.03 and 5.62 and at 2<sup>nd</sup> visit was 2.41 and 2.17 and reduction in MIDAS score at baseline was 19.2 and 19.8, at 1<sup>st</sup> visit was 10.5 and 10.8 and at 2<sup>nd</sup> visit was 5.2 and 5.4 in group I and II respectively. The difference was significant ( $P < 0.05$ ).

Graph I Comparison of parameters



## Discussion

Efficacy of anticonvulsant drugs for migraine prophylaxis has been tested since long, with sodium valproate being the first drug approved from this group.<sup>7,8</sup> Efficacy of sodium valproate in migraine prophylaxis has also been proven in many studies, where sodium valproate has been compared with different drugs in various doses. The prophylactically effective dose of sodium valproate ranges from 500 to 1500 mg/day.<sup>9</sup> The present study was conducted to assess efficacy of propranolol plus flunarizine combination and valproate monotherapy in migraine prophylaxis in a tertiary care teaching hospital in Western Odisha.

Present study is in consistent with the study of Dakhale et al<sup>10</sup> who compared the efficacy and safety of low-dose sodium valproate and low-dose propranolol sustained release (SR) in the prophylaxis of common migraine headache. The study included 60 patients with common migraine headaches ( $\geq 2$  attacks/month) treated for 12 weeks. The patients were randomly divided into two treatment groups treated by sodium valproate 500 mg/day and propranolol SR 40 mg/day, respectively. The primary outcome measures were the percentage of responders (i.e.,  $>50\%$  decrease in mean headache frequency) at the end of 12 weeks and decrease in mean headache frequency (per 4 weeks) at the end of 12 weeks. The patients were assessed at 0, 4, 8, and 12 weeks of the study. Fifty-five patients completed the study. At the end of the treatment, both sodium valproate and propranolol caused a significant reduction in frequency, severity, and duration of migraine headache. Propranolol caused significantly greater reduction in the severity of headache than sodium valproate. The percentage of responders was 60% in sodium valproate group and 70% in propranolol group. Drowsiness was the most common adverse effect noted in both the groups.

In our present study we found that, headache which was 9.12 and 8.14 respectively in Group 1 and Group 2 at baseline; reduced to 6.03 and 5.62 at 1<sup>st</sup> visit and further reduced to 2.41 and 2.17 in 2<sup>nd</sup> visit respectively and reduction in MIDAS score at baseline was 19.2 and 19.8, at 1<sup>st</sup> visit was 10.5 and 10.8 and at 2<sup>nd</sup> visit was 5.2 and 5.4 in group I and II respectively. The mechanisms of action of propranolol in migraine prophylaxis are not fully understood; it is proposed that propranolol reduces central hyperexcitability through  $\beta_1$ -mediated inhibition of noradrenaline release, thus reducing central catecholaminergic hyperactivity, and enhances antinociception, antagonism of 5-HT<sub>1A</sub> and 5-HT<sub>2B</sub> receptors, which decreases neuronal excitability, and  $\beta_2$ -mediated inhibition of nitric oxide (NO) synthesis by blocking inducible NO synthase.<sup>11</sup>

Banerjee et al<sup>12</sup> in their study found that mean  $\pm$ SD was 35.023 $\pm$ 8.476 and 37.27 $\pm$ 12.44 in Group V and PF respectively and p value was 0.0951 at the baseline, when we studied EQ -VAS and Mean $\pm$  SD in case of duration of headache was 11.76 $\pm$ 3.427 and 10.27 $\pm$ 2.44 and p value was 0.1105. So, in both occasion we found non-significant result. Change of Headache Frequency done within group V (Repeated Measure ANOVA) followed by Wilcoxon match pair post-hoc test, and Mean $\pm$  SD was 9.054 $\pm$ 2.107, 6.027 $\pm$ 1.236 and 2.649 $\pm$ 1.317 respectively from baseline to follow up and p value was very much significant.

## Conclusion

In the present study it is found that valproate and propranolol plus flunarizine combination both were highly effective in migraine prophylaxis.

## References

1. Ichikawa M, Katoh H, Kurihara T, Ishii M. Clinical Response to Valproate in Patients with Migraine. *J Clin Neurol*. 2016;12(4):468-475.
2. Bhat, Majid F, Sidhu, Harpreet S, Goyal M. Evaluation of propranolol, flunarizine and divalproex sodium in prophylaxis of migraine. *International Journal of Basic & Clinical Pharmacology*. 2017;10(6):2463-9.
3. Dakhale GN, Sharma VS, Thakre MN, Kalikar M. Low-dose sodium valproate versus low-dose propranolol in prophylaxis of common migraine headache: A randomized, prospective, parallel, open-label study. *Indian J Pharmacol* 2019; 51:255-62.
4. Reveiz-Herault L, Cardona AF, Ospina EG, Carrillo P. Effectiveness of flunarizine in the prophylaxis of migraine: A meta-analytical review of the literature. *Rev Neurol*. 2003;36(10):907-12.
5. Mitsikostas DD, Polychronidis I. Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. *Funct Neurol*. 1997; 12(5):267-76.
6. Aluisio AR, Zehtabchi S. Valproate for Adult Migraine Prophylaxis. *Am Fam Physician*. 2016;94(9):22
7. Chowdhury MI, Anwar Ullah AKM, Omar Hassan KM, Majumder S. Sodium Valproate in Migraine Prevention: Efficacy is the same as Propranolol. *JAFMC Bangladesh*.2012;8(2):32- 8. 8. Bordini CA, Arruda MA, Ciciarelli MC, Speciali J. Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. *GArq Neuropsiquiatr*. 1997;55(3B):536-41.
8. D'Amico D, Usai S, Grazi L, et al. The impact of primary headaches on patients' lives: Italian experience with the MIDAS and the SF-36 questionnaires. *Headache Care*. 2004;1:123-8. 10. Dakhale GN, Sharma VS, Thakre MN, Kalikar M. Low-dose sodium valproate versus low-dose propranolol in prophylaxis of common migraine headache: A randomized, prospective, parallel, open-label study. *Indian journal of pharmacology*. 2019 Jul;51(4):255.
9. Lucas C, Géraud G, Valade D, Chautard MH, Lantéri-Minet M. Recognition and therapeutic management of migraine in 2004, in France: results of FRAMIG 3, a French nationwide population-based survey. *Headache*. 2006; 46(5):715-25.
10. Ratul Banerjee, Abhijit Das, Shankar Prasad Nandi, Ananya Mandal. Comparing Efficacy of Propranolol Plus Flunarizine Combination and Valproate Monotherapy in Migraine Prophylaxis in Rural Bengal -A Randomized Control Trial. *International Journal of Health and Clinical Research*, 2020;3(10):46-53.