International Journal of Basic & Clinical Pharmacology
Dixit M et al. Int J Basic Clin Pharmacol. 2024 Nov;13(6):884-890
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20243039

Original Research Article

Is the combination of propranolol and flunarizine better than propranolol, flunarizine and amitriptyline alone in prophylaxis of migraine? An observational study at a tertiary care centre of North India

Madhumita Dixit*, Abhishek K. Singh, Dwividendra K. Nim, Rakesh C. Chaurasia

Department of Pharmacology, Moti Lal Nehru Medical College, Prayagraj, Uttar Pradesh, India

Received: 14 September 2024
Accepted: 07 October 2024

***Correspondence:**
Dr. Madhumita Dixit,
Email: dixitmadhumita600@gmail.com

ABSTRACT

Background: Migraine is a primary headache disorder marked by recurrent attacks of pain and associated symptoms. Propranolol is traditionally considered highly effective for migraine prophylaxis, but other drugs have recently shown promise.
Methods: This study was a prospective, observational, randomized, parallel-arm, unicentric trial conducted in the neurology department of a tertiary care hospital in North India. Patients with migraine without aura were randomly assigned to one of four treatment groups. After obtaining consent, patients were randomized using a random number table. Group 1 received propranolol (80 mg), group 2 received flunarizine (10 mg), group 3 received a combination of propranolol (40 mg) and flunarizine (10 mg), and group 4 received amitriptyline (10 mg) daily. The primary outcome was a change in the frequency of migraine days, while secondary outcomes included changes in moderate-to-severe headache days and disability levels.
Results: The combination of propranolol (40 mg) and flunarizine (10 mg) was significantly more effective in reducing the frequency of migraine attacks at the end of 3 months compared to the group receiving amitriptyline (10 mg). However, no significant differences between the groups were observed at baseline, 1 month, and 2 months. For other outcomes, including adverse drug reactions (ADRs), there were no significant differences between the groups.
Conclusions: The combination of propranolol (40 mg) and flunarizine (10 mg) demonstrated superior efficacy over amitriptyline (10 mg) after prolonged treatment, while its effectiveness was comparable to other groups at earlier time points. ADRs were similar across all groups.

Keywords: Efficacy, Safety, Disability, Pain, Headache

INTRODUCTION

Migraine is a common primary headache disorder. It is episodic and disabling to a great extent. It is the second most common cause of headache, and the most common headache-related, and neurologic, cause of disability in the world.[1] It strikes sufferers a few times per year in childhood and then progresses to a few times per week in adulthood, particularly in females.[2] According to the global burden of disease 2015 report, for individuals under 50 years of age, both male and female, it was identified as the third leading cause of disability.[1] A community-based study aimed at estimating prevalence, burden, and risk factors of migraine from Eastern India concluded that 1-year prevalence of migraine was 14.12%.[3]

Migraine is typically characterized by episodic headaches accompanied by specific features such as sensitivity to light, sound, or movement, and is frequently associated with nausea and vomiting. A comprehensive description

defines migraine as a recurrent syndrome of headaches combined with various neurological dysfunction symptoms in differing combinations.[4]

The pathogenesis of migraine headache is complex, involving both neural and vascular elements.[5] The treatment usually takes longer duration and consists of usually multiple drugs for longer period of time.

Migraine pharmacotherapy can be divided into two categories: prophylaxis and treatment. Commonly used prophylactic medications include β-adrenergic blockers, tricyclic antidepressants, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, anticonvulsants, and antidepressants, among others.

These drugs can cause number of adverse effect and involvement of polypharmacy increases the risk for ADRs which can affect patient's health and the quality he is having. Along with it, there is unwanted financial burden for patients and a burden to healthcare system of country. Patients in case of migraine are usually on polypharmacy for a longer duration of time so are more susceptible to development of ADRs.

WHO defined drug utilization research in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".[6] The ultimate goal of drug utilization research must be to assess whether drug therapy is rational or not.[6]

Drug utilization studies can be used to estimate the number of patients exposed to particular drugs in a given period of time, or it can also be used to understand the pattern of use of a particular drug for a specific disease and can be compared to other alternative drugs for the same disease. It also deals with the outcomes of drug use.

This present study will deal with drug utilization study for 3 common drugs or combinations used in prophylaxis of migraine and assessment of their comparative efficacy and safety namely propranolol, flunarizine, a combination of propranolol plus flunarizine, amitriptyline daily.

Propranolol which is a beta blocker is the most common and one of the most effective first-line medications used for migraine prophylaxis. Flunarizine is a nonspecific calcium channel blocker that has shown evidence of some efficacy in migraine prophylaxis. Amitriptyline is an antidepressant which has shown to have some benefit in migraine prevention.

METHODS

Study design, location and duration

This study was conducted after prior permission and approval from institutional ethics committee. It was designed as randomized, prospective, open labelled, parallel group study which was conducted at a single centre at a tertiary care centre of North India over a period of 1 calendar year from July 2019 to June 2020.

Inclusion criteria

Patient of either sexes, with age ≥18 years, with confirmed diagnosis of migraine who needed prophylactic treatment based on clinical presentation and/or criteria proposed by headache classification committee of the international headache society (IHS) as per the international classification of headache disorders, 3rd edition (ICHD-3) 1 and who was willing to give consent. Patients with migraine were considered for preventive treatment in any of the following situations, attacks significantly interfere with patient's daily routines despite acute treatment. Frequent attacks (≥4 monthly headache days). Contraindication to, failure, AEs with acute treatments or overuse of acute treatments, with overuse defined as: 10 or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused and 15 or more days per month for nonopioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs [including aspirin]).

Exclusion criteria

Age less than18 years with any other types of headaches not confirmed to be migraine including Headache attributed to trauma or injury to the head and/or neck, cranial and/or cervical vascular disorder, non-vascular intracranial disorder, infection, homeostasis or headache attributed to a substance or its withdrawal. Any type of migraine cases who does not require prophylaxis are also excluded from the study. The exclusion criteria also include headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure, headache associated with psychiatric disorder, painful lesions of cranial nerves and other facial pain. Those not willing to give consent are also excluded.

Methodology

On the very first visit, patients were evaluated for general information, present and past symptoms, general and systemic examination and the symptoms related to migraine. Patient diagnosed as a case of migraine requiring prophylactic treatment attending the outpatient department of a tertiary care centre, were enrolled after selecting them on basis of inclusion and exclusion criteria after signing the consent from provided to them in both Hindi and English language.

After getting consent the patients were randomised using random number table in three treatment groups. Group one received propranolol (80 mg), group 2 received flunarizine (10 mg), group 3 received a combination of propranolol

(40 mg) and flunarizine (10 mg) and group 4 received Amitriptyline (10 mg) daily dose.

The primary outcome of this part was change in frequency of migraine days.

The secondary outcomes were change in moderate to severe headache days and change in disability. ADRs were also assessed for comparing safety of individual groups

A 28-day prospective baseline period using a headache diary was ensured. Headache characteristics (pain quality, intensity, location, and relationship with routine physical activity) and use of acute headache medication were adequately assessed with a headache diary. Subjects indicate whether a headache was present (yes/no), its peak severity (mild/moderate/severe) and duration (<4 or ≥4 h), acute medication intake type (triptan/ergotamine/other) and migraine associated symptoms. Response to treatment was also recorded.

Patients were evaluated at baseline for number of migraine days per month, moderate to severe days per month and disability assessment by migraine disability assessment (MIDAS questionnaire). The intensity of pain was measured on numeric pain scale. They were followed for a three months period during which they were instructed to maintain a headache diary. Patients were asked to return on days 1, 2 and 3 months.

Diagnosis confirmed diagnosis of migraine was done based on clinical presentation and/or criteria proposed by IHS as per the ICHD-3.[1]

Clinical scoring system

Pain assessment

For pain assessment 11-point numerical rating scale was used. NRS is responsive and easy-to-use in everyday practice; evidence from trials in other painful conditions suggests that the NRS may offer a higher discriminatory capability than a categorical scale for pain exacerbations.[7,8]

The NRS can be administered verbally or in a written format, is simple and easily understood, and is easily administered and scored. NRS typically consists of a series of numbers with verbal anchors representing the entire possible range of pain intensity. Generally, patients rate their pain from 0 to 10. Zero represents "no pain," whereas 10 represents the opposite end of the pain continuum (e.g., "the most intense pain imaginable," "pain as intense as it could be," "maximum pain").[8]

Disability assessment

Once a diagnosis of migraine has been established, it is important to assess the extent of a patient's disease and disability. In this present study MIDAS score was used to access disability. It is a well-validated, easy-to-use tool and reliable instrument to evaluate different aspects of migraine caused disability.[4,9]

In an international study aimed to access reliability of MIDAS score (MIDAS) it was concluded that the reliability and internal consistency of the MIDAS were similar to that of a previous questionnaire (Headache impact questionnaire).[10]

However, the MIDAS required fewer questions, was easier to score, and provided intuitively meaningful information on lost days of activity in three domains.[10]

Statistical evaluation and interpretation

For all statistical evaluation significance level was taken 95% ($p<0.05$ was taken to indicate statistical significances). The power of study was 80. The normality of the data was accessed with Shapiro-Wilk test. All tests were two tailed with significance level of 0.05. Friedman test and post hoc Wilcoxon-Signed rank test was used for individual sample repeated measures. Independent sample Kruskal-Wallis's test and Kruskal-Wallis one way ANOVA was used to compare between the groups. All statistical analyses were performed using SPSS software version 23.

RESULTS

Patients attending medicine OPD on particular days with symptoms of migraine who have confirm diagnosis of migraine done based on clinical presentation and/or criteria proposed by IHS as per the (ICHD-3) and who require prophylactic treatment for migraine were invited to participate in the study.

For prophylactic treatment of the study 98 patients met inclusion criteria and were enrolled for study initially. The 17 of them did not came for follow up 81 patients completed the follow up and were included in final analysis (Figure 1).

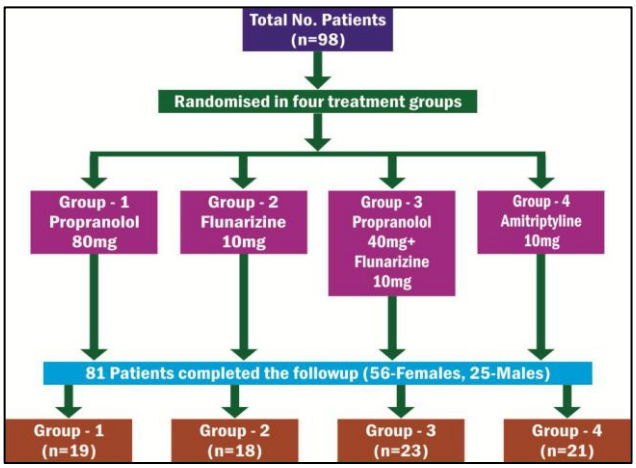

Figure 1: Study plan.

Demographic distribution details

In our study, total 81 cases were observed 56 of which were females and 25 males. Mean age of presentation was 32.98±7.71, group wise mean age of presentation was in group 1 (35.21±8.74), group 2 (32.27±7.96), group 3 (33.30±7.67), group 4 (31.19±6.34).

The cases were randomly divided in four groups. Group 1 (n=19) received propranolol (80 mg), group 2 (n=18) received flunarizine (10 mg), group 3 (n=23) received a combination of propranolol (40 mg) + flunarizine (10 mg) and group 4 (n=21) received amitriptyline (10 mg) daily dose.

Primary outcome

To evaluate the decrease in frequency of migraine days per month at 1 month, 2 month and 3 months, Friedman's test and post hoc Wilcoxon Signed-Rank test was applied and it was observed that each of the drug reduced the frequency of migraine attacks at 1 month, 2 month and 3 months significantly ($p<0.05$)

To evaluate the difference in frequency of migraine days per month between the 4 groups of patient's independent sample Kruskal-Wallis's test was performed at different time intervals namely at baseline, 1 month, 2 months, 3 months. The test revealed that there was significant difference between groups at 3 months ($p=0.023$) (Table 1).

On evaluating further Kruskal-Wallis 1-way ANOVA test was applied, pairwise comparisons were made for number of monthly migraine attack at 3 months. There was statistically significant difference found between group 3 and 4 at 3 months (Table 2).

To evaluate the change in number of moderate to severe headache days per month at 1 month, and 3 months, Friedman's test and post hoc Wilcoxon Signed-Rank test was applied and it was observed that each of the drug reduced the frequency of migraine attacks at number of moderate to severe Headache days per month at 1 month and 3 months.

To evaluate the change in moderate to severe headache days in between each group independent sample Kruskal-Wallis's test was performed at baseline and at 3 months. The test revealed that there was no significant difference between the groups at 3 months ($p=0.065$) (Table 3).

Secondary outcome

To evaluate the disability limitation within the groups at baseline and at 3 months Wilcoxon Signed-Rank test was applied and the disability was reduced significantly for each of the four groups at 3 months ($p<0.05$).

For evaluating the disability limitation comparison between groups, Independent Sample Kruskal-Walli's test was applied for MIDAS score at baseline and at 3 months. It showed no statically significant difference between the groups at both time periods (Table 4).

For evaluating the ADRs comparison between groups, Independent Sample Kruskal-Wallis's test was applied and there was no statistically significant difference observed between the groups (Table 5, Figure 2 and 3).

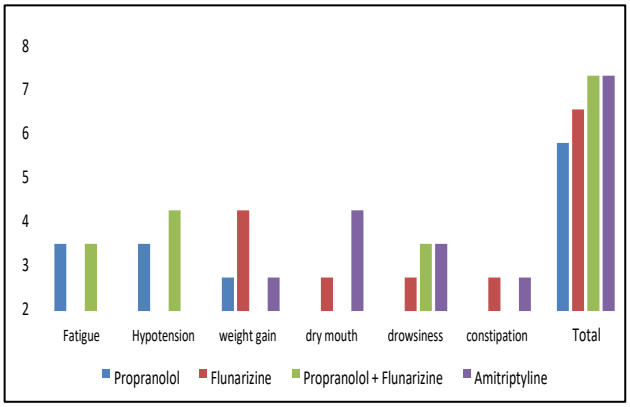

Figure 2: ADRs for different drugs used for prophylaxis of migraine.

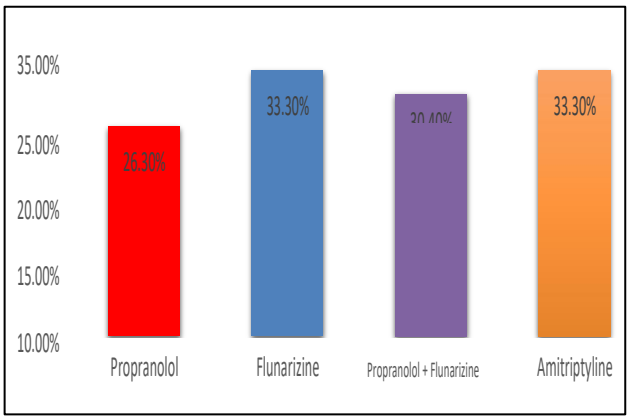

Figure 3: Percentage ADRs for different drugs used for prophylaxis of migraine.

Table 1: Comparative analysis of drug groups used for prophylaxis of migraine for number of monthly migraine days.

Variable	No. of monthly migraine days at baseline	No. of monthly migraine days at 1 month	No. of monthly migraine days at 2 months	No. of monthly migraine days at 3 months
P value	0.444	0.505	0.162	0.023

Table 2: Comparative analysis of drugs used for number of migraine daysper month at 3 months.

Groups	No. of migraine days per month at 3 months, p value
Propranolol+ flunarizine-propranolol (group 3- group 1)	1.000
Propranolol+ flunarizine-flunarizine (group 3- group 2)	0.455
Propranolol+ flunarizine-amitriptyline (group 3- group 4)	0.015
Propranolol-flunarizine (group 1-group 2)	1.000
Propranolol-amitriptyline (group 1-group 4)	0.470
Flunarizine-amitriptyline (group 2-group 4)	1.000

Table 3: Comparative analysis of drugs used for no of moderate to severe headache days per month.

Variable	Baseline no. of moderateto severe headache daysper month	At 3 months no of moderateto severe headache days per month
P value	0.552	0.065

Table 4: Comparative analysis of drugs used for MIDAS score.

Variable	MIDAS score at baseline	MIDAS score at 3 months
P value	0.816	0.168

Table 5: ADRs of different group of drugs used prophylaxis of migraine.

Variables	Propranolol, (n=19)	Flunarizine, (n=18)	Propranolol + flunarizine, (n=23)	Amitriptyline, (n=21)
Fatigue	2	0	2	0
Hypotension	2	0	3	0
Weight gain	1	3	0	1
Dry mouth	0	1	0	3
Drowsiness	0	1	2	2
Constipation	0	1	0	1
Total	5	6	7	7
Percentage	26.3%	33.3%	30.4%	33.3%

DISCUSSION

In the present prospective observational study, a trial, which was carried out at department of medicine at Swaroop Rani Nehru hospital, Prayagraj and Moti Lal Nehru medical college, Prayagraj over a period of one year from 2019 to 2020, efficacy and safety profiles of various drugs used in acute and prophylactic treatment of migraine in outpatient department of above-mentioned hospital was studied.

The patients were diagnosed for migraine attending outpatient department of medicine department on specified dates of Swaroop Rani Nehru hospital, Moti Lal Nehru medical college Prayagraj, based on the criteria led by IHS. Further patients were evaluated based on criteria for instituting prophylactic therapy.

Cases were randomly divided in four groups. Group 1 (n=19) received propranolol (80 mg), group 2 (n=18) received flunarizine (10 mg), group 3 (n=23) received a combination of propranolol (40 mg) and flunarizine (10 mg) and group 4 (n=21) received amitriptyline (10 mg) daily dose. The groups were evaluated at baseline for number of migraine days per month, number of moderate to severe headache days per month and disability assessment by MIDAS Questionnaire. The intensity of pain was measured on numeric pain scale. They were followed for a three months period during which they were instructed to maintain a headache diary. Patients was asked to return on days 1 month, 2 months, 3 months.

The ADRs for each group was observed after administration of the drug. ADR causality assessment was done with the Naranjo probability scale for each group. in recent years the "Naranjo ADR probability scale," has gained popularity among clinicians because of its simplicity.[11,12]

Outcome measures

On comparing the frequency of migraine days per month at baseline, 1 month, 2 months, 3 months within each group it was observed that the reduction was significant in each of the group.

On comparing the frequency of migraine days per month at baseline, 1month, 2 month and 3 months in between all

the groups, there was significant difference between the groups at 3 months (p=0.023). At Baseline, 1 month and 2 months there was no significant difference between the groups. On further evaluating, the significant difference was found in between group 3-group 4 (propranolol + flunarizine-amitriptyline) p=0.015. There was no significant difference between group 1-4 and group 2-4 similar to our study

Demirkaya et al in their study concluded that there was no significant difference between flunarizine and amitriptyline in reducing the frequency and severity of migraine.[13] There was no significant difference between these two while comparing the adverse effects caused by them.

There was no significant difference between groups 1-2, 2-3 and 1-3 as found in our study similarly Bordini et al in their double-blind trial comparing propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis concluded that no significant differences were found in the baseline period between the 3 groups.[14] Comparing the values from 3 groups during the last 20 days on drugs period, no significant differences were found either. The percentage decrease in the frequency of migraine attacks for propranolol group was 55% (from 2.8 to 1.26), for the flunarizine group was 54% (from 2.6 to 1.2) and for two-drugs group was 61% (from 2.9 to 1.13). Shimell et al conducted a comparative trial of flunarizine and propranolol in the treatment of migraine.[15] Fifty-eight patients were entered into a double-blind 4-month treatment trial. There was no significant difference between the two groups in terms of patient profile, onset of response to therapy, final response to therapy, incidence of dropout from the trial or incidence of side-effects. Ludin et al analysed the clinical efficacy of flunarizine and of propranolol for the prevention of migraine attacks assessed in a multicentre double-blind study lasting four months which was preceded by a single-blind placebo period of one month.[16] He observed that both drugs produced a significant reduction of the number of attacks. Propranolol furthermore significantly reduced the severity of attacks and the number of analgesics used during the attacks. In both groups no severe side effects were observed.

On comparing the change in moderate to severe headache days at baseline and at 3 months within each group it was observed that the change was significant in each of the group.

On comparing the change in moderate to severe headache days at baseline and at 3 months in between the groups no significant difference in between the groups was observed.

On comparing the disability assessment by MIDAS questionnaire at baseline and at 3 months within each group, it was observed that the change was statistically significant in each of the group.

On comparing the disability assessment by MIDAS questionnaire at baseline and at 3 months between the groups, there was no significant difference observed between the groups.

On comparing ADRs between various groups, group 2 and 4 showed maximum number of ADRs (33.33%) while group 1 showed minimum (26.30%).

A lot of caution has been exercised to conduct this present study however there are several limitations for our study. This study is done over a period of 12 months including 6 months of follow-up. So, some dietary and lifestyle parameter changes might have influenced the study. There may be the question of compliance with the use of study drugs. Another limitation of this study might be the individual difference in pain perception for different individuals. The final limitation is the power of the study and also the duration of the Study to ascertain long term effects and safety. Larger groups and longer follow up as needed for acquiring more information.

CONCLUSION

To conclude, on the basis of efficacy each of the drug reduced the frequency of migraine attacks at 1 month, 2 month and 3 months significantly. While comparing the individual groups it was found that combination of propranolol (40 mg) and flunarizine (10 mg) was significantly better in reducing the frequency of migraine attacks at the end of 3 months when compared to group receiving amitriptyline (10 mg) though at baseline, 1 month and 2 months there was no significant difference between the groups.

On comparing change in number of moderate to severe headache days and disability assessment at baseline and at 3 months within groups it was observed that change was statistically significant in each of the group while there was no significant difference between the groups. As per ADRs comparison between groups, there was no statistically significant difference observed between the groups. Though these findings were evident from present study but it may need further validation and larger sample size.[1]

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dixit M, Singh AK, Nim DK, Chaurasia RC. Is the combination of propranolol and flunarizine better than propranolol, flunarizine and amitriptyline alone in prophylaxis of migraine? An observational study at a tertiary care centre of North India. Int J Basic Clin Pharmacol 2024;13:884-90.