WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 6, Issue 1, 810-828. Research Article ISSN 2277– 7105

A COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF ORAL FLUNARIZINE TO ORAL PROPRANALOL IN PROPHYLAXIS OF MIGRAINE IN A TERTIARY CARE HOSPITAL IN BANGALORE

[1]Dr. Pavithra Krishnan, [2]*Dr. Shabeer D., [3]Dr. Basavaraj Bhandare, [4]Dr. Satyanarayana V.

[1,2]Post Graduate Student, Department of Pharmacology, Rajarajeswari Medical College and Hospital, Bangalore.

[3,4]Professor, Department of Pharmacology, Rajarajeswari Medical College and Hospital, Bangalore.

Article Received on
28 Oct. 2016,

Revised on 18 Nov. 2016,
Accepted on 08 Dec. 2016

DOI: 10.20959/wjpr20171-7593

***Corresponding Author**
Dr. Pavithra Krishnan
Post Graduate Student, Department of Pharmacology, Rajarajeswari Medical College and Hospital, Bangalore.

INTRODUCTION

Headache disorders are a public-health concern given the large amount of associated disability and financial costs to society. As headache disorders are most troublesome in the productive years of life, between the ages of 20 and 35, estimates of their financial cost to society – principally from lost working hours and reduced productivity, are massive.[1]

It is a common disorder thought to exist in 12% of general population. It has a prevalence of 18%in woman, 6% in men and 4% in children.[2]

Migraine is a chronic neurological disease characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. The word derives from the Greek word *hemikrania*, "pain on one side of the head", *hemi-* which means half and *-kranion*, which means skull.[3]

Migrane is defined as “Migraine is a benign and recurring syndrome of headache associated with nausea, vomitingandwith certain features such as sensitivity to light, sound, or movement and other symptoms of neurologic dysfunction in varying admixtures”.[4]
Migraines were first divided into the two types - migraine with aura (*migraine ophthalmique*) and migraine without aura (*migraine vulgaire*) in 1887 by Louis Hyacinthe Thomas, a French Librarian.[5]

Trepanation, the deliberate drilling of holes into a skull, was practiced as early as 7,000 BCE.[6] While sometimes people survived, many would have died from the procedure due to infection. It was believed to work via "letting evil spirits" escape.[7] William Harvey recommended trepanation as a treatment for migraines in the 17th century.[8]

The International Headache Society (IHS) also classifies migraine as migraine with aura and migraine without aura, aura being the complex of focal neurological symptom that precedes or accompanies an attack.[9] The effective management of migraine involves the active treatment of acute episodes (abortive) combined with non-pharmacological and pharmacological treatments for the prevention of migraine.

The goal of preventive treatment should be to prevent or reduce the frequency of migraine attacks, to reduce duration and severity of attack, to improve response to abortive medications, to improve patient function and quality of life.

Options for prophylactic therapy are limited as some have adverse side effects and a few drugs like beta blockers have specific contraindication.

Beta blockers exert anti migraine effects through their action on 5-HT_2 receptors. Propranolol 80-240 mg/day and Timolol 20-30 mg/day have been approved for migraine prevention by the FDA in the United States.[10] Adverse effects reported most commonly with beta-blockers were fatigue, depression, nausea, dizziness, and insomnia. These medications are contraindicated in certain disorders such as asthma, chronic lung disease, diabetes, hypoglycemia, bradycardia, hypotension, Raynaud's disease, peripheral vascular disease and severe depression.[11]

Calcium channel antagonists have been used for several years for prevention of migraine,

But none have been recommended as first line treatment for migraine by the FDA. Flunarizine, 5-10 mg/d, has proven efficacy in the prevention of migraine and is most commonly used.

The most common side effects reported with calcium channel antagonists are constipation and fluid retention in the ankles. Calcium channel antagonists are contraindicated in congestive heart failure, heart block, bradycardia, sick sinus syndrome and other cardiac problems. Flunarizine is associated with depression, weight gain and secondary Parkinson's

syndrome. It should be used with caution in elderly patients. Unlike beta blockers it can safely be used in asthmatic and diabetic patients.[12]

This study intends to compare Flunarizine, a cerebro-specific calcium channel antagonist and Propranolol, a gold standard beta blocker in the prophylaxis of migraine. As very few such comparative studies have been done on our population with the use of both Flunarizine and Propranolol, there is an additional advantage to study their efficacy and safety in migraine prophylaxis.

AIM OF THE STUDY

This study attempts to compare the therapeutic efficacy of Flunarizine (group II) with the gold standard prophylactic agent Propranolol (group I) in the reduction of migraine attacks and to assess the safety profile of the drugs in the two study groups at the end of a 3 month treatment period.

MATERIALS AND METHODS

The study entitled "A comparative study of theefficacy and safety of oral Flunarizine versus oral Propranalol in prophylaxis of migraine in a Tertiary Care Hospital in Bangalore**"** was conducted for a period of one year starting from November 2013 to December 2014 on patients diagnosed with migraine attending ENT Out Patient Department at Rajarajeswari Medical College and Hospital, Bangalore.

An oral and written informed consent was taken from the migraine subjects before theirinclusion in the study. The ethical clearance was obtained from the Institutional Ethical Committee. The study was conducted as per the WHO guidelines for controlled clinical trials as per the HELSINKI DECLARATION.

Patients were free to dropout/withdraw from the study without any need to give detailed reason for withdrawal. The investigator may withdraw the patient from the study if:

- Significant recurrent illness or requires surgical intervention during the study period.
- Serious adverse drug reactions during the study period.
- Patients who fail to comply with the requirements of the study protocol.

The subjects were selected based on the following inclusion and exclusion criteria.

INCLUSION CRITERIA

1. History of migraine (>1 year) diagnosed according to IHS criteria.
2. Patients with 3 to 12 migraine headaches and no more than 15 headache days to avoid tension type headache/status migranicus.
3. Age group between 18 to 65 years.
4. Proved otherwise healthy after clinical examination

EXCLUSION CRITERIA

1. Use of prophylactic medication like β blockers, Antiepileptics, MAOInhibitors, Calcium Channelblockers, Antidepressants, Botulinm toxins etc 3 months prior to inclusion in the study.
2. Tension type headache>5 days per month.
3. Patients with history of asthma, bradyarrythmias, diabetes and any other limitation to the use of beta blockers.
4. Use of vitamin supplements.
5. History of drug dependence or alcohol abuse or regular smoking of more than 20 cigarettes per day.
6. Abnormal LFT/RFT.
7. Pregnancy/lactation
8. Transformed migraine/Chronic daily headache/Cluster headache/Cluster migraine.
9. Any significant CVS, CNS, Renal or Respiratory dysfunction.
10. History of psychiatric disorder that may impair the ability of the patient to give written informed consent.
11. Participation in any clinical trial within 6 weeks preceding day 1 of study.
12. Patient refuses to give consent.

All the patients received the drug from a trained study investigator who also ensured that adequate instructions have been given to the patients before the medication.

Patients fulfilling the above mentioned criteria were recruited for the study and randomly assigned using computerized randomization table to either of the two groups.

GROUP 1: Tablet Propranolol 40 mg twice daily.
GROUP 2: Tablet Flunarizine 10 mg once daily.

Patients who got Tab Propranolol were asked to take the drug once in the morning and onecat bed time. Flunarizine was prescribed as a single dose at bedtime. All patients were issued a migraine diary and explained how to record the number and duration of attacks, severity of migraine headaches according to the visual analogue scale (VAS). They were asked to come for follow-up regularly at the end of 1^{st}, 2^{nd} and 3^{rd} month respectively. All patients were reminded of the follow-up through telephonic interview. During the follow-up migraine diaries of the included subjects were cross-checked along with the compliance to the drug. Patients were allowed to use concomitant rescue medication to abort migraine attacks and record the same in the diary issued.

Pateints were instructed to report to the investigator in case of any adverse reactions and these were monitored during the entire study period. The clinical Pharmacologist or the physiscian was consulted for the necessary action.

All the adverse drug reactions and treatment administered were recorded in the final report.

STATISTICAL METHODS

Descriptive statistical analysis has been carried out in the present study. Results oncontinuous measurements are presented on Mean ± SD (Min-Max) and results oncategorical measurements are presented in Number (%). Significance is assessed at 5% level of significance.

Studentt test (two tailed, independent) has been used to find the significance ofstudy parameters on continuous scale between two groups (Inter group analysis) Chisquare/Fisher Exact test has been used to find the significance of study parameters oncategorical scale between two or more groups.

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$).

* Moderately significant (P value: $0.01<P \leq 0.05$).

** Strongly significant (P value: $P \leq 0.01$).

Statistical software

The Statistical software namely SAS 9.0, SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

Table 1: Age distribution between the two groups

Age in years	Group I Propranolol		Group 2 flunarizine	
	No	%	No	%
<20	12	24	13	26
21-30	22	44	20	40
31-40	10	20	12	24
41-50	4	08	2	04
51-60	2	04	3	06
Mean± SD	29.20±8.04		28.28±10.80	

Samples are age matched between two groups (p=0.633) with no statistically significant difference.

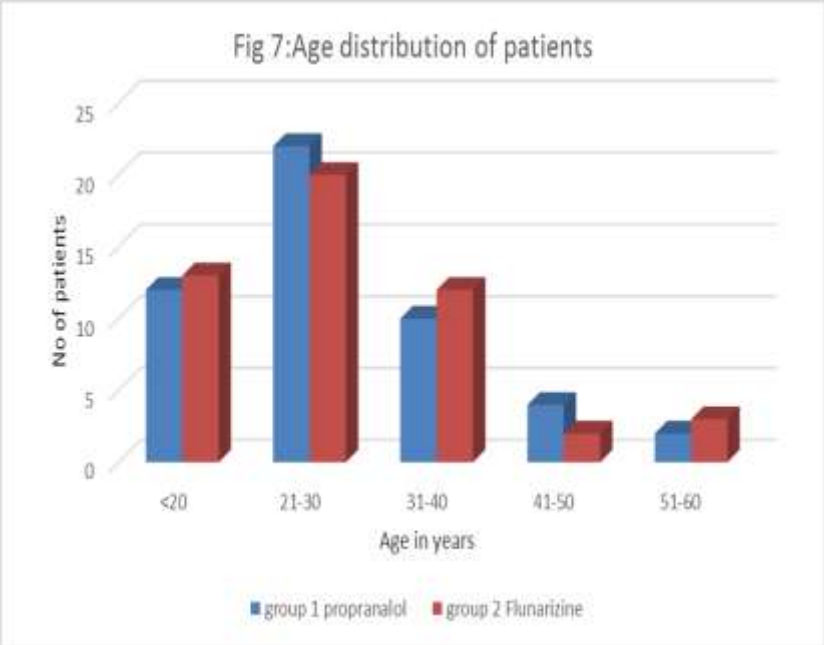


Table 2: Gender distribution between the two groups

Gender	Group I Propranolol		Group 2 flunarizine	
	No	%	No	%
Male	21	42	22	44
Female	29	58	28	56
total	50	100	50	100

There is no statistically significant difference (p=0.832) between genders among the two groups.

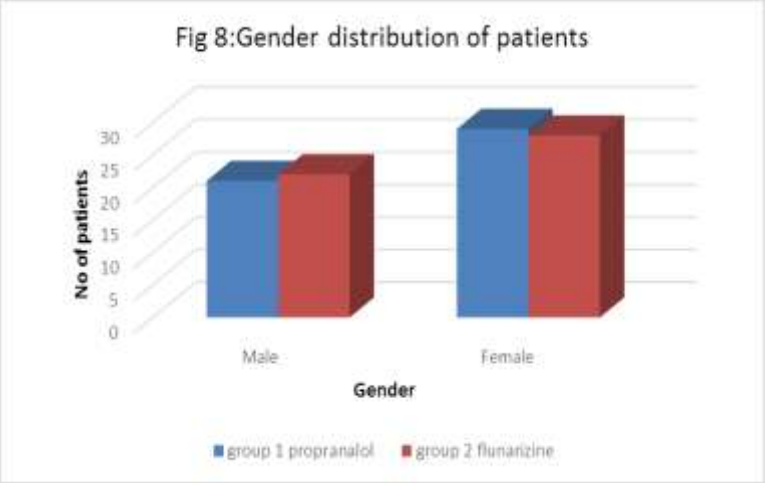


Table: 3 Type of migraine between the two groups

Type of migraine	Group I Propranolol		Group 2 flunarizine	
	No	%	No	%
With aura	15	30	33	66
Without aura	35	70	17	34
Total	50	100	50	100

No statistical significance between the two groups.(p=0.651).

Fig 9: Distribution of type of migraine

Table: 4 Duration of migraine in years between the two groups

DURATION OF MIGRAINE IN YEARS	Group I Propranolol		Group 2 flunarizine	
	No	%	No	%
1-5	27	54	23	46
6-10	21	42	23	46
>10	2	04	4	08
Total	50	100	50	100

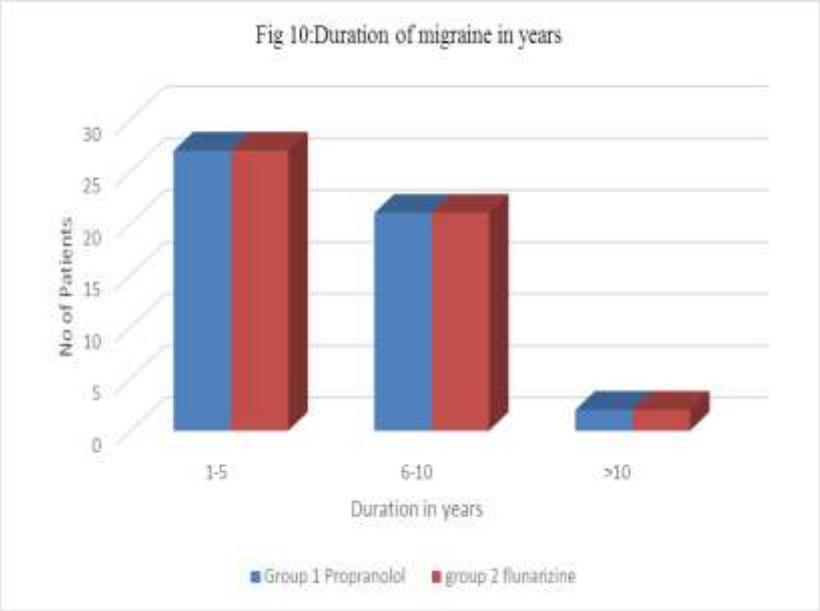


Table: 5 Positive family history of migraine between the two groups

FAMILY HISTORY	Group I Propranolol		Group 2 Flunarizine	
	No	%	No	%
Present	14	28	10	20
Absent	36	72	40	80
Total	50	100	50	100

No statistical significance between two groups (P=0.38).

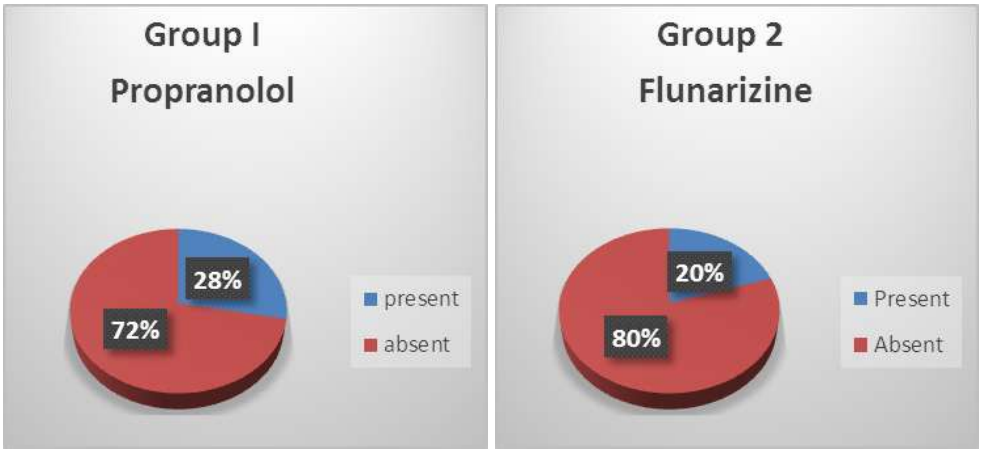


Fig 11: Family history of migraine between the two groups

Table 6: Baseline Migraine Characteristics(presented as Mean ± SD)

Baseline variables	Group I Propranolol	Group 2 Flunarizine	P value
Frequency/month (in days)	10.82±0.73	11.02±0.78	0.189
Average Duration (in hours)	12.84±1.20	12.76±1.28	0.748
Severity by VAS (%)	71.08±1.20	71.12±1.12	0.863

Table 7: Comparative evaluation of frequency of headaches per month between two groups on treatment

Study period	Group I Propranolol	Group 2 flunarizine	P value
Baseline	10.82 ± 0.73^{a1}	11.02 ± 0.86^{a2}	0.189
1st month	6.62 ± 0.68^{b1}	6.83 ± 0.72^{b2}	0.139
2nd month	5.62 ± 0.68^{c1}	4.88 ± 0.75^{c2}	<0.001**
3rd month	3.82 ± 0.62^{d1}	2.85 ± 0.71^{d2}	<0.001**
Significance Baseline-3rd month	<0.001**	<0.001**	
%change (Baseline-3rd month)	62.62%	75.92%	

Non similar superscripts(a1,b1,c1,d1)(a2,b2,c2,d2) are similar at 5% level of significance≤0.05).

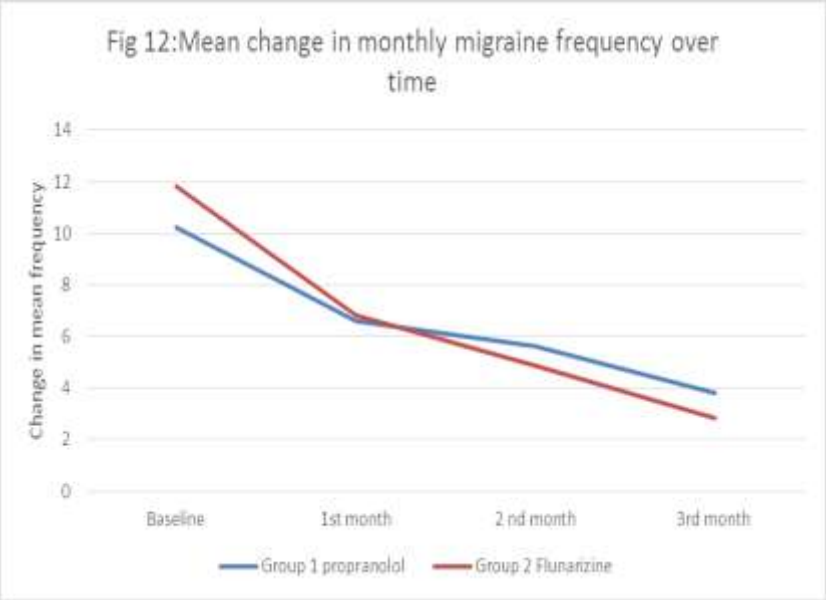


Table 8: Comparative evaluation of duration of headache in hours between the two Groups

Study period	Group I Propranolol	Group 2 flunarizine	P value
Baseline	12.84 ± 1.20^{a1}	12.20 ± 1.36^{a2}	0.748
1st month	8.87 ± 1.62^{b1}	7.66 ± 1.28^{b2}	0.008
2nd month	7.26 ± 1.36^{c1}	6.82 ± 1.18^{c2}	<0.001**
3rd month	6.08 ± 1.20^{d1}	3.26 ± 1.08^{d2}	<0.001**
Baseline-3rd month	<0.001**	<0.001**	
%change (Baseline-3rd month)	52.3%	73.27%	

Non similar superscripts (a1,b1,c1,d1)(a2,b2,c2,d2) are similar at 5% level of significance≤0.05).

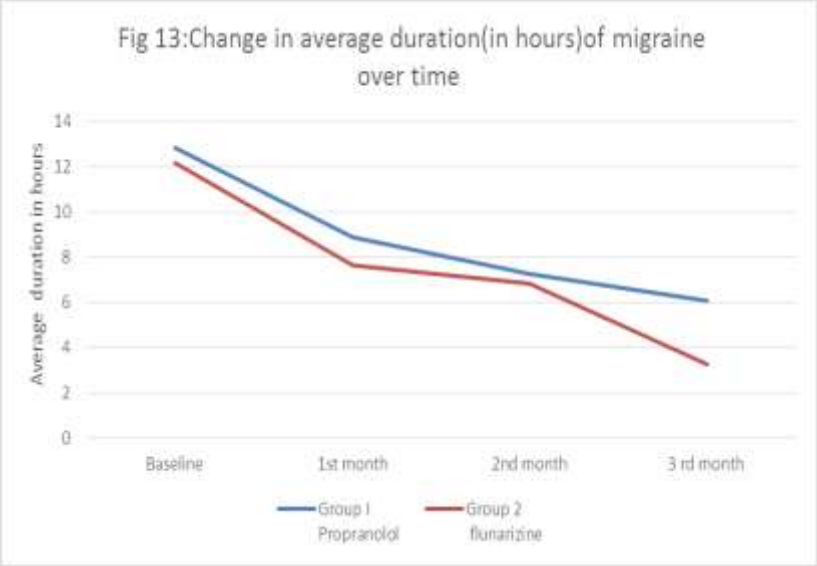
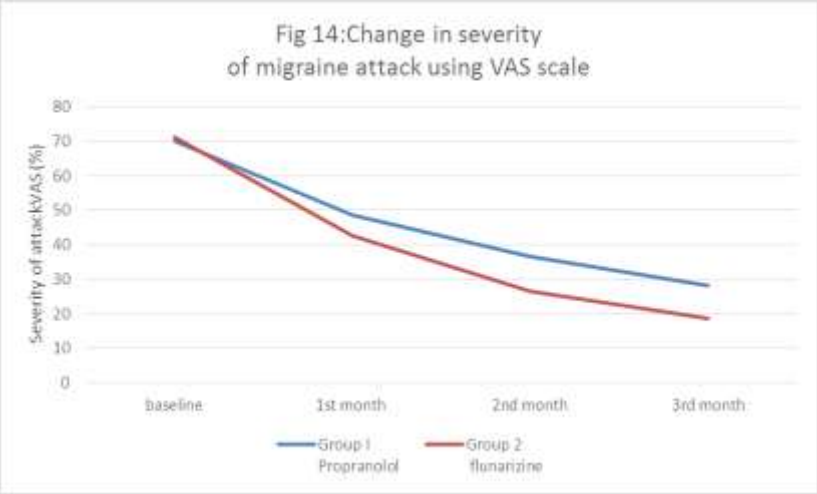


Table 9: Comparative evaluation of change in severity of migraine attack using VAS (in%) scale between the two Groups

Study period	Group I Propranolol	Group 2 flunarizine	P value
Baseline	70.08±1.88	71.12±1.86	0.863
1st month	48.56±3.64	42.60±3.88	0.001
2nd month	36.64±3.86	26.45±3.02	<0.001
3rd month	28.08±2.02	18.55±2.64	<0.001
Baseline-3rd month	<0.001	<0.001	
%change (Baseline-3rd month)	59.9%	73.9%	

Non similar superscripts (a1,b1,c1,d1) (a2,b2,c2,d2) are similar at 5% level of significance≤0.05).



Non similar superscripts (a1,b1,c1,d1)(a2,b2,c2,d2) are similar at 5% level of significance≤0.05).

Table 10: Responder rate [≥50%]

Responder rate [≥50%]	Group I Propranolol		Group 2 flunarizine		P value
Frequency/month	39	78%	40	80%	0.652
Average duration	40	80%	41	82%	0.762
Severity of attack	38	79%	40	80%	0.547

No statistical difference between the two groups at [≥50%] responder rate in all the migraine characteristics.

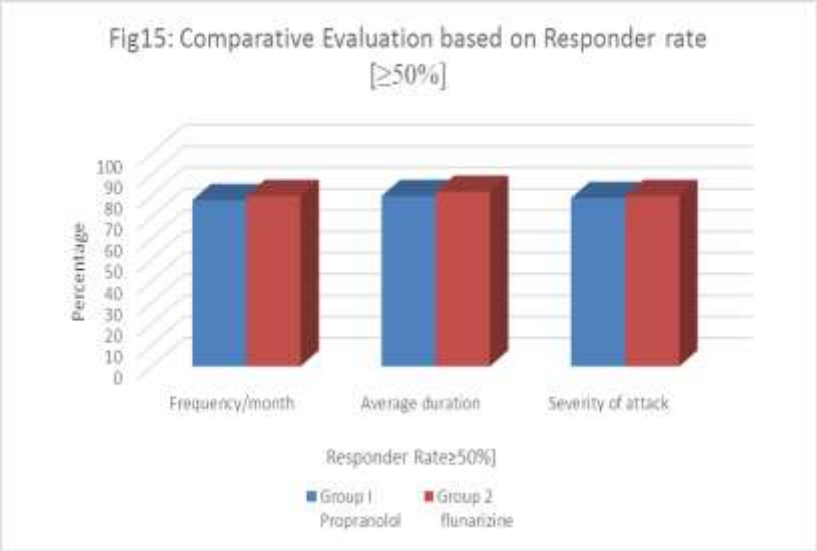


Table 11: Responder rate [≥75%]

Responder rate [≥75%]	Group I Propranolol		Group 2 Flunarizine		P value
	N	%	N	%	
Frequency/month	20	40	35	70	<0.05
Average duration	21	42	30	60	<0.05
Severity of attack	19	38	34	68	<0.05

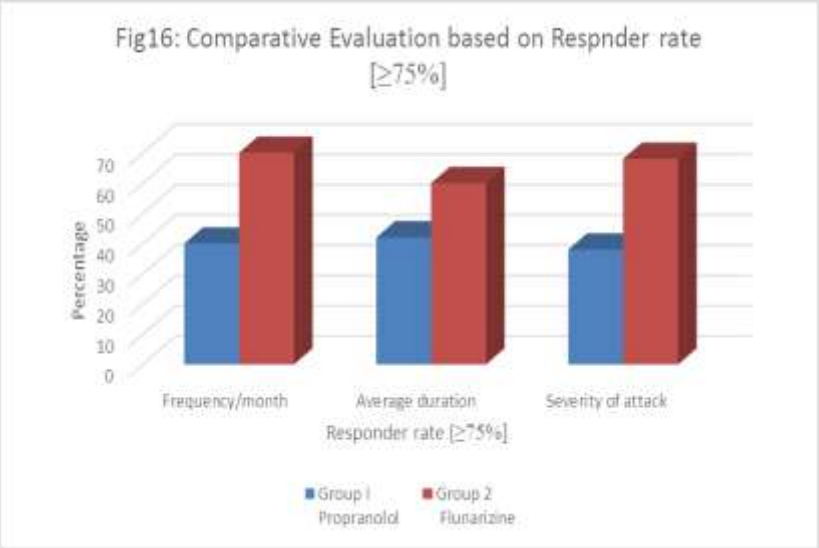


Table12: Comparative evaluation of body weight (kgs) in both treatment groups

Study period	Group I Propranolol	Group 2 Flunarizine
Baseline	56.06±9.08	55.05±10.64
1st month	56.28±11.62	56.88±9.06
2nd month	56.46±10.08	57.54±10.86
3rd month	56.88±8.98	57.94±11.04
Significance(p value) Baseline-3rd month	0.645	<0.001**

Table 13: Comparative evaluation of side effects between the two groups on treatment

Side effects	Group I Propranolol		Group 2 Flunarizine	
	No	%	No	%
Present	22	44	38	76
Absent	28	56	12	24
• Fatigue	8	16	10	20
• Dizziness	6	12	-	-
• Somnolescence	1	2	8	16
• Nausea	1	2	-	-
• Vomiting	-	-	-	-
• Weight gain	6	12	28	56

ANALYSIS OF RESULTS

Analysis of the results of the present study on shows that the age and gender distribution between the two groups in both study arms were age and sex matched. (p =0.633 and 0.762 respectively). The mean age was observed to be 29 years and the most common age group

was between 21-30 years. The study revealed a female preponderance in both the treatment groups. [**Table 1 and 2].**

The most common type ofmigraine was migraine without aura in both the groups**. [Table 3]** The length of migraine in years was compared between the two groups. Our study showed 54% of the patients in the Propranalol group with 1-5 years history of migraine while 46% of the patients in the Flunarizine group had a history of migraine for 1-5 years and 46% in 6-10 years.**[Table4]** Apositive family history was noted in 28% of patients in the Propranolol group and 20% in The Flunarizine group **[Table 5].** Baseline values of frequency, duration of headache and VAS (%) were statistically similar in both groups as shown in [**Table 6].** The aim of the present study was to evaluate the frequency of headaches per month inthe two treatment groups. The findings of this study show a significant reduction in thefrequency of migraine headaches at the end of the 1st month of treatment in both the groups with the significanc between baseline to 3rd month being<0.001(extremely significant).There was significant reduction in the first month itself in both the groups(≤0.05). Flunariizine showed statistically significant reduction in frequency of migraine attack when compared to propranolol**. [Table 7].**

On evaluation of the duration of migraine headache, the present study showed that Prpranolo treatment group showed a reduction from 12.84±1.20 to 6.08±1.20 which was statistically significant. (,0.001) Flunarizine group showed a reduction from 12.20±1.36 to 3.26±1.08 which is statistically significant. Between groups, Flunarizine showed better results when compared to propranolol group**. [Table 8].**

On evaluation of change in severity using the VAS scale, significant reduction is seen in both the griups. The percentage reduction from baseline to 3rd month in the prpranolo group was found to be 59.9% and in the flunarizine group it was found to be 73.9% **[Table 9].**

Both groups showed a statistically similar percentage reduction in the duration of headache at the 3rd month and at follow-up at the 6th month **(Figure 7).**

At ≥50% responder rate defined as at least 50% reduction from baseline showed that both the groups were highly efficacious with regards to frequency, duration and severity of migraine but no statistical significance between the two treatment groups were found**. [Table10].**

At ≥75% responder rate it was found that Flunarizine group was statistically significant over the propranolol group in frequency, severity and duration of migraine**. [Table 11].**

In the present study, Flunarizine group showed significant increase in weight gain from 55.05±10.64 to 57.94±11.04.28 patients in the group showed increase in weight at the end of the treatment period.

In the present study, 22 patients in the propranolol group and 38 patients from the fkunarizine group complained of side effects. In the propranolol group patients mailnly complained of fatigue and dizziness while in the flunarizine group weight gain, somnolescence and fatigue were the chief complaints**.[Table 12 and 13].**

DISCUSSION

Epidemiologic studies suggest that approximately 38% of migraineurs need preventive therapy, but only 3%–13% currently use it.[13] A host of drugs are availablefor preventive migraine treatment but their use is often limited by side effects and lack oftolerability.

This study aims to compare the efficacy and safety of Propranalol, the gold standard prophylactic drug with Flunarizine, acerebrospecific calcium channel blocker in migraine prophylaxis among patients diagnosed with migraine, attending the ENT OPD in Rajarajeswari Medical college and Hospital, Bangalore.

Propranolol is considered to be the reference prophylactic treatment for migraine. A meta-analysis performed in 1991 of studiesincluding 2403 patients included in placebo-controlled clinical trials reported a reduction of 44% in the frequency of headaches in patients receiving propranolol compared to 16% in the placebo group.[14] A more recent evidence-based review performed for the Cochrane Collaboration extending the analysis to over five thousand patients included in 58 trials confirmed the superiority of propranolol to placebo in the prophylaxis of migraine.[15]

There have been comparative studies between flunarizine and placebo with respect toefficacy, tolerability and side effects among adults diagnosed with migraine. Several open labaeled, randomized studies have shown consistent reduction of frequency of headache and also maintenance of its therapeutic effect on long term use over placebo.[13]

Many clinical studies have demonstrated the use of the above mentioned drugs in the prophylaxis of migraine but a comparative study of the two was lacking in our population. Therefore, the above study was conducted for a period of one year.

The two groups in the present study were age matched. The most common age group diagnosed with migraine was in 21-30 years in both the groups. Study by Russell et al suggests that the second and third decade of life is the most common age of onset of migraine.[16]

This study showed a higher female preponderece with a raio of 3:1 as shown in other studies.[107]

The relationship between t\migraine and female hormones has been established. Menstrual migraine without aura isa type of migraine where Attacks occur exclusively on day 1±2 (ie, days −2 to +3) of menstruation in at least 2 out of 3 menstrual cycles along with criteria satisfying migraine without aura according to IHS criteria.[17] There was no statistical difference between the two groups. (P=0.76).

Both the study groups had a higher percentage of patients diagnosed to suffer from migraine without aura and the mean duration of history of migraine was between 6 -10 years. A positive family history of migraine was noted in both the groups. Furthermore no significant difference between the treatment groups in the severity and duration of headache at baseline. All the groups were comparable for all the parameters including weight at the start of the study, which enabled us to have valid comparative statistical analysis.

A decrease in the mean frequency of migraine per month has been used as the primary outcome in various studies.[19] In the present study significant reduction is seen in the frequency of migraine attacks in both the group from baseline to completion of 3rd month at P<0.001.Both the drugs showed significant reduction from the first month onwards. The percentage change was higher in Flunarizine group (75.9%) in mean and wasstatistically significant when compared to the propranolol group.

Statistically significant difference were found between treatment groups for the reduction in mean duration of migraine attacks. Flunarizine showed statistically significant improvement when compared to propranolol. (p<0.001)Onset of action of both the drugs was significant from the first month of treatment.

The severity of migrane attacks was assessed using the Visual Analogue scale. Therewas significant reduction in pain in both the groups and reduction in pain started from first month onwards in both groups ($p<0.05$). The reduction in flunarizine group was statistically higher than the ($P<0.001$) propranolol group.

Responder rate is a robust efficacy measure of a drug in migraine prophylaxis.At≥50% responder rate(response defined as at least 50% reductionfrom baseline) both the groups were efficacious interms of frequency, duration and severity of migraine. No statistical difference between the two groups were found. At ≥75% responder rate, flunarizine was found to be statistically significant over propranolol in terms of frequency, duration and severity of migraine attacks. Similar results were found when Flunarizine and Propranalol were compared across trials.[20,21] Holroyd et al published a metanalysis comparing flunarizine and propranolol which included 31 flunarizine trials and 32 propranalol trials with 3000 patients.

The mean of reduction in frequency of migraine was similar to our study.[22] Flunarizine has shown higher degree of effectiveness over propranolol in our study which is similar to several other studies[20,23,24]

The baseline weight in both the groups showed no statistical difference .The mean change in weight in the propranolol group was a net gain of 0.22 kgs at the end of three months. In the flunarizine group our study showed a gain in body weight in 76% of the patients. The increase in weight ranged from 1-5 kgs. The mean gain in body weight was 2.2 kgs. The increase in body weight was statistically significant over the propranolol group ($p<0.001$). Older Studies have shown similar results with weight gain ranging from 22%-55%[99]. Flunarizine has also shown increase in BMI and serum leptin levels in a study conducted to record its effect on body weight.[25] The mechanism of weight gain in patieints treated with flunarizine seems to be by causing leptin resistance in the body.

Out of the 100 patients who completed the study, 22 patients in propranolol group and 38 patients in flunarizine group reported adverse events. No deaths werereported during the study or within 30 days after completion of study. All the AE s were mild to moderateinnature. Fatigue, somloscence, dizziness were among the most common adverse events reported. These results are similar to other studies which are in line with known tolerability profile of the drugs[99]. Since both drugs have different adverse effects, they can be accordingly prescribed in patients where they are contraindicated.

CONCLUSION

Like the pathogenesis of migraine, the mechanism of action of the prophylactic drugs for migraine are unclear. Since migraine is a commondebilitating disorder with a high prevalence, successful treatment of migraine has been a challenge. Both pharmacologic and non pharmacologic treatments need to be combined during and before the migraine attacks to treat the disease effectively. The key tool in the management of migraine has been the prophylactic drugs and hence a lot of research is focused towards the development of newer drugs in the prophylaxis of migraine. Although many drugs have been approved for the prophylaxis, a drug with good tolerability and minimum adverse effects is still lacking. In our study, an open labeled randomized comparison was done between Propranalol, a Beta blocker with Flunarizine, acerebrospecific calcium channel blocker. Our results show that, Propranalol, inspite of being the first line drug for treatment of migraine prophylaxis is not as efficacious as flunarizine. The study demonstrates that Flunarizine is more effective in reducing the frequency of migraine attacks, duration of migraine and has shown significant improvement in the severity of the pain. Both the study drugs showed different profiles of adverse events and flunarizine showed significant weight gain at the end of the study.

The highlights of the study include the homogeneity of the baseline characteristics in both demographic data and migraine features. Flunarizineshowed better results over the first line drug, namely, Propranolol. Larger sample size could not be recruited due to lack of time and man power. This study highlights the need to conduct similar comparative studies in varied settings on larger Indian population.

REFERENCES

1. Liption RB, Bigal ME, The epidemiology of migraine. Am J Med., 2005; 118: S3–S10.
2. Silberstein SD.Headache in clinical practice. 2nded: Taylor and Francis; 2002.
3. Anderson K, Anderson Lois E, Glanze Walter D. Mosby's Medical, Nursing &Allied Health Dictionary.4 ed, 1994; 998.
4. World Health Organization. The World Health Report 2001: Mental Health: New Understanding, New Hope[internet]. 2009 Jan[cited 2009 Jan 12]. Available from WHO: http://www.who.int/whr/2001/en/ index.html.
5. Miller, Neil. Walsh and Hoyt's clinical neuro-ophthalmology. 6 ed. Philadelphia: Lippincott Williams & Wilkins, 2005; 1275.

6. Mayseds, Margaret C, Simon. Human osteology: In archaeology and forensic science. Cambridge: Cambridge University Press, 2002; 345.
7. Colen C. Neurosurgery. Colen Publishing, 2008; 1.
8. Headache classification subcommittee of the International headache society. The international classification of headache disorders. 2nd ed. cephalalgia, 2004; 9-160.
9. Silberstein SD, Freitag FG. Preventive treatment of migraine. Neurology, 2003; 38–44.
10. Mathew N T, kurman R, Perez F. Drug Induced Refractory Headaches: Clinical features and Management. Headache, 1990; 30: 634-638.
11. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. Neurology, 1971; 21: 404–405.
12. 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: 907–912.
13. Lipton RB, BigalME, Diamond M, Freitag F, Reed ML, Stewart WF. The American Migraine Prevalence and Prevention Advisory Group. Migraine prevalence, disease burden, andthe need for preventive therapy. Neurology, 2007; 68: 343–349.
14. Holroyd KA, Penzien DB, Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. Headache, 1991; 31: 333–40.
15. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database: Syst Rev., 2004; 3: 3225.
16. Russell MB, Rasmussen BK, Brennum J et al. Presentation of a new instrument: the diagnostic headache diary. Cephalagia, 1992; 12: 369-374.
17. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. 2nd ed. (Cephalalgia, 24 - S 1). Oxford: Blackwell Publishing, 2004.
18. Dahlof C, Linde M. One-year prevalence of migraine in Sweden:a population based study in adults. Cephalalgia, 2001; 21: 664-71.
19. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schimitt J, Neto W. Schwabe S, Jacobs D. Topiramate for migraine prevention:a randomised controlled trial. JAMA, 2004; 291: 965-973.
20. Diener HC, Matias-Guiu J, Hartung E, Pfaffenrath V, Ludin HP, Nappi G, De Beukelaar F. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. Cephalalgia, Apr, 2002; 22(3): 209-21.

21. Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. Can J Neurol Sci., Aug, 1992; 19(3): 340-5.
22. Holroyd KA, Penzien DB, Rockicki LA et al. Flunarizinevs Propranolol. A meta-analysis of clinical trials. Headache, 1992; 32: 256.
23. Carlos AB, Marco AA, Marcelo CC, Jose GS. Propranolol vs FlunarizinePlus Propranolol In Migraine Without Aura Prophylaxis. Arq Neuro psiquiatr, 1997; 55: 536-541.
24. Shimell CJ, Fritz VU, Levien SL. A comparative trial of flunarizine and propranolol in the prevention of migraine. S Afr Med J., Jan 20, 1990; 77(2): 75-7.
25. Berilgen MS, Bulut S, Gonen M, Tekatas A, Dag E, Mungen B. Comparison of the effects of amitriptyline and Flunarizine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment. Cephalalgia, Nov, 2005; 25(11): 1048-53.