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Randomised Controlled Trial to Compare Safety and Efficacy of Propranolol with Flunarizine in Adult Patients Suffering from Migraine as Prophylactic Drugs

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A B S T R A C T

Background*:**Migraine is a primary neurovascular headache disorder characterize by moderate to severe headaches, most often unilateral and generally associated with nausea and increased sensitivity to light and sound. Several factors can trigger migraine are probable contributing factors while others are possible or unproven such as:stress, hormonal changes, skipped meal, smoking, odour etc.Propranolol (non selective beta blocker) is the most common and one of the most effective first line medication used for migraine prophylaxis. Flunarizine (Calcium channel blocker) is acknowledged in numerous countries and included in numerous national guidelines for prophylaxis of migraine.We therefore intended to carry out this study and produce more data to support the choice of a medication for migraine prophylaxis that is both more effective and has a better safety profile.Aim*:** The aim of our study was to compare safety and efficacy of propranolol with flunarizine in adult patients suffering from migraine as prophylactic drugs. ***Objectives*:** 1) To evaluate safety and efficacy of propranolol.2) To evaluate safety and efficacy of flunarizine. ***Material and Methods*:** This comparative, prospective, randomized, and academic interventional study was conducted in tertiary care hospital of North India. A total of 76 patients satisfying the eligibility criteria were randomized into 2 groups to receive either the Tablet Propranolol 40 mg per day for first 5 days then 40 mg twice a day for 2 months or Tablet Flunarizine 10 mg per day for 2 months. A general evaluation, physical examination and routine investigations were performed on the first visit and repeated after every one month of treatment for next 2 months. Patient also assessed with VAS (Visual Analogue Scale) for headache intensity 1 (mild) to 10 (excruciating), to check extent of a patient's disease.

***Results*:**Group A (89.2%) and Group B (52.8%) patients were in age group of 18-40 years. In Group A, dizziness (n = 20) was the most common adverse effect associated with propranolol, while in Group B; tiredness (n = 3) and weight gain (n = 3) were the most common adverse effects associated with flunarizine. There was statistically significant increase in BMI after 2 months among patients who were in Group B than those who were in Group A (p=0.045). There was statistically significant difference in the mean (SD) Heart Rate value of participants in Group A (75.65± 5.1) and Group B (80.14 ± 5.9) at the end of 2nd month (p=0.001).Also, there was statistically significant

improvement in headache frequency (p=0.01) headache intensity (p=0.004) and headache duration (p=0.04) in Group A as compare to Group B.
Conclusion*:** Flunarizine was associated with fewer adverse effects and Propranolol was associated with low headache frequency, headache intensity and headache duration as compared to flunarizine group. ***Trial Registration: Clinical Trials Registry – India (CTRI) Number CTRI/2023/06/053593 [Registered on: 06/06/2023]
***Keywords*:**Migraine, Prophylaxis, Propranolol, Flunarizine, Compare, Safety, *Efficacy*.

INTRODUCTION

Migraine is a primary neurovascular headache disorder characterize by moderate to severe headaches, most often unilateral and generally associated with nausea and increased sensitivity to light and sound. It is derived from Greek word "hemicrania" later converted into Latin as "hemigranea" with a French translation of such term as "migraine [1]."

Several factors can trigger migraine are probable contributing factors while others are possible or unproven such as:

- Stress in 80% (probable factors)
- Hormonal changes in 65% during mensuration
- Skipped meals in 57% (probable factor)
- Weather changes in 53% (probable factors)
- Excessive or insufficient sleep in 50% (possible factor)
- Odors in 40% (perfumes, colognes, petroleum distillates)
- Exposure to lights in 38% (probable factor)
- Alcohol ingestion in 38% (wine as a probable factor)
- Smoking in 36% (unproven factor)

Numerous things, such as vigorous physical effort, lack of food and sleep, anxiety or stress, menstruation changes, sensory stimuli, and changes in the weather, can make migraines worse [2].

Headaches classification committee of the international headache society has classified migraines into following subtypes:

Migraine without aura is a recurrent headache attack of 4-72 hours, typically unilateral in location, pulsating in quality, moderate to severe in intensity, aggravated by physical activity and associated with nausea and light and sound sensitivity.

Migraine with aura has recurrent fully reversible attacks lasting minutes typically one or more of these unilateral symptoms: visual, sensory, speech and language, motor, brainstem and retinal, usually followed by headaches and migraine symptoms.

Chronic migraine is a headache that occurs on 15 or more days in a month for more than three months and has migraine features on at least eight or more days in a month.

Probable migraine is a symptomatic migraine attack that lacks one of the features required to fulfil the criteria for one of the above and does not meet the criteria for another types of headaches [3].

While the underlying mechanism of migraine involves the trigeminovascular system and its connections to the cranial autonomic reflex, which act as a feed-forward system to facilitate the acute attack, the primary issue with migraine is in the brain [4].

Propranolol is the most common and one of the most effective first line medication used for migraine prophylaxis. The starting dose is 40 mg and can go up to 320 mg daily. It may take up to 12 weeks at an adequate dose for therapeutic benefits to become apparent [5].

Flunarizine is a potent calcium channel blocker and has proven its efficacy in prophylactic management of migraine It is started at different dose levels of either 5mg or 10 mg at bedtime [6].

With these backgrounds, the present study aims to focus on to find out that among two medicines which is most effective and safe to use.

MATERIAL AND METHODS

Study design: The study was conducted in Department of Pharmacology and Department of Neurology at Dr. R.P.G.M.C. Kangra at Tanda, Himachal Pradesh in India. Patients were selected on an outpatient department (OPD) basis. It was a comparative, prospective, randomized, and academic interventional study.

Study population: Adult migraine sufferers of age between 18-65 with informed consent from a range of socioeconomic backgrounds who have been diagnosed using diagnostic criteria and NCCT Head were taken as the study population.

Eligibility Criteria:

Inclusion Criteria

1) Patients willing to give written informed consent.
2) Male and female outpatients between 18-65 years of age with documented history of migraine (with or without aura) acc. to HIS criteria.
3) Duration of at least 3 months.
4) Frequency of two or more migraine headache per month.
5) Currently not on any prophylactic medication in the last 1 month.
6) Patients" ability to fill a reliable headache diary successfully

Exclusion Criteria

1) Patients not willing to be part of the study.
2) Patients with h/o asthma, diabetes, renal, cardiovascular, liver, neoplastic disease, neurological and mental disorders are excluded.
3) Active alcohol users.
4) Patients allergic or with known contraindications to any of study drugs.
5) Patients who have already taken either of the above-mentioned migraine prophylactic drugs.
6) Previous unresponsiveness to more than two antimigraine prophylactic drugs.
7) NCCT Head suggesting of any other disease except migraine i.e., abnormal fundus etc.

Patients were recruited according to eligibility criteria. After a written informed consent, the participants were assigned to one group either A or B, based on computer generated random numbers.

- Group A: Tablet Propranolol 40 mg per day for first 5 days then 40 mg twice a day for 2 months
- Group B: Tablet Flunarizine 10 mg per day for 2 months

Before initiating treatment, urine pregnancy test (UPT) was done in women of reproductive age group to rule out the pregnancy.

First visit of participants who did not took any prophylactic medication for past one month considering baseline period preceded the two months of active treatment phase. A general evaluation, and physical examination, routine investigations were performed on the first visit. Patient also assessed with VAS (Visual Analogue Scale) for headache intensity 1 (mild) to 10 (excruciating) disease. Patients were assessed monthly for next 2 months.

Daily headache diaries were given to each patient to record the number of migraine attacks, the pain severity by VAS and duration of attacks (hours). Diary data was summarised monthly.

Analysis of efficacy data and vital signs was conducted on eligible patients. Availability of baseline data i.e., data of first visit and data after visit of each month i.e., 1st and 2nd month were compared and set as the criteria for efficacy evaluability.

Investigations:

Following baseline investigations will be done and these investigations will be repeated after every 1 month of treatment (for safety). Hb, Random Blood Sugar,Liver function tests (Aspartate Transaminase (SGOT), Alanine Transaminase (SGPT), Serum Bilirubin),Lipid profile (Serum Cholesterol, Serum TG, Serum HDL, Serum LDL,),Vital signs (BP, Heart rate, weight), BMI, ECG.Patients were contacted telephonically on the next day of initiating the prophylactic treatment and enquired for any discomfort or side effects. Patients were also advised to report any serious adverse event during treatment period. Follow up of each patient were done monthly for 2 months. Adverse experience reported were recorded at each follow-up i.e. after each month for next 2 months. And if deemed necessary the medication was changed appropriately or stopped as per physician's advice.

Measurements of outcome
After two months of follow up, the results were evaluated using the following criteria:

Safety:
Any report of adverse events by the subjects during study. Any derangement in lab investigations from normal value.

Efficacy:
Patients having improvement in:

- Number of migraine attacks (Frequency)
- The pain severity by VAS (Intensity)
- Duration of attacks(hours).

Ethical approval and Clinical trial registration
The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional ethical committee approval vide letter no. IEC/028/2023; dated 17/4/2023. Written informed consent was obtained from all the participants. The clinicalTrials.gov Identifier is CTRI/2023/06/053593 [Registered on: 06/06/2023]

RESULTS

Total 76 patients were randomized into two groups resulting in 39 patients in Group A and 37 patients in Group B. Two patients of Group A and one patient from Group B were lost to follow-up due missed contact. 37 in Group A and 36 in group B taken for analysis. An intention to treat analysis was applied over them and analysis have been presented as follow:

Table 1: Treatment arms

Group	Drug
A (n=37)	Propranolol 40 mg
B (n=36)	Flunarizine 10 mg

Table 2: Comparison of Age group distribution of patients in both groups

Characteristics	Group A (n= 37)	Group B (n= 36)	p value*
Age group			
18-40	33 (89.2%)	19 (52.8%)	0.001
>40	4 (10.8%)	17 (47.2%)	

Table 3: Comparison of Gender-wise distribution of patients in both groups

Gender	Group A (n=37)	Group B (n=36)	p value*
Male	11 (29.7%)	7 (19.4%)	0.308
Female	26 (70.3%)	29 (80.6%)	

SAFETY

Table 4: Comparison of RBS between both groups

Random Blood Sugar	Group A (n= 37)	Group B (n= 36)	p value*
Baseline	116.2 ± 10.7	114.6 ±12.7	0.55
1 month	112.6 ± 6.25	114.2 ±8.19	0.35
2 months	111.1 ± 7.40	115.4 ± 8.85	0.02

Figure 1: Comparison of triglyceride levels between two groups

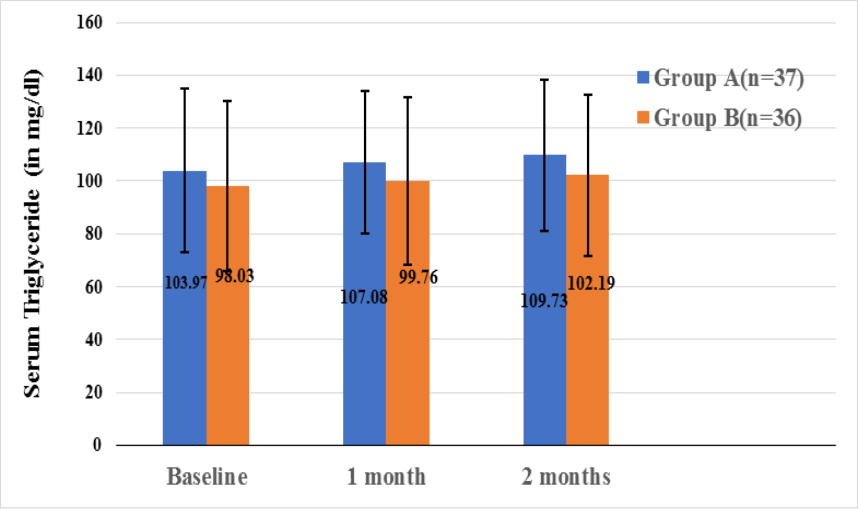


Figure 2: Comparison of LDL levels between two groups

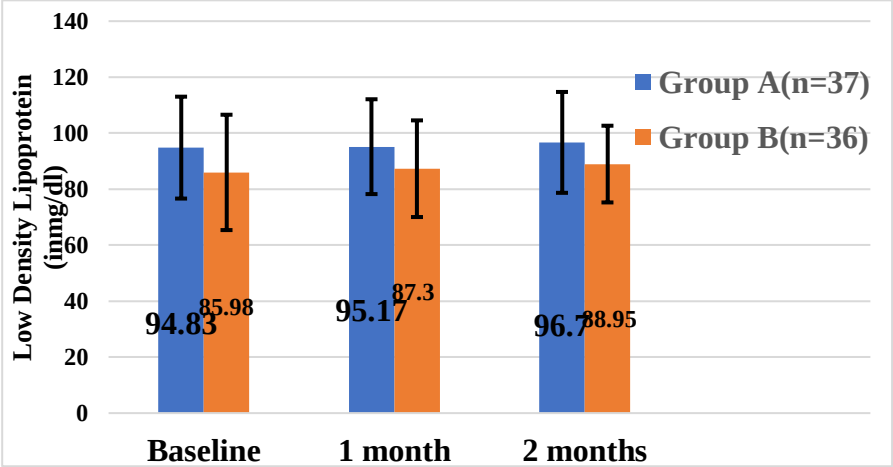


Table 5: Comparison of SBP between two groups

Systolic Blood Pressure	Group A (n= 37)	Group B (n= 36)	p value*
Baseline	123.43 ± 8.9	125.11 ± 9.2	0.43
1 month	119.51 ± 7.7	123.92 ± 8.7	0.02
2 months	116.16 ± 6.6	121.58 ± 8.2	0.003

Table 6: Comparison of DBP between two groups

Diastolic Blood Pressure	Group A (n= 37)	Group B (n= 36)	p value*
Baseline	71.81 ± 4.0	72.36 ± 6.3	0.66
1 month	70.59 ± 3.98	72.81 ± 5.42	0.051
2 months	68.81 ± 4.1	71.78± 4.7	0.006

Table 7: Comparison of Heart Rate between two groups

Heart Rate	Group A (n= 37)	Group B (n= 36)	p value*
Baseline	81.73 ± 5.8	80.86 ± 6.7	0.55
1 month	78.84 ± 5.0	80.17 ± 6.3	0.32
2 months	75.65 ± 5.1	80.14 ± 5.9	0.001

Table 8: Comparison of BMI between two groups

BMI	Group A (n= 37)	Group B (n= 36)	p value *
Baseline	22.03 ± 2.81	22.55 ± 2.40	0.488
1 month	22.12 ± 2.83	23.2 ± 2.35	0.06
2 months	22.42 ± 2.71	23.8± 2.32	0.045

EFFICACY

Table 9: Comparison of Headache Frequency per month between two groups

Headache frequency	Group A (n= 37)	Group B (n= 36)	p value *
Baseline	6.54 ± 2.17	7.19 ± 3.18	0.29
1 month	4.00 ± 1.92	4.86 ± 2.35	0.09
2 months	2.00 ± 2.35	3.47 ± 2.85	0.01

Figure 3: Comparison of Headache Frequency per month between two groups

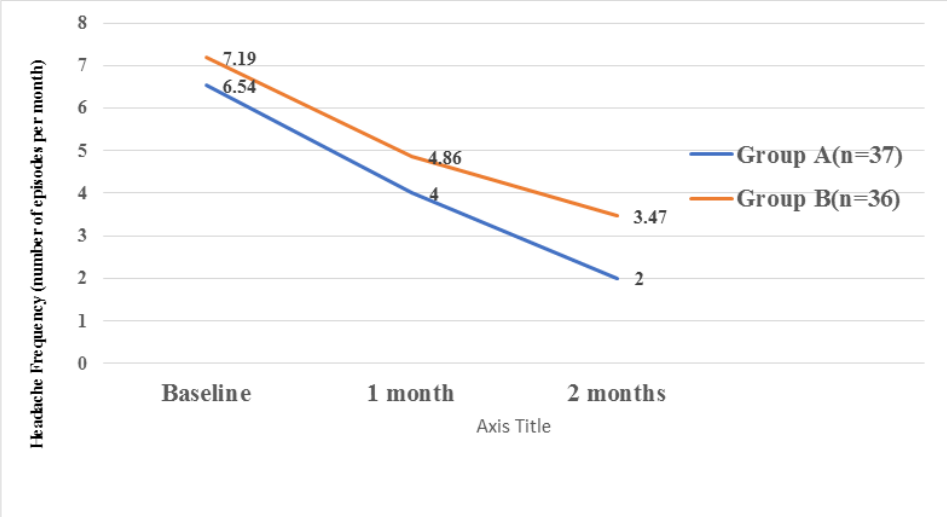


Table 10: Comparison of Headache Intensity (1-10) between two groups

Headache intensity	Group A (n= 37)	Group B (n= 36)	p value*
Baseline	7.59 ± 1.86	8.42 ± 1.68	0.04
1 month	4.95 ± 2.44	6.22 ± 2.05	0.01
2 months	2.49 ± 3.05	4.50 ± 2.69	0.004

Figure 4: Comparison of Headache Intensity between two groups

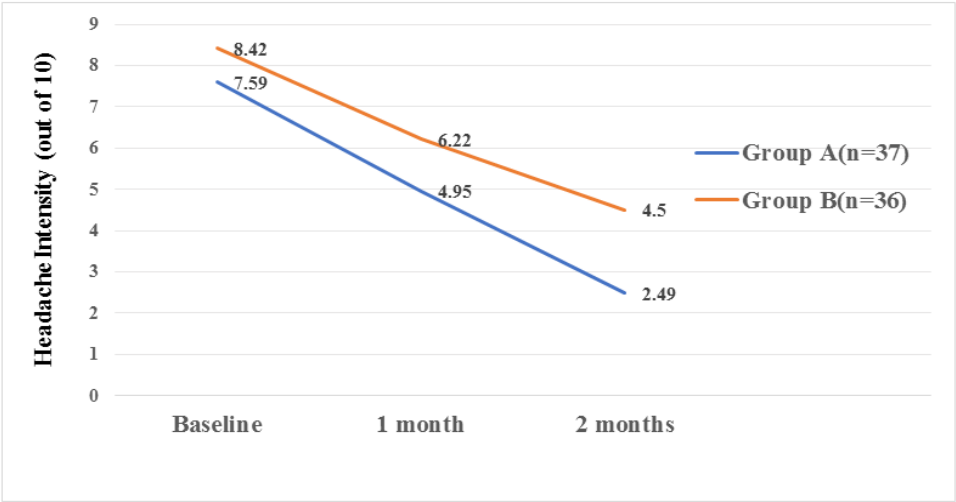


Table 11: Comparison of Headache duration per day (in hours) between two groups

Headache duration	Group A (n= 37)	Group B (n= 36)	p value*
Baseline	9.51 ± 6.01	10.03 ± 9.39	0.77
1 month	5.27 ± 4.43	6.03 ± 4.33	0.46
2 months	2.40 ± 3.18	4.05 ± 3.76	0.04

Figure 5: Comparison of Headache duration per day (in hours) between two groups

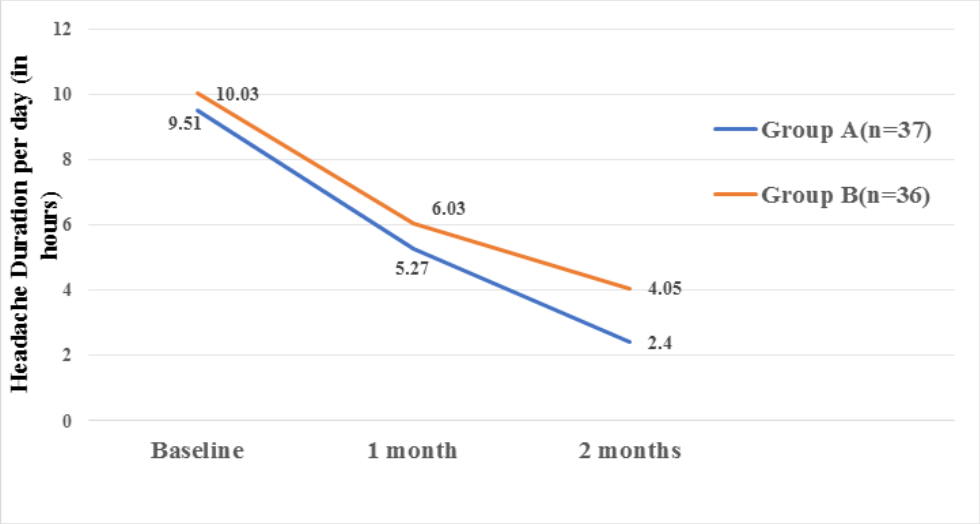
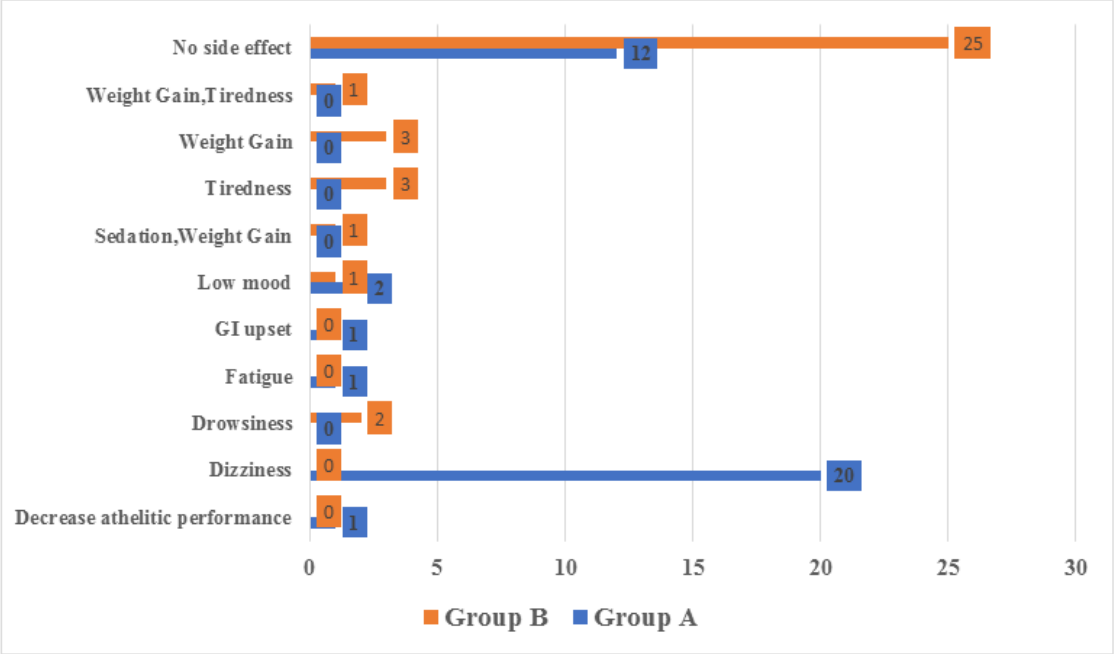


Figure 6: Comparison of treatment emergent adverse events between two groups



DISCUSSION

A total of 76 patients who were confirmed diagnosis with ICHD3 criteria and NCCT head enrolled in the study. Patients were divided into two groups; Group A received Tablet Propranolol 40 mg per day for first 5 days then subsequently 40 mg twice a day and Group B received Tablet Flunarizine 10 mg once daily for 2 months.

In our study out of total 76 enrolled patients; 89.2% patients in Group A and 52.8% patients in Group B belonged to age group 18-40 years.

Also 70.3% patients in Group A and 80.6% patients in Group B were females.

Safiri S. et al. in 2019, concluded that the number of YLDs (Years lived with disease) started increasing from birth, they peaked in the 30–34 age group and then gradually declined for both sexes and prevalence of migraine was higher in females, than in males, across all age groups. [7]This study is in concurrence with our study.

SAFETY

The study found that there was statistically significant increase in random blood sugar after 2 months among patients who were in Group B than those who were in Group A **(p=0.02)**.

A study by Groop L et al. found that propranolol lowered the mean basal glucagon concentrations and induced a more pronounced reduction of plasma glucagon thus increasing blood glucose concentrations.[8]Our study results were opposite to the studies done in past. The reason could be eating habits of patients and timing of random blood glucose monitoring of patients. Both could have leads to increase random blood glucose levels

The study found that triglyceride levels were statistically significantly more in Group A propranolol than Group B flunarizine **(p=0.03)** at two months & and LDL levels were significantly more in Group A than Group B at 1 month **(p=0.016)** and 2-month **(p=0.002)**. Our results are strongly supported by the fact that nonselective beta receptor antagonists like propranolol increase LDL (low-density lipoprotein), and increase triglycerides.[9] A study by Aronow WS et al. found that patients who were administered propranolol for 3 days to 1 year reported an increase in serum triglyceride levels.[10] Another study by Byington RP et al. supported that propranolol was found to increase serum triglyceride levels by about 17% (35 mg/dl).[11]

Systolic blood pressure was comparable in both groups at baseline (p=0.43).There was statistically significant difference in the mean (SD) SBP value of participants in Group A (119.51 ±7.7) & (116.16 ±6.6) and Group B (123.92 ±8.7) & (121.58 ±8.2) at the end of 1st month **(p=0.02)** and 2nd month **(p=0.003)** follow up. Subsequently mean (SD) diastolic blood pressure values of patients in Group A (68.81±4.1) and Group B (71.78 ±4.7) at the end of 2nd month decreased and were statistically significant (**p=0.006).** The heart rate was also significantly less in Group A as compared to Group B at 2 months **(p=0.001)**. A study by Gawel MJ et al.found that propranolol treatment was associated with significantly decrease in blood pressure (systolic and diastolic) and heart rate and flunarizine had no effect on cardiovascular function.[12]The study also found statistically significant increase in BMI in both groups between baseline and at 1 month **(p=<0.001)** and 2 months **(p=<0.001)**.

Subsequently our study found that there was statistically significant increase in BMI after 2 months among patients who were in Group B flunarizine than those who were in Group A propranolol **(p=0.04)**. A study by Gawel MJ et al. reported that BMI increased to a statistically significant more among patients taking either flunarizine (baseline 24.3 to termination 25.3 kg/m^2) as compared to participants who were on propranolol prophylaxis (baseline 25.0 to termination 26.0 kg/m^2).[12] These studies are in accordance to present study.

EFFICACY

There was statistically significant difference in less frequency of headache among participants who were in Group A (2.00 ±2.35) as compared to Group B (3.47 ±2.85) after 2 months **(p=0.01)** follow up. Less Intensity of headache among participants who were in Group A as compared to Group B after 1 and 2 months follow up **(p=0.004)**. Subsequently less duration of headache among participants who were in Group A (2.40 ±3.18) hours as compared to Group B (4.05 ±3.76) hours after 2 months follow up **(p=0.04)**. However, both groups showed statistically significant **(p<0.01)** decline in frequency, intensity, and duration of headache episodes over a period. A study by Ashtari F et al. found that both low-

dose topiramate (50mg/day) and propranolol (80mg/day) for 8 weeks could significantly reduce migraine headache frequency, intensity, and duration. However, compared with propranolol, low-dose topiramate showed better results.[13]Another study by Fallah R et al. found that monthly frequency and severity and duration of headache decreased with propranolol from 16.2 ± 6.74 to 8.8 ± 4.55 attacks, from 6.1 ± 1.54 to 4.8 ± 1.6 and from 2.26 ± 1.26 to 1.35 ± 1.08 hours respectively.[14] Study done by Gawel MJ et al. found that propranolol as well as flunarizine decreased the frequency of migraine but did not affect the severity and duration of migraine.[12]

A study conducted by Lai KL et al. found that patients treated with flunarizine showed significant reductions in the number of total headache days (-4.9 vs -2.3, p=0.12) and migraine days (-4.3 vs -1.4, p=0.01) compared to those treated with topiramate.[15]

A study by Luo N et al. found that 66.7% patients in flunarizine group and 72.7% patients in topiramate group had at least 50% reduction in their monthly migraine frequency compared to baseline.[16]Our study is in discordant with the study done by Gawel MJ et al. postulating that flunarizine do not affect the severity and duration of migraine.[12]In our study both propranolol andflunarizine decreases frequency, duration, and intensity of attack over months.

TREATMENT EMERGENT ADVERSE EVENTS

We found that propranolol in group A decreased athletic performance. Similar spectrum of decrease athletic performance or reduced physical capacity was reported by Stovner LJ et al. in patients treated with propranolol.[17]This can be attributed to the fact that inhibiting β2 receptors lowers blood supply to active skeletal muscle during submaximal activity and may minimize catecholamine-induced lipolysis and glucose metabolism activation, which ultimately results in a decline in athletic performance.[9]The present study found that more than half of the patients who were in Group A experiences dizziness while around two third patients who were in Group B had no side effects. A study by Stovner LJ et al. found that many patients on propranolol prophylaxis reported dizziness (35.8%) respiratory infections (35.8%), tiredness (16.1%) as side effects.[17]

Propranolol is a non- selective beta blocker. It has negative chronotropic and negative inotropic effects leads to decrease heart rate. In blood vessel it also blocks vasodilation leads to decrease blood flow to muscles. It also inhibits glycogenolysis, gluconeogenesis and lipolysis lead to decrease glucose and free fatty acid which act as fuel to muscle. All these factors contribute to dizziness during propranolol therapy.[9]Two patients of flunarizine Group B experienced drowsiness as side effect. Similar results were found in long term ,multi-centric trial conducted by Martínez-Lage JM ; out of 1435 patients 289 patients reported drowsiness.[18] However, in our study none of patient in group A propranolol experienced drowsiness. The reason behind drowsiness caused by flunarizine is its additive histamine H1 receptor blocking property.[19]

A study by Fallah R et al. reported that clinical side effects were seen in 10 % of Propranolol groups (mild hypotension in three and drowsiness in two study participants).[14] In Group A, one patient taking propranolol complained of fatigue. Within the same group, one patient also experienced GI distress. Similar study done by Anker Stubberud et al. supported that GI upset was more common in-patient taking propranolol as compare to flunarizine.[20]

A study by Gawel MJ et al. reported that participants in propranolol group (n=3) reported weight gain, depression, and fatigue while flunarizine group (n=5) reported only weight gain, bloating, increased headache.[12]Two patients in Group A and one patient in Group B reported low mood during treatment period. This was in concurrence with the study done by Karsan N et al. that mood changes or worsening of low mood in 17% (n = 33) patients received flunarizine.[21]
In our study, one patient from flunarizine Group B experienced sedation. In 2019 meta-analysis done by Stubberud et al. revealed similar results.[20]Flunarizine's ability to inhibit histamine (H1) is most likely the mechanism behind its sedative effects.[19]Weight gain was seen in 3 patients of flunarizine group. A study by Gawel MJ et al. reported that participants in propranolol group (n=3) reported weight gain, depression, and fatigue while flunarizine group (n=5) reported only weight gain, bloating, increased headache.[12]

CONCLUSION

The study concluded that compared to propranolol, flunarizine was associated with fewer adverse effects. Propranolol was associated with low headache frequency, headache intensity and headache duration as compared to flunarizine group.

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Conflict of interest: Nil

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