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Retraction

The article "A comparative study of propranolol versus amitriptyline at a low dose for prophylaxis of episodic migraine at a tertiary care centre" has been retracted by the Editor-in-Chief due to violations of the policies and practices of the International Journal of Basic & Clinical Pharmacology.[1] The retraction follows a complaint from the study institution regarding the presentation of false information in the study details, issues with ethical approval, and discrepancies in authorship.

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1. Banu N, Shaifali I, Chandra S, Saxena A. A comparative study of propranolol versus amitriptyline at a low dose for prophylaxis of episodic migraine at a tertiary care centre. Int J Basic Clin Pharmacol. 2024;13(5):619-23. DOI: https://doi.org/10.18203/2319-2003.ijbcp20242418.

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Original Research Article

A comparative study of propranolol versus amitriptyline at a low dose for prophylaxis of episodic migraine at a tertiary care centre

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ABSTRACT

Background: The aim of this study was to assess efficacy and tolerability of propranolol compared to amitriptyline at a low dose in a sample of Indian Population for prophylaxis of episodic migraine.
Methods: Episodic migraine patients aged 18 to 55 years, not on any preventive treatment were randomly allocated to receive propranolol (80 mg/day) or amitriptyline (10 mg/day). The primary efficacy outcome was the mean change in migraine attack frequency per month after 3 months of treatment. Multiple secondary efficacy outcomes and adverse events were also assessed.
Results: Both study groups showed a reduction of migraine frequency, severity of headache and disability due to migraine at 3 months. Propranolol significantly reduced the frequency of headache (51.6% vs 43.6%, p=0.03) and the number of rescue medications (53.1% vs 43.3%, p=0.01) compared with amitriptyline at 3 months. The responders with ≥50% improvement was significantly more in propranolol group compared to amitriptyline (60% vs 43.3%, p=0.02). There was no significant difference in the incidence of adverse events between the two groups.
Conclusions: Propranolol (80 mg/day) was more efficacious than amitriptyline (10 mg/day) in terms of significantly reducing the frequency of headache and the number of rescue medicine at 3 months. Both drugs were comparable in safety profile.

Keywords: Amitriptyline, Efficacy, Episodic migraine, Prophylaxis, Propranolol, Tolerability

INTRODUCTION

Migraine is a common neurological condition that affects daily functioning and productivity imposing substantial burden on patients and their families. It is one of the most prevalent and disabling medical illness in the world resulting in economic burden to individual and the society at large. Prevention is the major line of management for which many treatments are available which vary in efficacy and safety profile. Propranolol and amitriptyline are very old, drugs with known safety profile compared to other newer treatments. Both the drugs are recommended for migraine prophylaxis by scientific bodies like American Headache Society (AHS)/American Academy of Neurology (AAN) guidelines, National Institute for Health and Care Excellence (NICE) guidelines, Canadian Headache Society (CHS) guidelines and Scottish Intercollegiate Guidelines Network (SIGN) in varying doses. The recommended dose range for propranolol is 40-240 mg and for amitriptyline is 10-150 mg.[1-5] Majority of studies of both the drugs in migraine are in western population where high dose of the recommended range have been given. In India, as per the clinician's experience, the effective dose in Indian patients is much lesser.[5] Low doses if found efficacious will decrease the side effects related to the medication. There are lack of studies comparing the efficacy of propranolol and amitriptyline at low doses in Indian population. Hence this study was planned to assess their efficacy and safety profile at low doses.

METHODS

The study was conducted in the Department of Pharmacology in collaboration with the Department of Medicine at Rohilkhand Medical College and Hospital, Bareilly from February 2023 to October 2023.The study was conducted after approval from the Departmental Scientific Review Board and the Institutional Ethics Committee (IEC) of Rohilkhand Medical College. Written informed consent was obtained from all the study participants.

Study design

An open label, parallel, randomized, single center and prospective study. All patients were screened for a period of 1 month where they were asked to maintain a headache diary and record frequency, severity of headache, presence and nature of aura, and dose of rescue medicine taken on daily basis for a month. During the screening phase, for acute treatment, the following oral medications were used as per the standard of care by the treating physicians: Naproxen sodium (500-1000 mg), Paracetamol (500-1000 mg) or Naproxen+domperidone (500+10 mg). The patients fulfilling the criteria for episodic migraine (4-14 headache days per month) had their baseline routine investigations done including hemogram (blood counts, haemoglobin, ESR), liver function tests (bilirubin, transaminases), kidney function tests (blood urea, serum electrolytes, serum creatinine), random blood sugar and urinalysis (Routine). The patients with abnormal reports of baseline investigations were excluded from the study. The remaining patients were assigned into 2 groups by block randomization method using computer-generated random number tables. Group A received tablet propranolol with starting dose of 20 mg twice daily for 2 weeks, thereafter 40 mg twice daily and continued for another 10 weeks. Group B received tablet amitriptyline with starting dose of 5 mg once daily for 2 weeks followed by 10 mg once daily for next 10 weeks. When the clinician decided that the study medicines are not efficacious or safe for the patients, they were allowed to exit the study.

Study participants

A total of 60 patients of both sexes within age group 18-55 years, who fulfilled the ICHD-3 diagnostic criteria for episodic migraine (with/without aura) and were not on any preventive therapy were included. All patients with clinical phenotype of episodic migraine but with deranged routine baseline investigations, patients with severe depression and anxiety disorders or with 3-months previous history of antipsychotic, antidepressants or antianxiety medication, patients with known allergy to the study medications or developing severe adverse drug reactions during the treatment, pregnant and nursing mothers, patients with a history of asthma, chronic obstructive pulmonary disease, atrioventricular conduction defects, bradycardia, peripheral vascular disease, uncontrolled diabetes mellitus, uncontrolled hypertension, glaucoma, seizure disorder, cardiac diseases were excluded from the study.

Patient evaluation

Patients were followed up every month for a period of 3 months. A pretested, validated and structured proforma was used for collecting the data which covered detailed history of headache characteristics included in ICHD-3 criteria for diagnosis of episodic migraine, family history, triggering and relieving factors. Clinical examination included pulse rate and blood pressure measurements on each visit. Information on total migraine days, headache severity, disability and number of rescue medicine taken was collected on each visit. Adverse events, if any were also recorded.

Primary and secondary outcomes

The primary efficacy outcome was the reduction in migraine headache attack frequency per month at the end of 3 months. Secondary efficacy outcomes were proportion of patients having ≥50% reduction in migraine headache days per month, reduction in headache severity (visual analogue scale), reduction in headache induced disability (HIT-6), reduction in the number of rescue medication taken compared to baseline.[6] Adverse effects were documented, causality assessment was done using WHO-UMC scale and severity was assessed using Hartwig's Severity Assessment Scale.[7,8]

Statistical analysis

Based on convenient sampling method, a minimum of 30 patients in each group were recruited. The data was entered in MS excel worksheet and analyzed using statistical software SPSS 23.0 and MS excel. Continuous data was presented as mean+standard deviation. Categorical data was expressed as percentages. Appropriate statistical tests were applied depending upon the types of data, p value of <0.05 was considered significant at a confidence interval of 95%.

RESULTS

Sixty patients who met the inclusion criteria were enrolled in the study. Demographic characteristics of patients in both the study arms were comparable. The mean ages of propranolol and amitriptyline groups were 32.8 (±7.9) years and 32.7 (±8.1) years, respectively. In both the groups, females were predominant. Majority of patients had migraine without aura (Table 1). Propranolol (80 mg/day), decreased the headache frequency from baseline (7.1±2.54) to the end of 3 months (3.43±1.67) (p<0.0001) (Figure 1). Sixty percent of the patients had at least 50% reduction in headache frequency by the end of 3 months. Headache severity measured by VAS Score also decreased significantly from 7.67±0.61 at the baseline to 6.82±1.41 at the end of 3 months (p<0.0001) (Figure 2). Headache-induced disability measured by HIT-6 Score decreased

from 66.80±5.95 to 61.33±7.6 (p<0.0001) (Figure 3). With decreasing headache frequency, the intake of rescue medicine also decreased from 7.1±2.54 at baseline to 3.33±1.34 at the end of 3 months (p<0.0001) (Figure 4). The improvement was sustained throughout the study without loss of efficacy. Amitriptyline (10 mg/day), decreased the headache frequency gradually from 6.57± 2.49 at the baseline to 3.7±1.39 at the end of 3 months (p<0.0001) (Figure 1). Forty-three percent of the patients had at least 50% reduction in headache frequency by the end of 3 months. Headache severity measured by VAS Score also decreased significantly from 7.68±0.67 at the baseline to 7.26±0.58 at the end of 3 months (p=0.001) (Figure 2). Headache-induced disability measured by HIT-6 Score decreased from 66.77±5.65 to 62.73±5.86 (p<0.0001) (Figure 3). With decreasing headache frequency, the intake of rescue medicine also decreased from 6.07±2.12 at baseline to 3.43±1.48 at the end of 3 months (p<0.0001) (Figure 4). The improvement was sustained throughout the study without loss of efficacy.

Mean change of headache frequency from baseline to the end of treatment in propranolol group was -3.67±1.47 while in amitriptyline group it was -2.87±1.36 (p=0.03). The proportion of patients with ≥50% reduction in propranolol and amitriptyline group was 60% vs 43.3%, (p=0.02). The number of rescue medicine intake decreased from baseline in both the groups (-3.77±1.79 vs -2.63±1.50, p=0.01).

Headache severity and headache-induced disability decreased in both groups. This differences between the two groups were not statistically significant (Table 2). Mild adverse effects were observed in 9 (propranolol) and 7 (amitriptyline) patients. Drowsiness (10%), dry mouth (10%) and constipation (3.3%) were observed with amitriptyline, while fatigue (23.3%) and bradycardia (6.67%) were reported with propranolol (Table 3). Treatment protocol was not altered as adverse effects were self-limiting.

Table 1: Demographic characteristics of patients.

Characteristics	Group A (n=30) Propranolol 80 mg/day (Mean±SD)	Group B (n=30) Amitriptyline 10 mg/day (Mean±SD)	P value
Age	32.8 (7.90)	32.7 (8.12)	0.962
Female gender (%)	28 (93.3%)	29 (96.7%)	0.352
Type of migraine (%)			
With aura	1 (3.3%)	1 (3.3%)	
Without aura	29 (96.7%)	29 (96.7%)	
Frequency of migraine/month	7.1±2.54	6.57±2.49	0.414
Headache severity (VAS score)	7.45±0.79	7.46±0.85	0.969
Headache-induced disability (HIT score)	66.80±5.95	66.77±5.65	0.982
Rescue medication/month	6.22±2.11	6.65±4.46	0.632

VAS- Visual Analogue Scale, HIT- Headache Impact Test

Table 2: Comparison of primary and secondary outcomes of efficacy.

Parameter	Group A (n=30) Propranolol 80 mg/day	Group B (n=30) Amitriptyline 10 mg/day	P value
Change in frequency of headache from baseline (Mean±SE)	-3.67±1.47	-2.87±1.36	0.03
≥50% reduction in headache from baseline	19 (60%)	13 (43.33%)	0.02
Headache severity: change in VAS score from baseline (Mean±SE)	-0.85±1.28	-0.42±0.29	0.08
Headache induced disability: change in HIT Score from baseline (Mean±SE)	-5.8±5.52	-4.03±1.43	0.09
Change in rescue medicines intake from baseline (Mean±SE)	-3.77±1.79	-2.63±1.50	0.01

Table 3: Comparison of adverse events between patients receiving Propranolol (Group A) and Amitriptyline (Group B).

Adverse events	Group A (n=30) Propranolol 80 mg/day	Group B (n=30) Amitriptyline 10 mg/day	P value	Causality assessment
	No (%)	No (%)		
Present	9 (30)	7 (23.3)	-	
Drowsiness	0 (0)	3 (10.0)	0.07	Possible
Dry mouth	0 (0)	3 (10.0)	0.07	Probable
Fatigue	7 (23.33)	0 (0)	0.003	Possible
Constipation	0 (0)	1 (3.33)	0.31	Probable
Bradycardia	2 (6.67)	0 (0)	0.15	Probable

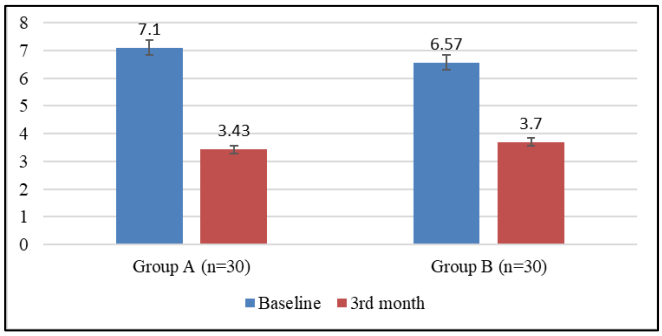

Figure 1: Reduction in migraine headache attack at the end of 3 months from baseline.

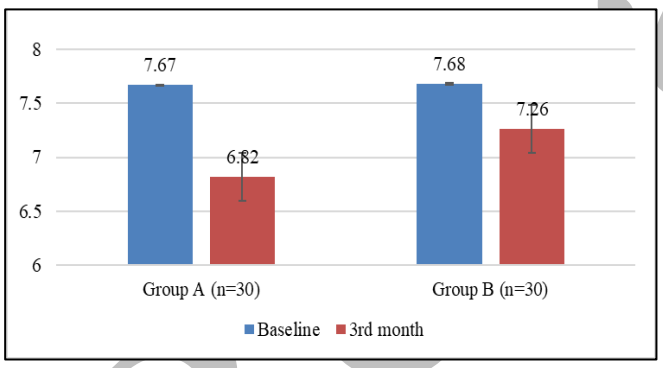

Figure 2: Reduction in headache severity at the end of 3 months from baseline.

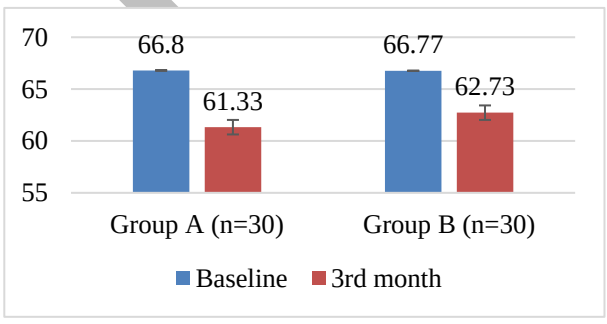

Figure 3: Reduction in headache induced disability at the end of 3 months from baseline.

DISCUSSION

On comparing the two groups, propranolol significantly reduced the frequency of headache (51.6% vs 43.6%, P=0.03) and the number of rescue medications (53.1% vs 43.3%, p=0.01) compared with amitriptyline group at 3 months. The responders with ≥50% improvement was significantly more in propranolol group compared to amitriptyline group (60% vs 43.3%, p=0.02). In the available literature, there are very few studies with head-to-head comparison of propranolol and amitriptyline in migraine prophylaxis. These studies were conducted between 1980-1995 mostly. In the study conducted in 1980 in Texas, the proportions of patients showing improvement on propranolol and amitriptyline were 62% and 42% respectively at the end of 6 months. The dose used in this study was 120-160 mg per day for propranolol and 50-75 mg for amitriptyline.[9] The efficacy with smaller dose in our study may be due to smaller body configuration of Indians, different metabolic rate, or genetic basis. A recent trial conducted in Dhaka, Bangladesh comparing the efficacy and safety of Propranolol (80 mg/day) versus Amitriptyline (50 mg/day) for migraine prophylaxis, reported significant reduction in headache frequency at the end of 3 months. Amitriptyline significantly reduced headache attack at the end of 3 months than Propranolol (71.24% vs 63.87%, p=0.0001). Though the adverse effects were slightly more in amitriptyline group than propranolol group, the adverse effects were mild in nature.[10] Both propranolol and amitriptyline was found to be safe and well tolerated over a course of 12 weeks. The adverse events were mild not requiring change in treatment. These were similar in comparison to previous studies.[10] Some studies with propranolol and amitriptyline on higher doses reported more adverse events.[11-13] This is the first study in a sample of Indian population that shows both low dose propranolol (80 mg/day) and low dose amitriptyline (10 mg/day) produce significant improvement in headache frequency, severity, and disability, and has good safety profile compared to higher doses in patients with episodic migraine.

Limitations of the study was open label study design, small sample size and short duration of follow up. Due to

methodological constraints, the study could not be blinded. Study in larger sample size is required to make definite conclusions on outcome and a longer follow up period may give us more informed results.

CONCLUSION

Though propranolol and amitriptyline are comparable, effective and safe in patients with episodic migraine, propranolol appears more effective than amitriptyline.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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