

Original Research Article

Propranolol versus topiramate in prophylaxis of migraines among children and adolescents: a randomized, double-blind clinical trial

Ramakant Yadav^{1*}, S. K. Shukla²

¹Department of Neurology, ²Department of PSM, UP University of Medical Sciences, Saifai, Etawah, India

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*Correspondence:

Dr. Ramakant Yadav,

E-mail: rkyadav_2003@yahoo.com

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ABSTRACT

Background: Migraine is a common health problem in children and adolescents. This study compares the efficacy and safety of propranolol and topiramate in preventing migraine among children and adolescents.

Methods: Seventy-six patients (10-18 years of age) with migraine without auras defined by the 2004 International Headache society criteria were included in a prospective double blind clinical trial were allocated to receive propranolol (0.5-2mg/kg per day) or topiramate (1-2mg/kg per day). The primary outcome measure was reduction in 50 % or more headache days in comparison to baseline headache frequency per month. Secondary outcome measures were headache related disability, migraine intensity and duration. Efficacy measures were recorded at the baseline and at 12 weeks of prophylactic treatment.

Results: In this study total of 76 patients with mean age of 12.43 years were evaluated, 40 in the propranolol group and 36 in the topiramate group. At the 12-week, the percentage of patients who had a relative reduction of 50% or more in the number of headache days were 67.5% patients in the propranolol group and 75.0% patients in the topiramate group. The monthly migraine frequency, headache related disability, intensity and duration were significantly decreased in both the propranolol and topiramate groups when compared to the baseline. No significant difference was observed between these two groups in term of reduction of frequency, headache related disability, severity and duration of attack. Fatigue, hypotension and exercise induced asthma were main side effects in propranolol group and weight loss, fatigue and loss of appetite, paresthesias in topiramate group.

Conclusions: Propranolol and topiramate were found effective and safe for the prevention of paediatric migraines.

Keywords: Migraine, Propranolol, Paediatric, Prevention, Topiramate

INTRODUCTION

Headache is one of the common health problem in children and adolescents affecting in their daily activities and school performances as well as causes school absenteeism.¹⁻⁴ The prevalence of migraine headaches among children and adolescents aged between 5 to 15 years ranged from 2.7-10.6%.³

The prevalence increases with age and is reported to be up to 28% in adolescents, aged 15 to 19 years.^{3,5,6}

Management of migraine headaches in children and adolescents consists of change in lifestyle, abortive treatments, and preventive treatments.⁷⁻⁹

Preventive management is recommended when the frequency of migraine attacks is three or more per month or the migraine attacks are significantly disabling as assessed by a scoring system such as the paediatric Migraine Disability Assessment Scale.^{10,11} Propranolol have long been used for the prevention of migraine in children and adolescents with variable effects.^{12,13}

Topiramate has been approved for use in migraine prevention in adults in Europe by the FDA.¹⁴ Randomized, double-blind, placebo-controlled studies showed the effectiveness of topiramate in significant reduction of monthly migraine frequency in children and adolescents.¹⁵ Some studies have showed the effectiveness of topiramate in reducing monthly migraine frequency in children.¹⁶⁻¹⁹ We conducted a randomized, double-blind clinical trial to evaluate the efficacy and safety of propranolol and topiramate as preventive treatments for migraine headaches among children and adolescents residing in rural area.

METHODS

A prospective randomized, double-blind clinical trial to compare the efficacy of propranolol and topiramate as prophylaxis for paediatric migraine was conducted in tertiary care teaching hospital of Uttar Pradesh University of Medical sciences (UPUMS) situated in the rural area. The patients were enrolled from out-patient services of the Neurology department. Seventy-six patients, 10-18 years of age with common migraine as defined by the 2004 international headache society criteria were enrolled in our study from 2015 to 2016. The study was approved by local ethical committee. A complete history of the patients, migraine characteristics as well as a complete general medical history was recorded along with a general and neurological physical examinations were performed.

Inclusion criteria

- Children and adolescents, aged 10-18 years, diagnosed with migraines (without aura) according to the International Headache Society criteria.²⁰
- More than 4 migraine attacks per month.

Exclusion criteria

- Focal neurologic deficit
- Severe adverse effects related to the study treatment drugs
- Known concomitant serious disease (Respiratory, hepatic, renal, cardiovascular, or thyroid disease).

In the prospective baseline period of four weeks, the previous medications either for preventive or acute treatment, were halted. The frequency, intensity, duration and headache related disability of the migraine patients was recorded. Each patient was given a diary to record the frequency and intensity and duration of each migraine.

Patients who completed the prospective baseline phase of the study were randomized into two treatment groups. One group of participants received propranolol as the preventive treatment for migraines (the propranolol group); and the other group of participants received topiramate as the preventive treatment for migraine is

(the topiramate group). Propranolol and topiramate tablets were provided in similar packages

The propranolol was administrated with a dose of 0.5-2mg/ kg per day and topiramate was administrated with a dose of 1-2mg/kg body weight per day for the 12 weeks. Adjustment of the dose of propranolol and topiramate in presence of intolerability or occurrence of serious side effects related to the treatment drugs was considered. Patients were permitted to take analgesics for abortive treatment of acute migraine attacks throughout the study.

Patient information about the characteristics of migraine attacks (including the frequency, intensity and duration of attacks) during the double-blind phase was recorded using diaries. Each patient was provided with a diary for 12 weeks, in which all migraine attack characteristics consist of the duration in hours and the intensity of attacks were recorded. The Pediatric Migraine disability assessment scale (PedMIDAS) which assess the effect of migraine on school, home, play and social activities was used to determine headache related disability at baseline and end of trial.

Follow up visits were scheduled at 4, 8 and 12 weeks during the double-blind phase of the study. At each visit, the diaries were checked and information collected. Patients were evaluated using detailed questionnaires to investigate the occurrence of the side effects.

Efficacy measures

To measure the efficacy of sodium valproate and topiramate treatments, the frequency, intensity of migraine attacks, headache related disability and 50% responder rate to the treatments were evaluated. All required data for calculating the intended measures were based on information obtained from the diaries.

Frequency of migraine attacks was defined as the mean number of migraine attacks that fulfilled the IHS criteria for migraine without aura each 4-week period. The intensity of attacks was Graded on a 0-3 scale 0= Normal, 1= Mild, 2- Moderate, 3= severe.²¹ Migraine intensity was defined as the mean intensity of migraine attacks per each 4-week period. Headache related disability was assessed by PedMEDAS score of 11-139 (range 0-240) with score of 0-10 indicate No disability, 11-30 Mild disability, 31-50 Moderate disability and >50 Severe disability.¹⁰

A 50% responder rate was defined as the percentage of patients who had a migraine frequency that was reduced greater or equal to 50%.

Safety measures

At each visit of the double-blind phase, safety of the treatment drugs was assessed by asking the patients' history of side effects occurrence during the last 4 weeks

with a detailed questionnaire. The relation of the side effects to the treatment drugs was also assessed at each visit by interviewing the patients. Special attention was paid to the occurrence of sleepiness, decreased appetite, weight loss, exercise induced asthma, hypotension and vomiting.

Statistical analysis

The evaluation of the efficacy and safety of the treatments was based on information obtained from the diaries, patient history. Descriptive statistics were calculated for the treatment group and for the total population separately. The comparison between the baseline values and 12 weeks of treatment during the double-blind phase values was performed using paired t test. In order to analyze the treatment comparability, a

student's t test for independent samples. Results are expressed as a mean \pm SD and $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS software version 24.

RESULTS

In our study, a total of 84 participants fulfilled the inclusion criteria during the study period. Eight patients were excluded, 2 due to lack of consent and 6 lost the follow up. Seventy-six-patients (43 male and 33 female) enrolled in the study, with a mean age of 12.43 years.

At the baseline, the mean (SD) of monthly migraine frequency was 7.01 ± 1.48 , monthly migraine intensity was 2.34 ± 0.77 and mean PedMIDAS score was 47.80 ± 12.82 .

Table 1: Characteristics of the patients at baseline.

Characteristics	All patients	Propranolol group	Topiramate group
Age years (Mean)	12.43	12.53	12.33
Sex			
Female	28	13	21
Male	48	27	15
Headache related disability (PedMIDAS Score)	45.48 \pm 12.99	46.35 \pm 12.24	45.97 \pm 14.58
Frequency of headache (per month)	7.01 \pm 1.48	6.87 \pm 1.6	7.16 \pm 1.38
Intensity of headache (per month)	2.34 \pm 0.77	2.37 \pm 0.74	2.30 \pm 0.82
Headache duration (Hours per attack)	6.63 \pm 2.35	6.67 \pm 2.98	6.58 \pm 1.38

Table 2: Efficacy results after 3 months of preventive therapy.

Parameters	Propranolol group	Topiramate group
Primary outcome		
$\geq 50\%$ relative reduction in headache frequency- no. (%)	30 (75%)	30 (71.42%)
Secondary outcomes		
Headache frequency		
At baseline	6.87 \pm 1.646.	7.16 \pm 1.38
At week 12	2.52 \pm 1.34	2.39 \pm 1.91
t Value	13.97	13.39
p value for patient's comparison with baseline	0.00001	0.00001
PedMIDAS score ⁺⁺		
At baseline	46.35 \pm 12.24	45.97 \pm 14.58
At week 12	22.07 \pm 5.51	21.61 \pm 7.94
t value	12.32	9.72
p value for patient's comparison with baseline	0.00001	0.00001
Headache intensity		
At baseline	2.37 \pm 0.74	2.30 \pm 0.82
At week 12	1.12 \pm 0.68	1.00 \pm .80
t value	11.18	7.18
p value for patient's comparison with baseline	0.00001	0.00001
Headache duration (Hours)		
At baseline	6.67 \pm 2.98	6.58 \pm 1.38
At week 12	4.45 \pm 2.40	3.94 \pm 3.06
t value	3.78	4.74
p value for patient's comparison with baseline	0.001	0.0001

Patients were randomly allocated into two treatment groups (propranolol n=40 and topiramate n=36). There were no statistically significant differences between the treatment groups regarding the participant age, the baseline means of monthly migraine frequency, migraine related disability (PedMIDAS), migraine intensity and duration of headache. (Table 1) represents demographic profile and baseline characteristics of the patients.

At the 12 weeks, the percentage of patients who had a relative reduction of 50% or more in the number of headache days was 67.5% patients in the propranolol group and 75.0% patients in the topiramate group.

In the secondary outcome the reduction in the mean of monthly migraine frequency intensity, headache disability score and headache duration was also significant for both groups Propranolol and topiramate when compared with baseline values (Table 2).

The reduction of monthly migraine frequency, intensity and disability showed no statistically significant differences for the propranolol group and the topiramate group when compared with each other.

Safety measures

Treatment related adverse effects were reported in 5 patients of the propranolol group, which was fatigue in 2, exercise induced asthma in 2 and hypotension in 1. In the topiramate group, 4 subjects experienced mild treatment related adverse effects that included mild appetite loss in 2, weight loss in 1 and paresthesias in 1. No serious side effects were reported in both treatment groups.

DISCUSSION

In this study, we evaluated the frequency, intensity, duration and headache related disability of monthly migraine attacks in children and adolescents aged 10-18 years at baseline and after 12 weeks treatment period. The results of the patients receiving propranolol or topiramate treatment were compared at baseline and after 12 weeks of treatment. The frequency of probable adverse effects related to the propranolol and the topiramate treatment and the safety of the treatments were evaluated.

In this study both propranolol and topiramate treatments resulted in significant reductions in the frequency and intensity of monthly migraine attacks, and headache related disability from the baseline through 12-week of treatment. The percentage of patients who had a relative reduction of 50% or more in the number of headache was 67.5% in the propranolol group and 75.0% in the topiramate group in comparison of baseline period with 12 weeks of treatment. Propranolol was effective in producing more than 50% reduction in migraine attacks in 60-80 % of patients in other studies which was comparable with our study.²⁵⁻²⁷ A reduction of 50%

frequency to the topiramate treatment varies in different studies, from 43.1-95.2% which was comparable with our study.^{15,16,18,20} In our study the intensity of headache, headache related disability (PedMIDAS), duration of headache attacks also improved in both propranolol and topiramate groups when compared with baseline which was in agreement with other studies.²²⁻²⁴

Both treatments were well tolerated and no life-threatening side effects were reported. The frequency of side effects related in our study were 13.4%, in propranolol group and 15% in topiramate group which were mild and were similar to other studies.

The side effects related to topiramate administration varied considerably among studies from 14-18%. The most frequent reported side effects were weight loss, anorexia, abdominal pain, sedation, paresthesias, and difficulties in concentration.¹⁵⁻¹⁹

No dropouts occurred in our study due to adverse effects. To the best of our knowledge, the current study is the first study that compares the effectiveness of propranolol and topiramate treatment as a prophylaxis of migraine headaches among children and adolescents residing in rural areas. A limitation of our study was that it had no placebo group.

CONCLUSION

Propranolol and topiramate were effective in prevention of migraine headaches in children and adolescents. Both drugs were well tolerated and safe.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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