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ORIGINAL ARTICLE

Topiramate and Propranolol for Prophylaxis of Migraine

Razieh Fallah · Mohammad Saleh Divanizadeh · Mehran Karimi · Mehrdad Mirouliaei · Ali Shamszadeh

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Abstract
Objective To compare efficacy and safety of topiramate (TPM) and propranolol for migraine prophylaxis in children.
Methods In a parallel single-blinded randomized clinical trial, 5–15 y-old referred migraineurs to Pediatric Neurology Clinic of Shahid Sadoughi Medical Sciences University, Yazd, Iran from May through October 2011, were evaluated. Patients were distributed into two groups, 50 of whom were treated with 3 mg/kg/d of topiramate (TPM) and another group of 50, were treated with 1 mg/kg of propranolol for 3 mo. Primary endpoints were efficacy in reduction of monthly frequency, severity, duration and headache related disability. Secondary outcome was clinical side effects.
Results Fifty two girls and 48 boys with mean age of 10.34±2.31 y were evaluated. Monthly frequency, severity and duration of headache decreased with TPM, from 13.88±8.4 to 4.13±2.26 attacks, from 6.32 ±1.93 to 2.8±2.12, and from 2.36±1.72 to 0.56±0.5 h, respectively. Monthly frequency, severity and duration of headache also 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 h, respectively. Pediatric Migraine Disability Assessment score reduced from 31.88±9.72 to 9.26± 7.21 with TPM and from 33.08±8.98 to 23.64±9.88 with propranolol. Transient mild side effects were seen in 18 % of TPM and in 10 % of propranolol (P=0.249) groups.
Conclusions Topiramate is more effective than propranolol for pediatric migraine prophylaxis.

Keywords Headache · Migraine · Prophylaxis · Topiramate · Propranolol

R. Fallah
Department of Pediatrics, Research Center of Pain, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

M. S. Divanizadeh
Department of Pediatrics, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

M. Karimi
Department of Pediatrics, Growth Disorders of Children Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

M. Mirouliaei
Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

A. Shamszadeh
Department of Computer Engineering, Engineering and Basic Sciences Faculty, Islamic Azad University, Sari Branch, Sari, Iran

M. Karimi (✉)
Shahid Sadoughi Hospital, Ave - Sina Blvd, Shahid Ghandi Blvd, Yazd, Islamic Republic of Iran
e-mail: mehrankarimi@ssu.ac.ir

Introduction

Migraine is the most common acute intermittent primary headache in children which occurs in up to 10.6 % of 5–15 y-old children [1]. During past 50 y, several diagnostic criteria for pediatric migraine have been proposed and now, second edition of the International Classification of Headache Disorders (ICHD-II) for Children Migraine that was published by the International Headache Society in 2004, has been accepted [2].

Preventive or prophylactic therapy is indicated in children with frequent (one or more headaches in a wk) or disabling [missing school, home or social activities or a Pediatric Migraine Disability Assessment score (pedMIDAS) above 20] headaches [1].

Preventive medications such as calcium channel blockers, cyproheptadine, beta blockers and anticonvulsants have been used in children [3]. Based on practice parameter evidences,

only flunarizine had a level of effectiveness, but, it is not available in many countries including the USA [1].

Propranolol has been used for children migraine prevention for many years with positive results. However, the studies showed a mixed response pattern with variability between patients. When propranolol is used, pulse rate and orthostatic blood pressure must be checked every 3 mo and pulse rate must be more than 60 beats per min after 1 min of exercise. Propranolol is contraindicated in diabetic, asthmatic or allergic children and children who take part in strenuous physical activities. Increased incidence of depression in adolescents limits propranolol usage [1] as well.

Recently, antiepileptic drugs including topiramate (TPM) are more commonly used in adults and adolescents for migraine prophylactic therapy [1]. Safety of topiramate in Iranian epileptic children has been reported as well [4]. But few pilot studies and placebo-controlled trials were done about efficacy and safety of TPM in children migraine prevention [5]. Therefore, more randomized clinical trials and comparison of effective migraine preventive drugs are needed to detect more effective drugs and to approve their use in pediatric migraine.

The purpose of this study was to compare efficacy and safety of topiramate and propranolol for migraine prophylaxis in children in Yazd, central city of I.R. Iran.

Material and Methods

A randomized single-blind clinical, open-label, parallel group study was conducted on referred migraineur children to Pediatric Neurology Clinic of Shahid Sadoughi Medical Sciences University, Yazd, Iran from May through October 2011.

Eligible participants included 5–15 y-old children who had migraine headache based on ICHD-II criteria [2] in clinical evaluation by pediatric neurologist for at least 6 mo before the study, did not use any migraine preventive therapy and had frequent (one or more headache attack per wk) or disabling (PedMIDAS more than 20) headaches and had to undergo preventive therapy.

Exclusion criteria consisted of headaches other than migraine and secondary headaches, presence of metabolic acidosis, kidney dysfunction, renal stone, diabetes mellitus, asthma or any other serious systemic diseases, or those who had not completed 3 mo of treatment period.

Headaches other than migraine, secondary headaches and systemic diseases were excluded by pediatric neurologist clinical evaluation of patients by taking history, physical examination, laboratory evaluation if indicated and brain magnetic resonance imaging when increased intracranial pressure was suspected, either by historical suspicion or physical examination [1].

This trial used equal randomization and allocation ratio was 1:1 for the two groups.

Simple randomisation was done by a computer generated random number list which was prepared by an investigator with no clinical involvement in the trial and no restriction was exerted. First of all, resident of research obtained parents' consent and called the one who was independent of the recruitment process for allocation consignment.

The trial adhered to established procedures to maintain separation between the person who took outcome assessment and the staff who delivered the intervention.

The drug was delivered by nurse of the clinic and was packaged and labeled according to a medication code schedule that was generated before the trial. Inside all packages, amount of drug in one tablet and the drug dosage were written. After opening of the packages, drug dosage was determined by pediatric neurologist based on weight of the child.

Primary and secondary outcomes were assessed by the resident of research who was not informed of the drug group assignment. Investigators, staff and participants were all kept masked to outcome measurements and trial results.

Informed consent was taken from patients' parents and the study has been approved by the Ethic Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Sample size based on Z formula and confidence interval of 95 % with 80 % power, type one error of 5 %, good response (more than 50 % decrease in monthly headache frequency during the follow-up period) of 76 % for TPM in another study [6] and an effect size (difference in frequency of good response between the two groups) of 30 % for the primary efficacy end point, was assessed in 41 children per group. For more accuracy, total sample size was determined to be 100 children.

After evaluation for inclusion and exclusion criteria, eligible patients were distributed into two groups. In both groups, the drugs were administered orally in two divided doses and in the lowest dosage. In group one, 50 children were treated with 3 mg/kg/d of topiramate (TPM) and in group two, 50 children were treated with 1 mg/kg of propranolol and then, the drugs were continued for 3 mo.

During the treatment period, patients were followed up by pediatric resident of research and in monthly consecutive visits of the children in Pediatric Neurology Clinic of Shahid Sadoughi Medical Sciences University, Yazd, Iran, clinical information about frequency, severity and duration of headaches, Pediatric Migraine Disability Assessment score [7] and drug side effects were evaluated by interviewing children or their parents and physical examination of patients was recorded in questionnaires.

Severity of headache was assessed by asking each child to grade majority of headache pain on visual analogue scale (VAS) [8] on a 10-point scale as no pain = scale of 0 and the most severe pain=10. A VAS is a horizontal or vertical

Table 1 Comparison of some characteristics of children in both groups

Group Data		Propranolol	Topiramate	*P* value	Statistical test that was used
Sex	Female Male	23 27	29 21	0.23	Chi-square
Type of migraine	Without aura With aura	30 20	36 14	0.2	Chi-square
Positive family history of migraine	Yes No	47 3	45 5	0.8	Chi-square
Age in years (mean ± SD)		10.68±2.35	10.11±2.24	0.15	Independent *t*-test
A onset age of migraine (mean ± SD)		8.8±1.94	8.05±2.54	0.09	Independent *t*-test
Monthly headache frequency (mean ± SD)		16.20±6.74	13.88±8.4	0.13	Independent *t*-test
Severity of headache (mean ± SD)		6.1±1.54	6.32±1.93	0.53	Independent *t*-test
Headache duration in hours (mean ± SD)		2.26±1.26	2.36±1.72	0.63	Independent *t*-test
Headache disability: pedMIDAS(mean ± SD)		33.08±8.98	31.88±9.72	0.52	Independent *t*-test

10 cm long line, that is marked at the extremes with "no pain" and "worst pain imaginable". The children were asked to place a mark on the line that represented their pain level. Throughout the study, acetaminophen and ibuprofen were permitted for symptomatic relief of moderate to severe headache attacks.

At the end of the 3 mo follow up period, drug efficacy and safety were evaluated. Monthly headache frequency was compared to the related number of it before and 3 mo after the drug use. More than 50 % of reduction in monthly headache frequency was considered as effective and good response.

Primary endpoint was with respect to efficacy in reduction of more than 50 % in monthly headache frequency, headache severity, duration of headache and pedMIDAS which was evaluated before and 3 mo after drug use.

Secondary outcome was clinical side effects of the drugs in the duration of treatment.

The data were analyzed using SPSS: 15 statistical software. Chi-square test or Fisher exact test were used for data analysis of qualitative variables. Comparing of mean values in one group was done by paired *t*-test and mean values of the two groups were compared using independent *t*-test. Differences were considered significant at *P* values of less than 0.05. This study is registered in Iranian clinical trials with registration number: IRCT201111282639N6. Meanwhile, the researchers got no support from the drugs company. The design and conduct of this trial was straightforward, and the authors did not have any losses to follow-up or exclusions .

Results

Finally, 100 children including 52 girls and 48 boys with mean age of 10.34±2.31 y were evaluated. Comparison of some characteristics of the children is shown in Table 1, which indicates that no statistically significant differences were seen in regard to sex distribution, migraine type, positive family history of migraine, mean age, mean onset age of migraine, monthly headache frequency, severity,duration and disability of headache in both groups. After 3 mo of treatment, more than 50 % reduction in monthly headache frequency was seen in 41 children (82 %) of topiramate (95 % confidence interval:0.75–0.93) and in 31 patients (62 %) of propranolol groups (95 % confidence interval :0.45–0.71) and TPM was statistically significantly more effective. (*P*=0.02) Tables 2 and 3 show headache characteristics before and after treatment in propranolol and topiramate groups, respectively and indicate that both drugs were effective in reduction of monthly frequency, severity, duration and disability of headache.

Table 2 Headache characteristics before and after treatment in propranolol group

Time Data	Before treatment Mean ± SD	After treatment Mean ± SD	*P* value	Statistical test that was used	Effect size	95 % CI for that effect size estimate
Monthly headache frequency (mean ± SD)	16.20±6.74	8.8±4.55	0.0001	Paired *t*-test	0.43	0.11–1.01
Severity of headache (mean ± SD)	6.1±1.54	4.18±1.6	0.0001	Paired *t*-test	0.52	0.16–1.20
Headache duration in hours (mean ± SD)	2.26±1.26	1.35±1.08	0.001	Paired *t*-test	0.36	0.07–0.87
Headache disability: pedMIDAS (mean ± SD)	33.08±8.98	23.64±9.88	0.0001	Paired *t*-test	0.45	0.12–1.05

Table 3 Headache characteristics before and after treatment in topiramate group

Time Data	Before treatment Mean ± SD	After treatment Mean ± SD	*P* value	Statistical test that was used	Effect size	95 % CI for that effect size estimate
Monthly headache frequency (mean ± SD)	13.88±8.4	4.13±2.26	0.0001	Paired *t*-test	0.62	0.22–1.41
Severity of headache (mean ± SD)	6.32±1.93	2.8±2.12	0.001	Paired *t*-test	0.65	0.24–1.47
Headache duration in hours (mean ± SD)	2.36±1.72	0.56±0.5	0.0001	Paired *t*-test	0.58	0.19–1.33
Headache disability: pedMIDAS (mean ± SD)	31.88±9.72	9.26±7.21	0.001	Paired *t*-test	0.79	0.33–1.76

Comparison of headache characteristics after treatment and number of acetaminophen and ibuprofen usage during follow up period in both groups, is presented in Table 4 which shows that TPM is more effective than propranolol in reduction of monthly frequency, severity, duration and disability of headache and number of analgesic consumption. No serious adverse events were seen in the two groups. Clinical side effects were seen in 18 % (*N*=9) of TPM (hyperthermia in four, anorexia and weight loss in three and drowsiness in two children) and in 10 % of propranolol groups (mild hypotension in three and drowsiness in two children). No statistically significant differences were seen from viewpoint of safety between the two drugs (*P* value=0.249).

All side effects disappeared in 1 to 2 wk and treatment was not stopped in any of the patients who suffered from them.

Discussion

Various drugs have been used for migraine prophylaxis in children. In the present study, efficacy and safety of topiramate and propranolol were compared and results showed that TPM was more effective in reduction of monthly frequency, severity, duration and disability of headache which is in agreement to another Iranian study on adult migraineurs. However, in this study, duration of headache decreased with TPM, from 2.36±1.72 to 0.56±0.5 h and with propranolol from 2.26±1.26 to 1.35±1.08 h. But in Isfahan, Iran study, headache duration decreased with TPM from 16.37±7.26 to 6.23±5.22 h and with propranolol from 15.10±6.84 to 7.27±6.46 h [9]. In children, duration of migraine headache was shorter than in adults [2].

In the present study, good response or effectiveness (more than 50 % of reduction in monthly headache frequency) was obtained with propranolol in 62 % of children.

In a double-blind, crossover clinical trial of Ludvigsson on 32 children aged 7–16 y, propranolol in dosage of 1 mg/kg/d was more effective than placebo [10]. In another clinical trial on 33 children aged 6–12 y, self-hypnosis was superior to 3 mg/kg/d propranolol [11].

In the third clinical trial, frequency, severity, and duration of headaches were equal using propranolol and placebo [12].

In this study, in children to whom propranolol was given, side effects including mild hypotension in 6 % and drowsiness in 4 % were seen. However, this trial was too small to confirm safety of propranolol. In another study, insomnia occurred in 18 % with propranolol [10]. But, in study by Olness et al., the patients did not show any adverse effect [11] and Forsythe et al. did not find any significant difference in side effects between placebo and propranolol and adverse effects such as abdominal pain, increased appetite, worsening of headaches and fatigue occurred in both the groups [12].

Table 4 Comparison of headache characteristics after treatment in both groups

Group Data	Propranolol Mean ± SD	Topiramate Mean ± SD	*P* value	Statistical test that was used	Effect size	95 % CI for that effect size estimate
Monthly headache frequency (mean ± SD)	8.8±4.55	4.13±2.26	0.001	Independent *t*-test	0.54	0.25–0.99
Severity of headache (mean ± SD)	4.18±1.6	2.8±2.12	0.0001	Independent *t*-test	0.34	0.12–0.66
Headache duration in hours (mean ± SD)	1.35±1.08	0.56±0.5	0.0001	Independent *t*-test	0.42	0.17–0.79
Headache disability: pedMIDAS (mean ± SD)	23.64±9.88	9.26±7.21	0.0001	Independent *t*-test	0.64	0.32–1.15
Number of acetaminophen usage during follow up period (mean ± SD)	14.22±2.4	7.48±2.1	0.01	Independent *t*-test	0.83	0.45–1.46
Number of ibuprofen usage during follow up period (mean ± SD)	8.34±3.5	3.26±1.43	0.001	Independent *t*-test	0.69	0.36–1.24

In the present study, more than 50 % of reduction in monthly headache frequency was attained with topiramate in 82 % of patients. However, in other studies, the proportion of those whose monthly headache frequency decreased more than 50 % varied 55–100 % [6, 13–17]. Possible explanations for these discrepancies are differences in: age, drug dosage, race, sample size and design of the study.

In this study, topiramate was effective in improvement of headache disability by reduction of Pediatric Migraine Disability Assessment score which is in agreement to other studies [18, 19].

In the present study, both drugs were safe and no serious clinical adverse event was seen in the two groups. Safety of TPM has also been reported in other researches [13, 14, 19, 20].

In this study, in children who took TPM, side effects including hyperthermia in 8 %, anorexia and weight loss in 6 % and drowsiness in 4 % were seen and all of these side effects were mild and transient and were not significant enough to cause exclusion from the study. Weight loss was the most common side effect in two other studies [13, 19].

In Lewis et al. study, upper respiratory tract infection, paraesthesia and dizziness were more frequent in TPM than in placebo group [14]. In a study in Barcelona, 33.3 % of children whom were treated with TPM, showed side effects none of which were serious [16]. In Winner et al. study, upper respiratory tract infection, anorexia, weight loss, gastroenteritis, paraesthesia and drowsiness were more frequent in TPM than in placebo group [13].

In Cruz et al. study, 27 % of 7.3–20.5 y migraineurs whom were treated with TPM had side effects and drug dose was more in patients with adverse effects: 2.8± 1.5 mg/kg/d *vs*. 1.27±0.7 mg/kg/d [6].

In an Indian study, weight loss, reduced concentration in school, drowsiness and paraesthesia were more important adverse effects of TPM [19].

Topiramate may also cause cognitive and concentration dysfunction [19, 21].

The limitations of this study were lack of placebo and no assessment of cognitive function in TPM treated children.

In summary, based on results of present study, both topiramate and propranolol are safe and effective for pediatric migraine prophylaxis in reduction of monthly frequency, severity, duration and disability of migraine headache in children. But, topiramate is more effective.

Conflict of Interest None.

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