Comparison of Propranolol and Pregabalin for Prophylaxis of Childhood Migraine: a Randomised Controlled Trial

MohammadKazem Bakhshandeh Bali[1], Ali Akbar Rahbarimanesh[1], Manelie Sadeghi[2], Mostafa Sedighi[3], Parvaneh Karimzadeh[4], and Mohammad Ghofrani[4]

[1]Bahrami Children Hospital, Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Community Medicine, Research Development Center of Bahrami Children Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Pediatrics, Kermanshah University of Medical Sciences, Kermanshah, Iran
[4]Department of Pediatric Neurology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract- Migraine involves 5-10% of children and adolescents. Thirty percent of children with severe migraine attacks have school absence and reduced quality of life that need preventive therapy. The purpose of this randomised control trial study is to compare the effectiveness, safety and the tolerability of pregabalin toward Propranolol in migraine prophylaxis of children. From May 2011 to October 2012, 99 children 3-15 years referred to the neurology clinic of Mofid Children's Hospital with a diagnosis of migraine enrolled the study. Patients randomly divided into two groups (A&B). We treated children of group A with capsule of pregabalin as children of group B with tablet of propranolol for at least 8 weeks. In this study, 99 patients were examined that 91 children reached the last stage. The group A consistsed of 46 patients, 12(26.1%) girls, 34 (73.9%) boys and the group B consisted of 45 patients, 14(31.1%) girls, 31 (68.9%) boys. Basis of age, gender, headache onset, headache frequency, migraine type, triggering and relieving factors there was no significant difference among these groups (P>0.05). After 4 and 8 weeks of Pregabalin usage monthly headache frequency decreased to 2.2±4.5 and 1.76±6.2 respectively. Propranolol reduced monthly headache frequency up to 3.73±6.11 and 3.34±5.95 later 4 and 8 weeks respectively. There was a significant difference between these two groups according to headache frequency reduction (P=0.04). Pregabalin efficacy in reducing the frequency and duration of pediatric migraine headache is considerable in comparison with propranolol.

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Keywords: Migraine; Preventive therapy; Pregabalin; Propranolol

Introduction

Migraine headache is a common neurologic disease with a prevalence of 5-10% in children and adolescents. According to epidemiologic surveys, about one third of children with severe migraine attacks experience absence from school & decreased quality of life (1-3). Migraines are frequently misattributed to other causes such as refractive eye errors, sinusitis or attention attracted behaviors. Prevalence of migraine headaches constantly increase through childhood and an unexplained gender switch occurs from male to female in adolescence. The mean age of migraine onset is 7 years for girls and 10.9 years for boys, respectively. Migraine headaches are characterized by recurrent attacks of vigorous, throbbing, nauseous frontal or temporal headache which last for hours (1,4). Aura defined as transient neurological symptoms specially sensory and/or visual symptoms occurring in 15% of patients (5). Preventive medications should be considered in patients with two or more headache attacks per month, severe debilitating or intolerable headache, an inadequate response to acute treatment, hemiplegic migraine and migraine plus prolonged aura. The main groups of conventional migraine prophylactic agents are antidepressants-adrenergic blockers, calcium channel inhibitors and antiepileptic drugs (AEDs) (6-7). The first report regarding effectiveness of Propranolol for migraine prophylaxis was published in 1966 by Rabkin *et al*., AEDs have been studied for prophylaxis of migraine

Corresponding Author: A.A. Rahbarimanesh
Bahrami Children Hospital, Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 936 1119156, Fax: +98 21 77551584, E-mail address: dr.mkbakhshandehbali@yahoo.com

since 1970, and the initial drug was carbamazepine (8-9). Right now AEDs are used progressively for migraine treatment because they efficiently reduce the frequency of attacks and are generally well tolerated. Recently, other AEDs such as Pregabalin have been introduced as migraine prophylaxis agents (10-11). Pregabalin is a high-tendency ligand for the α2-δ subunit of voltage related calcium channels, which is responsible for the development of pathologic changes leading to neuropathic pain in humans. Pregabalin diminishes release of several neurotransmitters including glutamate, noradrenaline, and substance. P via calcium influx reduction (12-13).

However, little attention has been paid to compare the efficacy of various preventive medications in pediatric population. The aim of this randomised control trial study is to compare the effectiveness, safety and tolerability of Pregabalin compared with Propranolol in migraine prophylaxis of children.

Materials and Methods

From May 2011 to October 2012, 99 children, aged 3-15 years who were referred to the neurology clinic of Mofid Children's Hospital with the diagnosis of migraine (based on the second edition of the international headache classification criteria), were enrolled the study. Patients were included if they had one of the following: 1. two or more headaches per month, 2. severe debilitating or intolerable headache, 3. no reductionin headache with rescue treatments, 4. poorly tolerated or unpleasant rescue medications. The data collection tool in our study was a questionnaire that contained questions about headache triggering factors, epidemiologic and demographic data, electroencephalographic and imaging results.

Complete physical plus neurological examination, primary laboratory screening tests and neuroimaging studies were performed. Exclusion criteria were: increased headache with valsalva maneuvers, continuously increasing headache, change in behavior and school activity, and detection of papilledema, focal neurological signs and focal neuroimaging lesions. Patients were randomly divided into two groups (A&B). Patients in group A were treated with Pregabalin(PGB) capsules (50 to 75 mg/day) while patients in group B received Propranolol(PRL) tablets with a dose of 10 to 20 mg/day divided in 2 doses for at least 8 weeks. We assessed headache frequency, severity and duration within four weeks interval from the beginning of study and compared the efficacy of drugs in two groups. Paired sample T-test, Z-test and chi-square have been used in statistical analysis. All of the ethical perspectives of this study have been confirmed in Ethics Committee of the Shahid Beheshti University of Medical Sciences. This study was registered in Iranian registry of clinical trial (IRCT) with a number of IRCT2012090910508N1.

Results

Of 99 patients enrolled, 91 completed the treatment course. Group A consisted of 46 patients, 12(26.1%) girls, 34(73.9%) boys, with age ranging from 5 to 15 years (mean, 9.95±2.4 years). Group B consisted of 45 patients, 14(31.1%) girls, 31 (68.9%) boys, with age ranging from 5 to 15 years (mean, 9.81±2.7 years). The mean age of migraine onset in group A and group B was 7.45±2.53 and 7.37±2.36 years, respectively. The mean headache frequency per month in group A was 12.18±20.7, ranging from 6 attacks per year to 4 attacks per day. The mean headache frequency per month in group B was 10.52±12.53, ranging from 5 attacks per year to 2 attacks per day. The quality of pain in 17(37%), 15(32.6%), 7(15.2%), 4(8.7%) and 3 (6.5%) of the group A was tightening, throbbing, vague and persistent, stabbing and unexplainable respectively. The quality of pain in 16(35.6%), 11(24.4%), 9(20%), 5(11%) and 4(8.9%) of group B were tightening, throbbing, vague and persistent, stabbing and unexplainable respectively.

Pain location was occipital, frontal, retro orbital and without a specific location in 10(21.73%), 6(13.04%), 11(23.91%) and 19(41. 3%) of patients in group A respectively. Pain location was occipital, frontal, retro orbital and without a specific location in 8(17.77%), 7(15.55%), 9(20%) and 21(41. 66%) of patients in group B respectively. The triggering factor was noise, stress, hunger, light, sleeplessness, fatigue and other factors in 7(15.21%), 9(19.56%), 2(4.34%), 7(15.21%), 12(26.08%), 4(8.69%) and 5(10.86%) cases of group A respectively .The triggering factor was noise, stress, hunger, light, sleeplessness, fatigue and other factors in 9(20%), 13(28.8%), 1(2.22%), 8(17.77%), 7(15.55%), 3(6.66%) and 4(8.88%) cases of group B respectively. The relieving factor in 21(45.7%), 10(21.73%), 8(17.4%), 6(13.04%) and 1(2.17%) cases of group A was sleep, silence, analgesics, eating and darkness respectively. The relieving factor in 21(46.66%), 9(20%), 7(15.55%), 7(15.55%) and 1(2.22%) cases of group B was sleep, silence, analgesics, eating and darkness respectively. In group A, 25(54.3%) had migraine without aura while 16(34.78%) had migraine with aura, the most common types of auras being visual, auditory, abdominal pain and

motor. Thirty (66.7%) and 15 (33.33%) of patients in group B, had migraine without aura and migraine with aura respectively which visual, auditory, abdominal pain, motor and olfactory were the most auras.

The associated signs and symptoms were photophobia, phonophobia, nausea, vomiting and without symptoms in 16 (34.78%), 15(32.6%), 9(19.56%), 8(17.39%), and 12(26.1%) children of the group A respectively. The associated signs and symptoms were photophobia, phonophobia, nausea, vomiting, dizziness, abdominal pain and without symptoms in 14(31.11%), 11(24.44%), 14(31.11%), 11(24.44%), 2(4.44%), 1(2.2%), and 10(22.3%) children of group B respectively. According to preventive medication, 18(39.13%), 12(26%), 2(4.34%), 2(4.34%) and 15(32.6%) cases of group have used sodium Valproate, Propranolol, Cyproheptadine, Lamotrigine and no prophylaxis respectively. 16(35.55%), 4(8.88%), 3(6.66%), 2(4.44%) and 21(46.7%) patients of group B have used Sodium Valproate, Topiramat, Risperidon, Cyproheptadine and no prophylaxis respectively. Basis of age, gender, headache onset, headache frequency, migraine type, triggering and relieving factors there was no significant difference among these groups (P>0.05).

After 4 and eight weeks of PGB administration headache frequency decreased to 2.2±4.5 per month as 81.8% reduction and 1.76±6.2 per month as 85.45% reduction respectively. Propranolol reduced monthly headache frequency up to 3.73±6.11 as 64.54% reduction and 3.34±5.95 as 68.25% reduction respectively. There was a significant difference between these two groups regarding headache frequency reduction (P=0.04). After a 4 weeks follow up period, severity and frequency of headache was reduced more than 50% in 25(55.5%) and 36(78.3%) of patients in group A and B, respectively. Six (13%) of group A and 13(28.9%) of group B patients had no changes, in addition 4(8.7%) and 7(15.55%) of patients had a <50% decrease in headach's severity and frequency in group A and B, respectively(Figure 1). Also, 7(15.2%), 37 (80.43%) and 2 (4. 34%) patients of group A compared to 19(42.2%), 20 (44.4%) and 6 (13.33%) patients of group B had no change, reduction of more than fifty percent(responder) and reduction less than fifty percent of severity and duration of headache in the 8 weeks follow-up respectively (Figure 2). There was a significant difference between these two groups in view of headache duration and severity reduction after 4(P=0.036) and 8(P=0.021) weeks reviews.

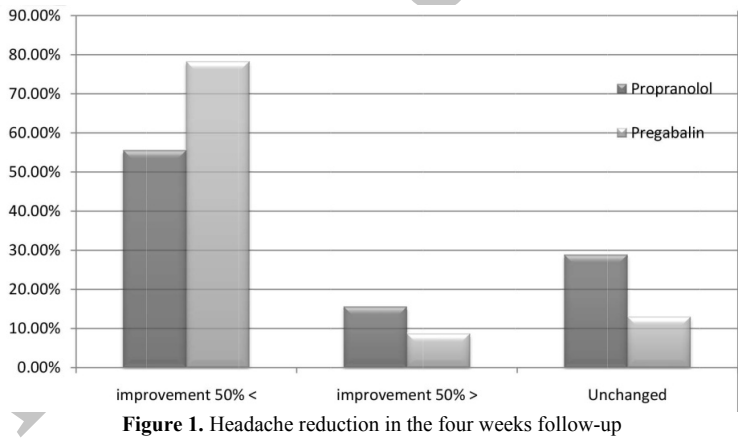

Figure 1. Headache reduction in the four weeks follow-up

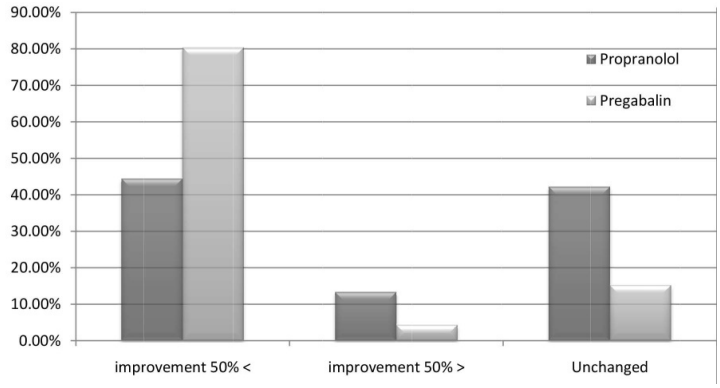

Figure 2. Headache reduction in the eight weeks follow-up

Discussion

In the present study, Pregabalin was associated with a 83.5% decrease in headache frequency and 79.4% decrease in headache severity, which shows more effectiveness compared to Propranolol. This result has been obtained despite higher headache intensity and resistance to anti-migraine prophylactic agents in patients receiving Pregabalin. Compared to other reports, Pregabalin has been proven to be more effective than Propranolol. Ashrafi *et al*., reported headache frequency decline up to 72% by sodium valproate vs 69% for propranolol. However in their cohort patients with refractory headache and history of prior prophylactic medications usage were excluded from the study (4). Lewis *et al*., repoted that amitriptyline and cyproheptadine decreased the frequency of headaches up to 62% and 55% respectively (14). According to a double blind placebo controlled trial by Winner *et al.,* ,topiramate reduces more than 75% of monthly headache attacks in children (15). Mathew et al., expressed a 50% efficacy of gabapentin in 46.4% of adults with migraine (16). In a comparative review designed by Mitsikostas *et al*., 65% and 71.4 % of patients responded to flunarizin and sodium valproate respectively (17). Miller treated migrainous adolescents with levetiracetam and showed that 52.6% of patients fully recovered and the number of monthly headache was reduced as 73% (18). Prophylactic efficacy of Pregabalin in comparison with topiramate among 100 patients with migraine were examined by Rizzato *et al*., 76.6% of Pregabalin users and 75.3% of topiramate users had reduced monthly frequency of migraine(19). Calendre et a*l*., reported a significant reduction in the headache frequency in adults after 12 weeks of treatment with Pregabalin (20). Interestingly, Pregabalinis more effective control in headache in children compared to adults. Our finding of 83.5% headache reduction with Pregabalin is strongly more than Pizzolato *et al*., (2). However 67.4% of patients in our study vs 85% of patients in Pizzolato *et al*., study had used other preventive drugs showed that Pizzolato*et al*., patients had more headache intensity than ours (2). Approximately 6.6% of our patients who had used Pregabalin and 13.2% of those treated with propranolol suffered from side effects. Somnolence (4.4%), increased appetite (2.2%) and dizziness (6.6%) were side effects of Pregabalin versus constipation (4.4%) and muscle contraction (2.2%) as the most complications of Propranolol. The rate of side effects due to Pregabalin in this study was lower than other prophylactic medications in other studies. Mathew *et al*., reported gabapentin side effects in about 13.3%, the most common side effects wasdizziness (16). According to Miller *et al*., levetiracetam was associated with adverse effects in 15.8% of cases, the most common symptoms being weakness, drowsiness,dizziness, irritability, hyperactivity, aggressive behavior and mood swings (18). In Mitsikostas *et al*., study, 57.1% of sodium valproate and 47.6% of flunarizin consumer's consumers had complications (17). Pregabalin complication rate in our study was much less than Calendre *et* a*l*., who reported dizziness (40%), somnolence (29%), abnormal thinking (16.7%), constipation and fatigue (13.3%) (20). Side effects including somnolence (11%), dizziness (4.3%), abdominal pain (2.1%), fatigue (2.1%), and blurred vision (2.1%) were reported in 13% of Pizzolato *et al*., cases which is higher than our study (2). This inconsistency in Pregabalin complication rates may be due to lower dosage administration in the current study compared to others. In our study, the mean Pregabalin dose was 50 mg per day while the average dose in Calendre *et al.,* and Pizzolato *et al*., study was about 225 and 150 milligrams respectively. It is clear that at higher doses more drug side effects may occur.

Pregabalin efficacy in reducing the frequency and duration of pediatric migraine headache is considerable in comparison with Propranolol. Pregabalin seems to be a well-tolerated and impressive choice for migraine prophylaxis in children.

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