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Original Article (Pages: 8907-8913)

Prophylactic Efficacy of Cinnarizine versus Propranolol in the Treatment of Childhood Migraine: A Single-Blind Randomized Clinical Trial

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Abstract

Background

Although the development of effective and safe treatments for prophylaxis of migraine headaches represents an important public health concern, only a few medications have been approved by the specific treatment of patients with migraine. We aimed to compare the efficacy of cinnarizine with propranolol in the prophylaxis of pediatric migraine headache.

Materials and Methods

In a Randomized Clinical Trial, children aged 6-14 years were selected from the patients with migraine admitted to the neurology clinic of Bandar Abbas pediatric Hospital, affiliated to Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Eligible patients (n, 56) were randomly divided into two groups, each comprising 28 patients: the first group administered cinnarizine (37.5 mg/day in children aged 6–12 years and 50 mg/day in children aged 12–17 years), and the second group received propranolol (1-mg/kg/day). The frequency, severity of headaches over the trial period were assessed.

Results: After two months of treatment, both groups had significant reduction in headache frequency in comparison with baseline period (p= 0.047), although this difference between groups was not statistically significant. In addition, the mean severe migraine attacks at the end of the second month was significantly lower in the cinnarizine group compared with the propranolol group (p=0.048). At the end of the study 64% (n=18) of patients who had received the cinnarizine and 57% (n=16) of patients who had administered the propranolol, the drugs appeared to have a preventative effect on their headaches.

Conclusion: According to the results, Cinnarizine appeared as effective as propranolol for the prophylactic treatment of childhood migraine.

Key Words: Children, Cinnarizine, Headache, Migraine, Propranolol.

*Please cite this article as: Alebrahim Z, Moayedi AR, Nazemi A, Madani A, Montaseri M. Prophylactic Efficacy of Cinnarizine versus Propranolol in the Treatment of Childhood Migraine: A Single-Blind Randomized Clinical Trial. Int J Pediatr 2019; 7(1): 8907-13. DOI: **10.22038/ijp.2018.34534.3036**

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Received date: Jul.25, 2018; Accepted date: Aug.22, 2018

1- INTRODUCTION

Migraine is characterized by enhanced sensitivity of the nervous system that may be moderate to severe in intensity and is often associated with nausea, vomiting and heightened sensitivity to sound and light (1). Migraine headaches are a painful and debilitating disorder in childhood and are a frequent reason for referral to child neurology clinics (2-4). The prevalence of migraine in children is estimated at 7.7%. Approximately 10% of children aged 5–15 years suffer from migraine headaches (5). Migraine can negatively impact on patient's life through interruption of daily activities, absence from school, and restriction of social activities (2).

When the headache attacks are frequent (<1 headache per week), or there are more than one disabling headache a month (Pediatric Migraine Disability Assessment [PedMIDAS] score > 20), prophylactic therapy is necessary. The purpose of preventive therapy should to be to reduce frequency (1-2 > headaches per month), and disability (PedMIDAS score <10) (1, 6). Although the development of effective and safe treatments for prophylaxis of migraine headaches represents an important public health concern, only a few medications have been approved by the specific treatment of patients with migraine (7-10). Propranolol is a nonselective β-blocker that is primarily used to treat hypertension. There is quality evidence that propranolol is also an effective preventive agent for migraine headaches. It is one of the most commonly prescribed drugs for migraine prophylaxis (8). Cinnarizine inhibits smooth muscle cell contraction in the vasculature by blocking L-and T-type voltage-gated calcium channel. It has also been implicated in binding to histamine H1 receptors, muscarinic receptors, and dopamine D2 receptors and has antihistaminic actions (9, 13). These mechanisms can potentially contribute to preventive effects on migraine headaches. The efficacy and safety of cinnarizine in the prophylactic treatment of migraine have been demonstrated in a numerous experimental studies (14-21). Therefore, we performed a study to compare the efficacy of cinnarizine with propranolol in the prophylaxis of pediatric migraine headache.

2- MATERIALS AND METHODS

2-1. Study design and population

We conducted a single-blind randomized clinical trial (TCTR20180903005) to evaluate the effect to compare the efficacy of cinnarizine versus propranolol in the prophylaxis of pediatric migraine headache. Our cases were selected from the patients with alleged diagnosis of migraine admitted to neurology clinic of Bandar Abbas pediatric Hospital, affiliated to Hormozgan University of Medical Sciences, Bandar Abbas city, South West of Iran, from September 2017 to February 2018. Based on the previous research findings, the necessary sample size was calculated to be at least 29 patients in each treatment group to provide 80% power to detect an odds ratio of 2.5 at the 5% level.

2-2. Measuring tools: validity and reliability

All patients and their parents were asked to maintain a headache diary. They were asked to record all the features of the headache experience. Headache severity recorded on a three scale, and was defined as mild (no effect on daily activities), moderate (disrupts daily activities), severe (requiring immediate intervention and treatment) (1, 22). Furthermore, patients and their parents were asked to record adverse effects related to both drugs. The data were collected at the end of each month during the treatment phase. The

goal of prevention therapy is reduction of headache frequency (moderate migraine attacks were equal to 2 or less than 2 ≥) and improvement in headache-related disability (no severe migraine attacks) (1).

2-3. Intervention

Four weeks before initiation of medication a researcher-administered standard questionnaire was used as a data collecting tool in which all the parents were asked about their children's baseline characteristics and clinical details of the patients such as frequency, severity and duration of headache. After obtaining the patient consent, the eligible patients were randomly divided into two groups by a simple randomization technique. Even numbers were allocated to cinnarizine (Osvah Pharmaceutical Company, tablet 25 mg) in a dosage of 37.5 mg/day in children aged 6–12 years and 50 mg/day in children aged 12–17 years, and odd numbers received 1-mg/kg/day propranolol (Abidi Pharmaceutical Company, tablet 20 mg), which continued till the 2-month follow-up (1).

2-4. Ethical consideration

A patient screening form was used to assess the presence or absence of inclusion and exclusion criteria after obtaining an informed written consent from the parents of the participating children. This study was approved by the Ethics Committee of the Hormozgan University of Medical Sciences (Ref. no: HUMS.REC.1397. 1).

2-5. Inclusion and exclusion criteria

Children aged 6-14 years who had migraine with and without aura, defined by the International Headache Society criteria for migraine (22), were enrolled into the study. All patients experienced one or more headaches per week for at least 6 months or had severe disabling or intolerable headache before entry into the study. In addition, participants meeting the following criteria were excluded: children who had complicated migraine that required medications other than analgesics, past treatment with migraine prophylactic agent, persistent increasing headache, comorbid conditions such as seizures, abnormal neuroimaging, history of epilepsy, and history of contraindications to cinnarizine or propranolol administration.

2-6. Data Analyses

The mean (±standard deviation [SD]) frequency, intensity, and duration of migraine headaches at the end of each month were determined. A paired sample t test or, if conditions for its use were not valid, Wilcoxon's test were used to determine the differences in these parameters between each follow-up visit. For qualitative data, we used Fisher exact test or the Mann-Whitney U test, when appropriate. $P < 0.05$ was considered significant. To reduce the bias in analysis, all data were analyzed by a biostatistician who was not aware of the study groups.

3- RESULTS

3-1. General Results

A total of 58 children with migraine were entered in the study, and 56 patients (40 males, 16 females) completed the study. Two children (one patient from each group) were dropped because they did not cooperate with the study protocol **(Figure. 1)**. The ages of children ranged from 7 to 13 years with an average of 9.25 ± 1.8 years. The baseline characteristics of the children are summarized in **Table.1**. There were no differences in most of the Patients' characteristics between the two groups (**Table.1)**. At the end of first month of intervention, migraine frequency (mean number of headache attacks per month) in cinnarizine group was increased from 7.36 (±1.85) at baseline to 8.7 (±4.57) whereas slightly decreased from 7.93 (±2.69) to 7.8 (±4.36) in the propranolol group, although this difference between groups was not

statistically significant (p=0.46) (**Table.2**). After 2 months of treatment, both groups had significant reduction in headache frequency in comparison with baseline period (p= 0.047), so that migraine frequency in cinnarizine group was decreased from 7.36 (±1.85) to 1.1 (± 0.7), and that of the propranolol group from 7.93 (±2.69) to 0.66 (±0.54), although this difference between groups was not statistically significant (p= 0.059) (**Table.2**). According to **Tabe.2**, in the cinnarizine group, mean number of mild migraine attacks was increased at the end of the first and second months. Mean mild migraine attacks in propranolol group was increased at the end of the first month and slightly reduced in the second month. Both cinnarizine and propranolol effectively reduced the mean number of moderate and severe migraine attacks after drug treatment for 2 months compared to baseline period (**Table.2**). The propranolol group was significantly more effective in reducing the number of mild (p= 0.002), and moderate (p= 0.038) headache attacks at 2 months compared with cinnarizine group. However, the mean number of severe migraine attacks at the end of the second month was significantly lower in the cinnarizine group compared with the propranolol group (p=0.048) (**Table.2**). At the end of the second months, 18 patients of 28 who had received the cinnarizine (64%), and 16 of 28 who had administered the propranolol (57%), the drugs appeared to have a preventative effect on their eadaches. There was no statistically significant difference in the effectiveness of the prophylactic effect between the two drugs (p=0.58).

3-2. Adverse effects

None of the patients discontinued medication because of adverse effects.

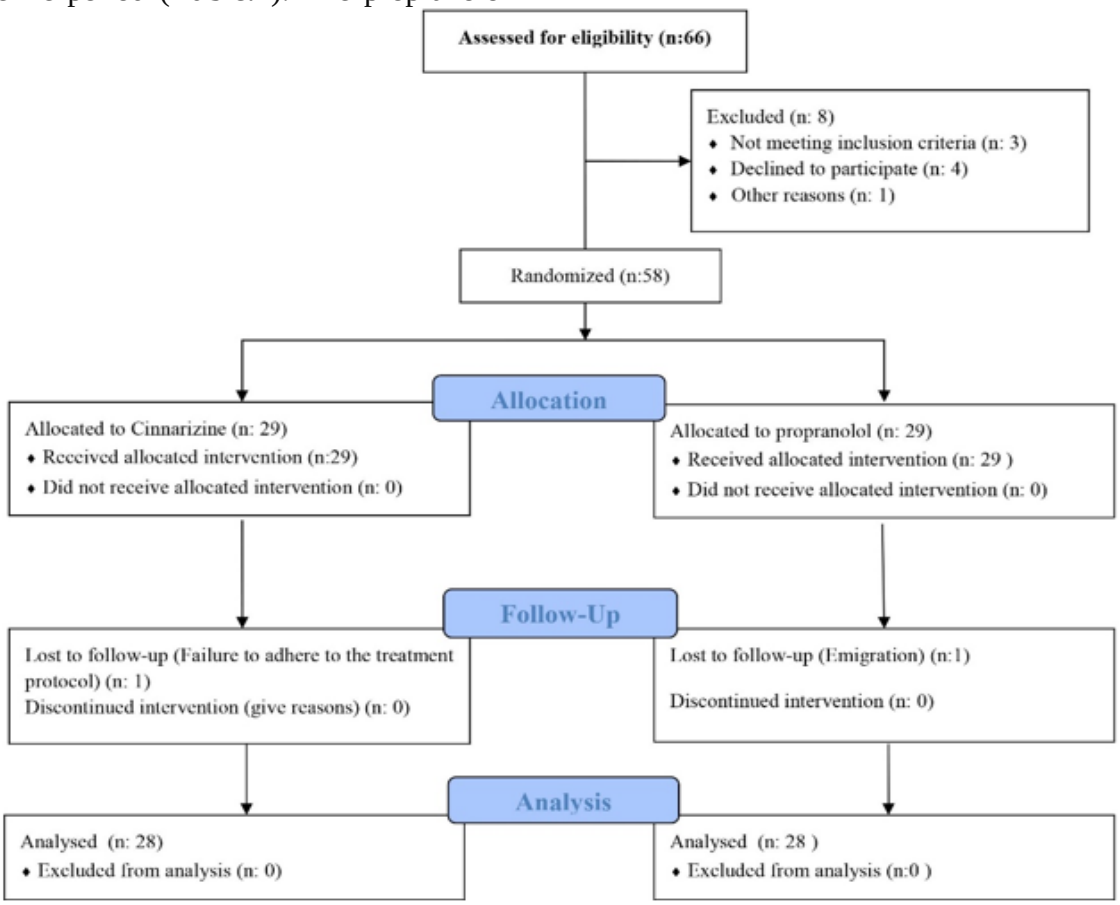

Fig1: Flow Diagram of the study protocol.

Table-1: Baseline characteristics of the children in the two treatment groups in the pre randomization phase

Characteristics		Cinnarizine Number (%)	Propranolol Number (%)	P-value
Gender	Male	19 (33.93)	21 (37.5)	0.77
	Female	9 (16.07)	7 (12.5)	
Migraine types	With Aura	4 (7.14)	11 (19.64)	0.068
	Without Aura	24 (42.86)	17 (30.36)	
Migraine form	Pulsating	28 (50)	25 (44.64)	0.236
	Non- Pulsating	0	3 (5.36)	
Lateralisation	Unilateral	18 (32.14)	9 (16.07)	0.031
	Bilateral	10 (17.86)	19 (33.93)	
Pain location	Frontal	6 (10.71)	6 (1071)	0.59
	Temporal	17 (30.36)	20 (35.71)	
	Occipital	1 (1.79)	0	
	Generalize	4 (7.14)	2 (3.57)	
Nausea and/or vomiting	Yes	26 (46.43)	24 (42.86)	0.67
	No	2 (3.57)	4 (7.14)	
Photophobia and Phonophobia	Yes	14 (25)	12 (21.43)	0.79
	No	14 (25)	16 (28.57)	
Aggravation by physical activity	Yes	24 (42.86)	19 (33.93)	0.21
	No	4 (7.14)	9 (16.07)	
Family history of headache	Yes	25 (44.64)	28 (50)	0.24
	No	3 (5.36)	0	
Family history of migraine	Yes	24 (42.86)	26 (46.43)	0.67
	No	4 (7.14)	2 (3.57)	
Headache attacks in 24 hours	0-6 AM	0	0	0.014
	6-12 PM	2 (3.57)	0	
	12-6 PM	20 (35.71)	12 (21.43)	
	6-12 PM	6 (10.71)	16 (28.57)	
Headache history (Month)	0-6	7 (12.5)	4 (7.14)	0.32
	6-12	19 (33.93)	18 (32.14)	
	12-24	2 (3.57)	4 (7.14)	
	> 24	0	2 (3.57)	
Duration of migraine attacks (Minute)	30-60	16 (28.57)	16 (28.57)	0.28
	60-120	2 (3.57)	6 (10.71)	
	> 120	10 (17.86)	10 (17.86)	

* P- values ≤ 0.05 were considered statistically significant.

Table-2: The frequency of migraine headache attacks

Scale of headache intensity	Prescribed drugs	Mean number of migraine attacks (± SD)		
		Before treatment	First Month	Second Month
Mild	Cinnarizine	0.43 (±0.79)	0.86 (±1.15)	1.04 (±1.23)
	Propranolol	0.36 (±0.83)	1.67 (±1.89)	0.25 (±0.44)
p- value		0.74	0.054	0.002*
Moderate	Cinnarizine	4.43 (±2.89)	4.79 (±3.98)	2.82 (±4.42)
	Propranolol	4.5 (±2.8)	3.04 (± 3.02)	0.96 (±1.4)
p- value		0.93	0.07	0.038*
Severe	Cinnarizine	2.5 (±2.89)	3.11 (±2.85)	0.29 (±0.66)
	Propranolol	3.07 (±2.98)	3.15 (±1.86)	1.35 (±2.74)
p- value		0.47	0.96	0.048*
Total headaches with any intensity	Cinnarizine	7.36 (±1.85)	8.7 (±4.58)	1.1 (±0.7)
	Propranolol	7.93 (±2.69)	7.8 (±4.36)	0.66 (±0.59)
p- value		0.36	0.46	0.059

*p- values ≤ 0.05 were considered statistically significant; SD: Standard deviation.

4- DISCUSSION

In the current study, we evaluated the efficacy of cinnarizine versus propranolol in chidren with migraine headaches. The results have shown that both cinnarizine and propranolol effectively reduced the number of migraine attacks after treatment for 2 months compared to baseline period. The propranolol group was significantly more effective in reducing the number of mild and moderate headache attacks (p=0.002, p=0.0368, respectively); while the mean number of severe migraine attacks was significantly lower in the cinnarizine group (p=0.048). Cinnarizine is a medication derivative of piperazine and it is characterized as an antihistamine. It was assumed that its underlying mechanisms are probably due to blockade of serotonin or Calcium ions (Ca^{2+}) channels (23). In some different recent studies, authors concluded that cinnarizine is an effective and well option for treatment of migraine. In similar investigation, Togha et al. conducted a clinical trial to evaluate the efficacy and safety of cinnarizine versus propranolol in the prophylaxis headaches in children, in both treatment groups, the frequency, intensity of attacks significantly decreased (17). In another study they designed a trial to assess the efficacy and safety of the cinnarizine in patients with migraine who were refractory to propranolol and tricyclic antidepressants in comparison with sodium valproate. Their results showed that both drugs caused the reduction of attacks, intensity, and duration of headaches (15). Bostani et al. compared the efficacy and safety of cinnarizine and sodium valproate in migraine prophylaxis. They found significantly decrease headache duration and headache frequency among those treated with both drugs (16). A controlled study was conducted by Ashrafi et al. to demonstrate the efficacy and safety of cinnarizine in the prophylaxis of migraine in children. Results of this study indicate the use of cinnarizine is effective and safe for prophylaxis of migraine headaches in children (18). An open-label trial on 80 patients treated with cinnarizine, 55 of them indicated a greater than 66% reduction in frequency of headaches (14). Our findings are consistent with mentioned previous studies indicating that cinnarizine is a safe and effective medication for children with migraine.

5- CONCLUSION

Both cinnarizine and propranolol drugs demonstrated efficacy in reducing frequency and severity of headache attacks and the prevention of migraine headaches among the children who suffer from migraine. Although more extensive studies are still required for final statements, the present finding suggests that cinnarizine as effective as propranolol for the prophylactic treatment of childhood migraine.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

The authors are grateful to all parents and patients for their participation in this study and Mrs. Miri for her help in collecting cases. This article is a part of the first author's dissertation for fulfillment of a Specialist in Pediatric from Department of Pediatrics, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. This study was supported by Hormozgan University of Medical Sciences (HUMS).

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