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Original Article

Efficacy and Safety of Cinnarizine in the Prophylaxis of Migraine in Children: A Double-Blind Placebo-Controlled Randomized Trial

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ABSTRACT

BACKGROUND: In spite of the high occurrence of migraine headaches in school-age children, there are currently no approved and widely accepted pharmacologic agents for migraine prophylaxis in children. Our previous open-label study in children revealed the efficacy of cinnarizine, a calcium channel blocker, in migraine prophylaxis. A placebo-controlled trial was conducted to demonstrate the efficacy and safety of cinnarizine in the prophylaxis of migraine in children. **TRIAL DESIGN:** A double-blind, placebo-controlled, parallel-group study conducted in a tertiary medical center in Tehran, Iran. **METHODS:** Children (5-17 years) who experienced migraines with and without aura, as defined on the basis of 2004 International Headache Society criteria, were recruited into the study. Children were excluded if they had complicated migraine, epilepsy, or a history of use of migraine prophylactic agents. Each participant was randomly assigned to receive cinnarizine (a single 1.5 mg/kg/day dose in children weighing less than 30 kg and a single 50 mg dose in children weighing more than 30 kg, administered at bedtime) or placebo. The frequency, severity, and duration of headaches over the trial period were assessed and adverse effects were monitored. **RESULTS:** A total of 68 children (34 in each group) with migraine were enrolled and 62 participants completed the study. After 3 months of taking cinnarizine or placebo, children in both groups experienced significantly reduced frequency, severity, and duration of headaches compared with baseline measurements ($P < 0.001$). However, compared with 31.3% of children in the placebo group, 60% of children in the cinnarizine group reported more than 50% reduction in monthly headache frequency ($P = 0.023$), suggesting that cinnarizine was significantly more effective than placebo in reducing the frequency of headaches. No serious adverse effects of the medications were observed in the treated children, including no abnormal weight gain or extrapyramidal signs. **CONCLUSION:** Our results indicate that the use of cinnarizine at doses administered in this study is effective and safe for prophylaxis of migraine headaches in children.

Keywords: children, migraine, cinnarizine, placebo, clinical trial

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Introduction

Migraine headaches are among the most common neurological complaints in patients referred to child neurology clinics. Approximately 10% of children and 28% of adolescents experience these headaches. Epidemiologic

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studies have revealed that the mean age of onset for migraine headaches is in the elementary school age range.[1] The complex cycle of migraine headaches accompanied by high absenteeism from the stressful environment of schools has a severe impact on the quality of life, possibly leading to the loss of the most productive hours in the daily lives of the affected children. Therefore, development of an effective and safe agent for the prophylaxis of migraine headaches in children is essential for improving the short-term condition and long-term educational and social outlook.[1-4]

Lifestyle changes and biobehavioral recommendations are among the most frequently advised measures for migraine prophylaxis. However, these approaches are not effective in a large portion of the children suffering from migraine headaches. Therefore, medications are commonly used in children with migraines. In spite of the widespread use of pharmacologic agents, at this time there is no Food and Drug Administration (FDA)-approved treatment for the prophylaxis of headaches in children with migraine.[1-10] A few prophylactic agents have been suggested by a number of low-quality studies. A recently published meta-analysis found only limited evidence to support the efficacy of topiramate (100 mg/day) in children with migraine.[3,9] However, studies in adults and children have demonstrated serious adverse effects of topiramate on cognition.[11-14] Therefore, an effective and safer agent is needed for use in children of school age. Moreover, almost all previous publications have called for better-designed studies that would provide the evidence supporting the efficacy and safety of agents currently considered for migraine prophylaxis in children.[3,15]

Calcium channel blockers have been demonstrated to be effective in migraine prophylaxis.[16] Cinnarizine is an L-type calcium channel blocker with a number of different proposed pharmacologic effects that may underlie the mechanism of action of its preventive effects on migraine.[17] This agent is inexpensive and has been available since the 1970s in a number of European countries and for more than 15 years in Iran.[16] The efficacy and safety of cinnarizine in the prophylaxis of migraine have been demonstrated in a number of studies.[16-20] Our group has conducted two clinical trials in adults (one open-label and one double-blind controlled) and one open-label trial in children to demonstrate the efficacy of cinnarizine in the prophylaxis of migraine in both patient populations.[17-19] However, these studies had major limitations and did not include a placebo-administered control group. Therefore, we performed a double-blind placebo-controlled trial to demonstrate the efficacy and safety of cinnarizine in a population of school-age children.

Material and Methods

Study design and location

We conducted a double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of cinnarizine as a prophylactic medication for headaches in school-age children with migraine. The study was conducted at the Children's Medical Center, a university-affiliated tertiary referral children's hospital in Tehran, Iran. The study was conducted between April 2012 and January 2014. The study design was approved by the ethical board committees of the medical center and Tehran University of Medical Sciences. Written informed consent was obtained from all patients and their parents. The trial is registered with the Iranian Registry of Clinical Trials, number IRCT201107216907N2.

Patients

Children aged 5-17 years who had migraine with and without aura, according to the 2004 International Headache Society criteria for migraine,[21] were enrolled into the study. All patients experienced four or more headaches per month for at least 6 months before entry into the study.

Inclusion and exclusion criteria

Patients were excluded from the study if they had complicated or status migraine that required medications other than analgesics, comorbid conditions such as seizures, a history of epilepsy, and if they were previously administered migraine prophylactic agents such as beta blockers, valproate, topiramate, or amitriptyline. Additionally, children with a history of serious adverse reactions to calcium channel blockers, such as cinnarizine, were excluded.

Study phases and randomization

The study was divided into two phases; a prerandomization phase, in which all patients meeting the inclusion criteria and their parents were familiarized with the study, followed by the random assignment of participants to receive either cinnarizine or placebo. The prerandomization phase lasted 4 weeks, whereas the treatment phase lasted 12 weeks. Participants were randomized to cinnarizine or placebo treatment group using a random number table to allocate consecutive patients into quaternary blocks.

Intervention and blinding

Participants in each arm of the study received either cinnarizine or placebo. In the cinnarizine group, the dose of the medication administered was based on body weight. For children weighing less than 30 kg, cinnarizine was administered at a dose of 1.5 mg/kg/day, whereas children who weighted more than 30 kg were administered 50 mg of cinnarizine. Both doses and the placebo formulation were administered as a single dose at 9 pm. All medication was dispensed by the trained staff of the central pharmacy of the medical center. All patients, their parents, interviewing staff, and the staff of the pharmacy of the medical center were unaware of the study arm assignment. Both cinnarizine and placebo formulations were dispensed to the patients in identical envelopes with similar appearance. Cinnarizine and placebo pills were identical in shape, color, and taste. These identical packages and their contents were provided by the laboratory of the School of Pharmacy of the Tehran University of Medical Sciences. The study duration was 4 months, including 4 weeks for the prerandomization phase and 12 weeks for the randomized treatment phase.

Pain measurement scale

To evaluate the duration and intensity of the headaches in each patient in a uniform manner across assessments, we used the Wong-Baker Faces Pain Rating Scale.[22] To ensure that the scale was administered correctly, all patients and their parents were instructed by trained interviewing staff during the prerandomization phase on how to correctly assess headache duration and intensity.

Outcome measures

All patients and their parents were asked to maintain a headache diary. They were asked to register all the features of experienced headaches (frequency, intensity, and duration), with the resulting data used as a primary outcome measure. The patients and their parents were asked to register these data daily during both the prerandomization and treatment phases. The interviewing staff collected the data at the end of