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Original Article

Effectiveness of cyproheptadine in the prevention of childhood migraine

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Abstract

Background Migraine is one of the causes of recurrent headache in childhood. Cyproheptadine is well known as an antihistamine, but there are few studies revealing the drug's effect in pediatric migraine.

Objective To determine the effectiveness of cyproheptadine in the prophylactic treatment of childhood migraine.

Methods A randomized placebo-controlled clinical trial study was performed at Medan. One hundred children with migraine according to the International Headache Society criteria were included in the study. Subjects were divided into two groups, and each group was given either 4 mg cyproheptadine or placebo for 12 weeks. Headache frequency was measured in headache days per month, duration was measured in hours and functional disability was measured by Pediatric Migraine Disability Assessment (PedMIDAS). The efficacy was measured before intervention; also 1, 2, and 3 months after intervention.

Results A total of 100 patients, with age ranging from 11 to 18 years old (with mean, 15.5 years), were treated with cyproheptadine or placebo for headache. Compared to baseline, there was a significant difference on PedMIDAS grading of migraines in both groups ($P<0.05$). Headache frequency and duration per month were significantly different after treatment with cyproheptadine ($P=0.009$, 95% CI 0.001 to 0.030 and $P= 0.029$, 95% CI 0.690 to 27.510, RR=4.36), compared to placebo group ($P> 0.05$), but there were side effects of cyproheptadine up to 73%.

Conclusion Cyproheptadine appears to be effective as an alternative prophylactic treatment of childhood migraine. However, pediatricians should consider the significant side effects of this drug. **[Paediatr Indones. 2009;49:286-91]**.

Keywords: *cyproheptadine, prophylaxis, childhood migraine*

Headache, more particularly migraine, is a frequent health problem in children and adolescents. Headaches are estimated to be occurred in up to 75% of adolescents and 25% of younger children. Migraine has the greatest impact on children and parents. It occurs in up to 10.6% children with age between 5 and 15 years, and 28% in children aged 15 to 19 years.[1] Although the attacks of migraine may start at any age, the incidence peaks in early to mid-adolescence.[2] Migraine, as defined by the research group on headache of the World Federation of Neurology, is a familial disorder characterized by recurrent attacks of headache, widely variable in intensity, frequency, and duration. Attacks are usually unilateral and are associated with anorexia, nausea and vomiting. In some cases, these are preceded by (or associated with) neurological and mood disturbances.[3] The World Health Organization

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(WHO) considers that severe-migraine can be as disabling as quadriplegia.[4,5]

Approach to migraine treatment involves acute (abortive) and preventive (prophylactic). Preventive treatment, given even in the absence of attacks, is aiming to reduce the frequency and severity of the migraine attack, make acute attacks more responsive to abortive therapy, and perhaps also improve the patient's quality of life.[6] On average, two thirds of patients will have 50% reduction in headache frequency with most preventive drugs.[4] Many clinical trials in children using expensive drugs such as sodium valproate and topiramate show good outcome. Cyproheptadine has a low cost, sometimes it is used by pediatric neurologist, however only Rao *et al*[7] who had studied this drug compared with other drug. Migraine is a common cause of headache in children and it significantly reduces school attendances, but not may has studied about the phenomenon.[8,9] We compared cyproheptadine with placebo to determine their effectiveness in prophylactic treatment of childhood migraine.

Methods

This was a randomized clinical trial with control placebo study. Conducted from February to May 2008. Subjects were recruited from eleven schools, including three junior high schools and eight senior high schools in Medan, North Sumatera. For each disorder, a series of detailed, primarily yes-no questions were asked. Each subject was asked: "Have you ever had a lot of trouble with headaches?", if they had a positive response, then they were asked if they took medication for the headaches and how recently the headache occurred. A positive response to this general headache question was used as a nonspecific, sensitive screening question to establish the at-risk study subjects to estimate the incidence of migraine in the study subjects on follow up.

Migraine was diagnosed by consultant-pediatric neurologist in accordance with The International Headache Society (IHS) criteria. We included all students diagnosed with migraine according to IHS, whose age ranging from 11 to 18 years, and who had experienced migraine. Informed consent was obtained from the parents. The selection criteria for study subjects were the following: one of the criteria such as; two or more attacks per month that produce disability lasting 3 or more days per month; contraindication to, or failure of, acute treatments; the use of abortive medication more than twice per week; and the presence of uncommon migraine conditions including hemiplegics migraine, migraine with prolonged aura, or migraines infarction. We excluded patients from the study in the presence of any of the following: chronic daily headaches; more than one type of headache including cluster headaches; coexisting medical, neurological, or psychiatric disorder; previous treatment with three or more migraine prophylactic medications; history of previous cyproheptadine use; history of noncompliance with previous migraine medications and obesity.

The study was approved by the Ethics Committee of University of North Sumatera. As part of the standard assessment, detailed questionnaires at initial and follow-up evaluations were obtained. This questionnaire included information about headache frequency, duration, and characteristics, as well as some general health screening, documentation of school absences, and ratings of functioning at home and school. Frequency was measured in headache days per month, duration was measured in hours, and functional disability was measured by Pediatric Migraine Disability Assessment Scale (PedMIDAS).

Pediatric Migraine Disability Assessment (PedMIDAS) was administered to all of the patients as part of this questionnaire at initial and follow-up evaluations. PedMIDAS was a six-item questionnaire. The initial three questions dealt with impact of headache on school; question 1 asked about school day absences; question 2 asked about partial day absences; and question 3 asked about functioning at 50% or less ability in school. The fourth question assesed the impact due to headache at home and included inability to perform homework and chores. The final two questions assesed disability in social functioning including sports; question 5 asked about complete absence from activities, while question 6 asked about functioning at 50% or less of their ability. PedMIDAS were asked after completion to rate their overall disability due to headache in the preceding 3 months (global rating), the patients were prompted with the choices of none to little, mild, moderate, and severe. Responses to this question were obtained prior

to discussing PedMIDAS scores and their significance with the patients. Mean PedMIDAS scores with standard deviations were determined for each of the four global rating responses.

Subjects were randomized into two groups using simple randomization method. Anthropometric data was recorded including body weight and the height. First group (A) received cyproheptadine 4 mg/day once daily during bedtime. The second group (B) received placebo containing saccharum lactis once daily during bedtime and requested to take it in the same manner as the cyproheptadine. Subjects did not know whether the capsule contained cyproheptadine or placebo, both groups got therapy for 3 months. All subjects were reassessed after 1 month for two group's cyproheptadine or placebo. At the follow-up visit, frequency and duration of headaches were determined for the preceding 4 weeks and headache scores from daily diaries were calculated at monthly intervals.

All headache diaries were filled in by the children. After the third month's treatment, each child was asked to indicate the preferred treatment in the diary. The code was opened for the treatment only, because it was considered ethically unacceptable to withhold adequate treatment until the whole trial was completed. Children were asked to report any adverse events during the follow-up visits and in the headache diaries. Diaries were collected when the tests were completed. Children who had not replied were contacted by phone.

Data was analyzed using Pearson chi-square, t-test, Mann-Whitney U-test, Wilcoxon ranks test, and also intention to treat analysis. The value 95% CI and values of $P < 0.05$ were considered to be statistically significant.

Results

From 11 schools, including three junior high schools and eight senior high schools in Medan, North Sumatera, we searched for childhood migraine candidates. Of the 3,025 children screening, there were 1,770 with chronic headache; 320 met IHS diagnostic criteria for migraine. There were 271 patients eligible for enrollment during the pre-specified dates and times of the study, however only 100 patients were participated in this study. They were randomly divided into two groups; 52 children in the treatment group with cyproheptadine and 48 children in placebo group. During the follow up the second months, there were two dropouts from the treatment group. The intention to treat analysis was performed on all subjects, until the end of study after 3 months.

From the questionnaires and physical examination before intervention, there were no significant differences on subjects' characteristic between the two groups (**Table 1**). Sixty-two (62%) of 100 patient had a clinical diagnosis of migraine without aura, and 38 (38%) had migraine with aura. Of these 100 patients, 18 subjects were male and 82 were female. The mean PedMIDAS raw score was for each global rating category for the total group, the initial group and the follow-up group. Based on the convergence of patient global ratings with PedMIDAS raw score, a PedMIDAS grading system was developed. Using a principle of non-overlapping, we ranged the scores to grade I (little to none and mild disability), 0-30; Grade II (moderate and severe disability), > 30.

Migraine frequency in cyproheptadine group (**Table 2**) decreased from 5.6 (SD 3.64) to 3.4 (SD 2.57), P=0.001 (95% CI 1.359 to 3.001); while in placebo group, the frequency was only decreased from 4.9 (SD 2.96) to 4.7 (SD 2.69), P=0.286 (95% CI -0.180 to 0.596). PedMIDAS scores obtained at the initial and follow-up of both groups are comparable.

Tabel 1. Baseline characteristics of migraine

Characteristic	Cyproheptadine (n=52)	Placebo (n=48)
Age, mean (SD), years	14.7 (1.77)	15.2 (19.66)
Sex, n (%)		
Male	10 (20.0)	8 (16.0)
Female	40 (80.0)	42 (84.0)
Body weight, mean (SD), kg	46.3 (7.11)	48.3 (7.26)
Trigger by foods, n (%)		
No	12 (24.0)	19 (38.0)
Yes	38 (76.0)	31 (62.0)
Migraine, n (%)		
Without aura	30 (60.0)	32 (64.0)
With aura	20 (40.0)	18 (36.0)
Frequency	5.5 (3.62)	4.9 (2.96)
Duration, n (%)		
1-2 hours	37 (71.2)	36 (75.0)
> 2 hours	15 (28.8)	12 (25.0)
PedMIDAS, mean (SD)	19.5 (11.55)	16.9 (9.19)
PedMIDAS grading, n (%)		
0 - 30	45 (86.5)	45 (93.8)
> 31	7 (13.5)	3 (6.3)

Table 2. Outcome severity and frequency each groups before and after treatment

Parameter	Cyproheptadine			Placebo		
	Mean (SD)	P	95% CI	Mean (SD)	P	95% CI
Frequency						
Before	5.6(3.64)			4.9(2.96)		
After	3.4(2.57)	0.001	1.359 to 3.001	4.7(2.69)	0.286	-0.180 to 0.596
PedMIDAS						
Before	19.5(11.50)			16.9(9.19)		
After	12.7(8.90)	0.001	5.202 to 8.398	16.1(9.38)	0.038	0.049 to 1.617

Table 3. Comparison of cyproheptadine with placebo after three months of intervention

Parameter	Cyproheptadine	Placebo	P	95% CI
Frequency, Mean (SD)				
3rd Month	3.4 (2.57)	4.7 (2.69)	0.009	(0.000 to 0.030)
PedMIDAS	50 (40.61)	48 (58.76)	0.001	(0.000 to 0.030)
Duration, n (%)				
3rd month				
1 – 2 hours	49 (98)	41 (85.4)		RR 4.36
> 2 hours	1 (2)	7 (14.6)	0.029	(0.690 to 27.510)
PedMIDAS grading,n (%)				
0 - 30	48 (96.0)	45 (93.8)		RR 1.29
> 31	2 (4)	3 (6.3)	0.674	(0.433 to 3.843)
Side Effects, n (%)				
No	14 (26.9)	32 (66.7)	0.001	(-0.510 to -0.130)
Yes	38 (73.1)	16 (33.3)		

For the follow-up group of cyproheptadine, the PedMIDAS score had improved to 12.7 (SD 8.90) from 19.5 (SD 11.50) at initial presentation (P=0.001) with 95% CI 5.202 to 8.398; while in placebo group the PedMIDAS score had improved to 16.1 (SD 9.38) from 16.9 (SD 9.19) at initial presentation (P=0.038) with 95% CI 0.049 to 1.617.

The result of cyproheptadine group (**Table 3**) compared with placebo were significant, frequency P=0.009 (95% CI 0.000 to 0.030), duration P=0.029 RR=4.36 (95% CI 0.690 to 27.510) and PedMIDAS score P=0.001 (95% CI 0.000 to 0.030). The mean 3 month migraine frequency was reduced by 3.4 (SD 2.57) in patients receiving cyproheptadine as compared with 4.7 (2.69) in patient receiving placebo. Adverse experience or side effects in cyproheptadine group were especially sleepy and increased appetite, as much as in 38 (73.1%) compared with placebo only 16 (33.3%).

Discussion

Pediatric migraine is a common problem that warrants greater attention. There is little information to rely on in deciding whether acute or prophylactic treatments are the most effective in children. The treatments that work best for adults may not be best for children.[9] Abu-Arefeh and Russel[8] reported migraine was a common cause of headache in children and causes significantly reduced school attendance. The study showed that migraine prevalence in students was still high, at least 10.6% in children aged 11 to 18 years. This study also demonstrated that the disability grade could be tracked during treatment. We used daily headache diaries and PedMIDAS. Visudtibhan[10] performed a cross-sectional study to determine the prevalence of migraine in seventh grade Thai student in four junior high schools in Bangkok, Thailand. All of 1789 students in participating schools completed the questionnaire. After two interviews, 248 students (13.8%) were diagnosed with migraine.[10]

Preventive treatment in population of children who have frequent, disabling migraine is the most efficacious agent, but encouraging data are emerging regarding topiramate and sodium valproate as well as the cyproheptadine.[11-15] Currently, no medications is approved by the Food and Drug Administration for prophylaxis of migraines in children. Seventeen

drugs were identified and included in the review. Of the drugs with available data are topiramate, valproic acid, flunarizine, amitriptyline, and cyproheptadine have shown efficacy in decreasing migraine frequency and duration in children.[16]

Cyproheptadine with both antiserotonergic and calcium channel blocker activities has not been subjected to rigorous study, however it has been widely adopted for migraine prevention in children. Effective doses for migraine prevention may be lower than doses used for other conditions. For example, the antidepressant dose of amitriptyline is 50 mg to 200 mg per day, while the dose for migraine prevention is usually 10 -100 mg/day. Dosing regimens vary widely, from single bedtime schedules to twice-daily regimens. A dose of 2 to 4 mg orally at bedtime is a rational starting point.[17, 18] The findings confirm that, at a dose of 4 mg/ day, cyproheptadine is an effective and well tolerated drug for migraine prevention. The therapeutic effect was consistent, decreased subjects in cyproheptadine group were dropped out.

The cause of migraine is unknown, and there are few reliable data that have identified risk factors or quantified their effects in children. A family history is common. Proposed precipitants in genetically predisposed children and adolescents include hunger, fasting, menses, exercise, stress (for example sleep deprivation), and foods (for example, chocolate).[19] Our subjects may be proposed by food; 67 (72%) including coffee, chocolate, meat, and noodle.

Migraine frequency in our study were decreased from 5.6 (SD 3.64) to 3.4 (SD 2.57), while PedMIDAS score were also decreased from 19.5 (11.5) to 12.7 (8.9). Other studies using topiramate and sodium valproate in children showed similar results.[20,21] The PedMIDAS questionnaire provided a developmentally sensitive, reliable, and valid assessment of the disability of childhood and adolescent headaches. The PedMIDAS' criteria validity supports its role as a component of assessing the impact of headaches on a child`s life. PedMIDAS relates to school and home functional ability. Hershey and Winner[1] reported children in their study showed a mean reduction of 22.3 points in their PedMIDAS score, indicating a reduction of nearly half of their disability due to headaches with treatment.[22] In this study only 6.8 points of showed a mean reduction.

In our study, we found side effects, including sedation and or increased appetite, 74% vs. 32% cyproheptadine group compared to placebo. Rao *et al*[7] reported cyproheptadine alone had improved the frequency, duration and severity significantly but side effects were more than in the combination group (cyproheptadine and propranolol).

Finally, the patient must understand that prophylactic therapy will not completely eliminate headache occurrence. The goal of prophylactic therapy is to decrease headache frequency and severity while possibly improving patient response to acute therapies. To conclude, our results indicate that cyproheptadine appears to be effective as alternative prophylactic treatment of childhood migraine, but its frequent and significant side effects need consideration when administering the drug.

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