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Original Article

Amitriptyline for migraine prophylaxis in adolescents

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Abstract

Background Migraine is the most common cause of recurrent headaches in children and adolescents. Amitriptyline efficacy as a prophylactic treatment for migraine in adults has been widely studied, but there is limited data on its use in children and adolescents.

Objective To determine the efficacy of amitriptyline for prophylactic treatment of migraine in adolescents.

Methods We conducted a single-blind, randomized, clinical trial study in Medan, North Sumatra, from July to October 2009. All participants had migraines, according to the International Headache Society criteria. They were divided into two groups, receiving either 10 mg amitriptyline or a placebo daily for 3 months. Headache frequency (days per month), headache duration (hours) and information to assess functional disability according to the Pediatric Migraine Disability Assessment Scale (PedMIDAS) were recorded by subjects. Efficacy was measured before, during and after intervention.

Results A total of 98 patients, aged 12 – 19 years (mean age 14.7 years) enrolled and were divided into the amitriptyline and placebo groups. Compared with baseline, there were significant differences in headache frequency and PedMIDAS score in the amitriptyline group (P=0.001, 95% CI 2.02 to 2.94 and P=0.001, 95% CI 7.64 to 9.76, respectively), but not in the placebo group (P >0.05) after 3 months of treatment. We also found that amitriptyline significantly decreased headache frequency, duration, and functional disability compared to the placebo, after 3 months of treatment (P < 0.05).

Conclusion Amitriptyline was effective for prophylactic treatment of migraine in adolescents after 3 months of intervention. **[Paediatr Indones. 2011;51:338-44]**.

Keywords: *amitriptyline, prophylaxis, migraine, adolescents*

Headaches, especially migraines, are a common problem in adolescents. The estimated prevalence of headaches over periods of between 1 month and lifetime in children and adolescents is 58.4%.[1] Migraine is a common cause of school absenteeism in children and adolescents.[2] The prevalence of migraine in children varies according to age, with 10.6% in children 5-15 years of age and 28% in those 15-19 years of age.[1]

Migraine treatment includes pharmacologic and non-pharmacologic methods. Pharmacologic treatment may be acute (abortive) or preventive (prophylactic). Acute treatment aims to stop migraine attacks immediately, or to reduce the headache intensity. Preventive treatment is given when there is no headache, and aims to reduce the frequency, duration and severity of migraine attacks, to increase the quality of life and to improve response to acute treatment in migraine attacks. Prophylactic treatment of migraine attacks in children has been poorly investigated.[3,4]

Amitriptyline is an antidepressant drug that affects the activity of monoamine neurotransmitters,

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including norepinephrine and serotonin. This medication inhibits the reuptake of norepinephrine and serotonin from the synaptic cleft, and is therefore effective for migraine prophylaxis.[5,6] Amitriptyline, according to the U.S. Headache Consortium Recommendations, American Academy of Neurology, American Academy of Family Physicians (AAFP) and American College of Physicians-American Society of Internal Medicine (ACP-ASIM), is useful for migraine prevention in adults. However, while its use in children is common, it is not well-studied.[7-14] The objective of our randomized, single-blind, placebo-controlled study was to evaluate the efficacy and safety of 10 mg amitriptyline daily, as preventive migraine treatment for adolescents 12 to 19 years of age.

Methods

A single-blind, randomized, clinical trial was conducted from July to October 2009 at three junior high schools and three senior high schools in Medan. All students were asked about headaches via a questionnaire. Those who experienced headaches then filled a more detailed questionnaire on migraine headaches.

A pediatric neurologist diagnosed migraine, with or without aura, according to International Headache Society (IHS) criteria. Collected data included history of illness, migraine frequency, intensity and duration, as well as weight and height. we included adolescents aged 12 to 19 years who suffered from migraines with one of the following: two or more migraine attacks per month that impair daily activities for 3 days or more in one month, contraindication or failure to receive acute therapy, use of acute treatment more than twice per week, unusual migraine state including hemiplegic migraine or migraine with prolonged aura. Written informed consent was obtained from parents/guardians. We excluded those with obesity, chronic daily headaches, more than one type of headache (including cluster headaches), other medical, neurological or psychiatric disorders, and those who previously received three or more migraine prophylactic treatments.

Subjects were divided into 2 groups by simple randomization. For 3 months, group I received 10 mg amitriptyline orally once daily and group II received a placebo containing saccharin. Supplements were similarly packaged and subjects were blinded to their contents. Subjects were supervised by teachers and parents when taking the supplement.

Before intervention, headache frequency (days per month), duration (hours) and disability were recorded. Disability was scored according to the PedMIDAS, and classified as mild disability (score $\leq$ 30), moderate disability (score 31-50) or severe disability (score $\geq$ 50). To monitor the migraine headaches, all subjects recorded frequency, duration, and medication side effects in diaries that were collected monthly. At the end of third month of treatment, all subjects were re-examined for headache frequency, duration and disability by PedMIDAS. During the study, subjects experiencing migraine headache were allowed to use abortive therapy.

Data was processed using SPSS version 15.0 and analyzed by chi-square test and t-test. Significance level was $P < 0.05$ with a 95% confidence interval (CI). This study was an intention-to-treat analysis. The Research Ethics Committee of the University of North Sumatra Medical School approved this study.

Results

Of 2050 adolescents screened initially, 1654 had recurrent headaches and 208 were diagnosed with migraine according to the IHS criteria. From those diagnosed with migraine, 98 subjects were willing to participate in this study. A total of 110 adolescents were not included for various reasons: 90 refused to join, 13 were obese, and 7 had chronic daily headaches). A flow chart of subject participation is shown in **Figure 1**. Subjects were divided into two groups by simple random sampling, with 50 subjects in the amitriptyline group and 48 subjects in the placebo group. All subjects completed the study through the end of the third month.

More adolescent girls (69%) had migraine than boys (31%). Seventy-seven percent of subjects had migraines without aura, while 23% experienced aura. Food triggers also influenced the incidence of migraines (70 subjects, 71.4%), such as coffee, chocolate, meat, instant noodles and foods containing monosodium glutamate (MSG). Baseline characteristics of subjects are shown in **Table 1**.

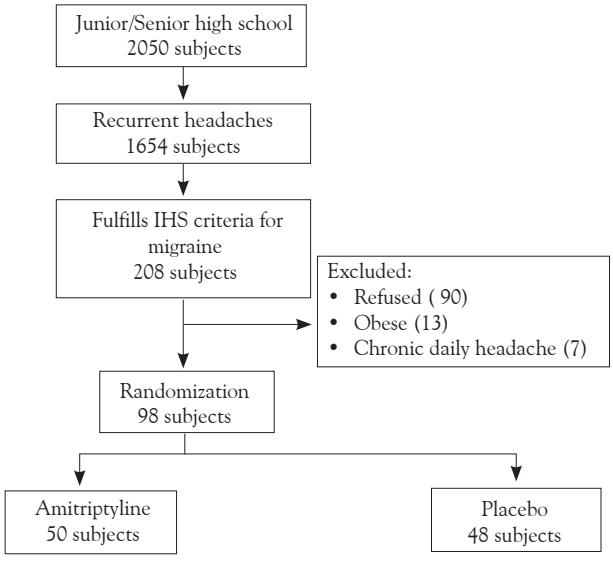

Figure 1. Flow chart of subjects through the trial

Mean PedMIDAS scores of the two groups before intervention were similar, 34.8 in the amitriptyline group and 34.4 in the placebo group, with the majority having scores within the range of 31 to 50 (moderate disability). In the amitriptyline group, there was a significant reduction in migraine frequency after 3 months of treatment , from 5.8 (SD 3.01) to 3.8 (SD 1.26) days, whereas in the placebo group there was no significant reduction in frequency (**Table 2**). We also found a significant reduction in the PedMIDAS score after 3 months of amitriptyline treatment, from 34.8 (SD 4.13) to 26.1 (SD 3.81). There was little change in the PedMIDAS scores of the placebo group, from 34.4 (SD 3.33) before treatment to 34.4 (SD 3.38) after 3 months of treatment.

Table 3 shows the significant differences in headache frequency between the first month compared to the second and third months of

Table 1. Baseline demographic and migraine characteristics of each group

Characteristic	Amitriptyline n=50	Placebo n=48
Mean age, years (SD)	15.0 (1.53)	15.5 (1.48)
Gender, n (%)		
Male	23 (46)	7 (15)
Female	27 (54)	41 (85)
Mean body weight, kg (SD)	43.9 (7.92)	48.3 (7.39)
Dietary factors as triggers, n (%)		
Not found	11 (22)	17 (35)
Triggers (coffee, chocolate, meat, instant noodles, MSG)	39 (78)	31 (65)
Migraine, n (%)		
Without aura	44 (88)	31 (65)
With aura	6 (12)	17 (35)
Mean frequency, days per month (SD)	5.8 (3.01)	4.9 (2,96)
Duration, n (%)		
< 1 hour	8 (16)	15 (31)
1-2 hours	22 (44)	21 (44)
> 2 hours	20 (40)	12 (25)
Mean PedMIDAS score (SD)	34.8 (4.13)	34.4 (3.33)
PedMIDAS score, n (%)		
≤ 30 (mild)	8 (16)	3 (6)
31 - 50 (moderate)	42 (84)	45 (94)

Table 2. Frequency and severity of migraine attacks before and after 3 months treatment

Parameter	Amitriptyline n=50			Placebo n=48		
	Mean (SD)	95% CI	P	Mean (SD)	95% CI	P
Frequency						
Before	5.8 (3.01)	2.02 to 2.94	0.001	4.9 (2.96)	-0.02 to 0.10	0.159
After	3.8 (1.26)			4.9 (2.94)		
PedMIDAS						
Before	34.8 (4.13)	7.64 to 9.76	0.001	34.4 (3.33)	-0.02 to 0.18	0.103
After	26.1 (3.81)			34.4 (3.38)		

Table 3. Comparison of amitriptyline and placebo groups after 3 months

Parameter	Amitriptyline n=50	Placebo n=48	95% CI	P
Mean frequency, days (SD)				
1st month	4.3 (2.57)	4.9 (2.89)	-2.54 to -0.35	0.010
2nd month	3.9 (1.17)	4.9 (2.93)	0.15 to 1.92	0.022
3rd month	3.8 (1.26)	4.9 (2.94)	0.19 to 1.99	0.018
Mean PedMIDAS (SD)				
3rd month	26.1 (3.81)	34.4(3.38)	6.79 to 9.68	0.001
Duration, n (%)				
1st month				
< 1 hour	10 (20)	15 (31)		
1 – 2 hour	23 (46)	20 (42)		
> 2 hour	17 (34)	13 (27)		0.163
2nd month				
< 1 hour	25 (50)	17 (35)		
1 – 2 hour	23 (46)	19 (39)		
> 2 hour	2 (4)	12 (25)		0.001
3rd month				
< 1 hour	34 (68)	18 (37)		
1 – 2 hour	16 (32)	22 (45)		
> 2 hour	0 (0)	8 (16)		0.001
PedMIDAS score, n (%)				
≤ 30 (mild)	47 (94)	7 (14)		
31-50 (moderate)	3 (6)	41 (85)		0.001
Side effects, n (%)				
None	20 (40)	34 (70)		
Drowsiness	14 (28)	5 (10)		
Weight gain	8 (16)	3 (6)		
Other	8 (16)	6 (12)		

amitriptyline treatment, compared to placebo. The mean PedMIDAS score after 3 months of amitriptyline treatment was also significantly reduced compared to placebo (P=0.001, 95% CI 6.79 to 9.68). The mean headache duration in the first month of treatment was not significantly different between the two groups (P = 0.163; 95% CI 0.02 to 0.18). However, in the second and third months of treatment, the mean headache duration was significantly reduced in the amitriptyline group. A comparison of PedMIDAS scores between the two groups after therapy revealed a significant difference between the two groups (P=0.001, 95% CI 0.001 to 0.03). Reported side effects were drowsiness (14, 28%) and weight gain (8, 16%), in the amitriptyline group. Fewer side effects were reported in the placebo group, with drowsiness in 5 (10%) subjects and weight gain in 3 (6%) subjects.

Discussion

We found that prophylactic treatment with amitriptyline for 3 months significantly reduced migraine headache frequency, duration, and disability compared to placebo. Decreased headache frequency was significant from the first month until the third month of amitriptyline treatment, while headache duration significantly decreased in the second month of treatment. Amitriptyline treatment also significantly reduced disability after 3 months of treatment, with most subjects experiencing a change from moderate to mild disability.

Migraine in children is an issue requiring greater attention. Adult treatments are not necessarily appropriate for children and adolescents.[3,4] Medications for migraine prophylaxis in children have been widely used, but there have been few pediatric clinical trials compared to those for adults. Topiramate, valproic acid and amitriptyline have been widely used as migraine prophylaxis in children and adolescents, but none have yet been approved by the Food and Drug Administration (FDA) for this use, although most studies with these medications showed decreased frequency and duration of migraine headaches.[15-17] Several neurological consortiums recommend various prophylactic drugs for children with migraines, including topiramate, valproic acid, amitriptyline,

and cyproheptadine.[18,19] We used amitriptyline in our study because it is affordable and limited research has been conducted on it.

Amitriptyline has been widely used for migraine prophylaxis, but its exact mechanism is unknown. Amitriptyline may work by affecting the activity of monoamine neurotransmitters, including norepinephrine and serotonin.[20] A recent experimental study showed that amitriptyline may reduce cortical spreading depression by inhibiting sodium channel currents and mRNA expression of sodium channels.[11]

Our subjects used a low dose of amitriptyline (10 mg per day taken orally) at bedtime. The low dose was chosen to reduce the risk of side effects and the risk of subjects' dropping out of the study. Treatment duration was 3 months, in order to monitor the effects. Previous studies have reported initial doses of amitriptyline used for migraine prophylaxis for children and adolescents to be 5-10 mg orally and 10 mg orally, respectively, taken at bedtime. Doses ranging from 10 to 75 mg per day were shown to be effective in reducing the migraine frequency.[6,12] Migraine prophylaxis duration may vary from 1 and 6 months, with patients generally showing improvement in as little as 1 to 2 months.[18]

In an adult study using headache frequency as the primary measurement, amitriptyline was superior to placebo for migraine prophylaxis at 8 weeks of treatment. For a subgroup with chronic daily headaches, amitriptyline was significantly superior to placebo at both 8 weeks and 16 weeks, with a similar but insignificant trend at 12 and 20 weeks.[8] Topiramate was at least as effective as amitriptyline, in terms of reducing the rate of mean monthly migraine episodes and other specific secondary outcome measures.[7] Amitriptyline and topiramate in combination may be beneficial for patients with migraine and comorbid depression, particularly in terms of side effects and associated displeasure due to monotherapy.[13]

We found the most common adverse reactions from amitriptyline were drowsiness and weight gain, but no subjects dropped out of our study during treatment. In three adult studies using amitriptyline compared to placebo, amitriptyline was effective for preventing migraine attacks, possibly related to its antidepressant effect.[7-9]

The mean PedMIDAS score reduction after 3 months of amitriptyline administration was 7.3 points, showing reduced migraine disability in that group compared to the placebo group. The PedMIDAS questionnaire is a sensitive, reliable tool, and valid for assessing disability due to headaches in children and adolescents. PedMIDAS assesses daily function at school and at home. Previous studies reported that adolescents with migraine headaches suffer the high levels of disability. In addition, higher depression scores were associated with more severe headache-related disabilities in adolescents, independent of headache frequency and severity.[21,22]

We found that 10% of adolescents screened had migraines, and consistent with a Thai study reporting the prevalence of migraines to be 13.8% in junior high school adolescents.[24] In addition, we observed that more adolescent girls than boys had migraines, at 69% and 31%, respectively. A study in USA reported migraine prevalence to be 8.6%, and the prevalence ratio for females versus males to be highest during the female reproductive/child-bearing years, consistent with a relationship between menstruation and migraine.[25] Screening is the first step to identify migraines, since only 50% of migraine patients seek physicians.[23] A systematic review study found the prevalence of migraine for those > 6 months old to be 7.7% (95% CI 7.6 to 7.8), with females being more likely than males to have migraines (OR 1.67, 95% CI 1.60 to 1.75).[1]

Seventy-one percent of our subjects reported migraines being triggered by certain foods, such as coffee, chocolate, meat, instant noodles and other foods containing MSG. While the cause of migraines is generally unknown, there are a few risk factors as well as genetics that may play a role in the occurrence of migraines in children. Other reported factors that may trigger migraines in children and adolescents include stress, menstruation in women, and other foods such as cocoa and coffee.[26]

Migraines with and without aura were found in 24% and 77% of subjects, respectively, in our study. Most children and adolescents have migraines without aura (70%).[4,5] A Finnish study found the incidence of migraines with aura increased from 5.2 per 1000 people in 1974, to 41.3 per 1000 people in 2002. The incidence of migraines without aura also increased from 14.5 to 91.9 per 1000 people in this time period.[27]

The average migraine headache duration in this study was more than 1 hour, with headache frequency of more than 4 times per month. Migraine headache duration in children has been reported to be 2 to 4 hours, while that in adults ranges from 4 to 72 hours. Prophylactic treatment may be indicated for children and adolescents who experience frequent headaches and disability due to migraines. Migraines occurring only 1 – 2 times per month usually do not require prophylactic treatment. However, for those with 3 – 4 migraines per month, therapy should be considered, and for those with $\geq$ 5 migraines per month, therapy should be given.[3,4]

A limitation of our work is that our study was a single-blinded clinical trial. Hence, possible bias exists in our results. A double-blinded clinical trial would reduce the risk of biased results. In conclusion, amitriptyline decreased migraine headache frequency, duration and disability compared to that of placebo. Therefore, amitriptyline may be an effective and well-tolerated prophylactic therapy for migraine headache attacks in adolescents.

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