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Riboflavin as migraine prophylaxis in adolescents

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Abstract

Background Migraine is a cause of recurrent headaches in children. Riboflavin has been shown to be efficacious in preventing migraine in adults. However, there has been little research on its use in children and adolescents.

Objective To assess the effectiveness of riboflavin for migraine prevention in adolescents.

Methods We conducted a randomized, double-blind, controlled trial in the Islamic Centre of the Musthafawiyah Mandailing Natal District, North Sumatera, from May to July 2010. Adolescents with migraines, as defined by the International Headache Society criteria, were included. Subjects were divided into two groups, receiving either 400 mg of riboflavin or placebo for 3 months. Headache frequency was measured in headache days per month, headache duration was measured in hours, and functional disability was measured using the Pediatric Migraine Disability Assessment Scale (PedMIDAS). Migraines were assessed before, during and after intervention. Student's t-test was used for statistical analysis.

Results A total of 98 patients, ranging from 12 to 19 years in age (mean age 14.0 years) were enrolled. We found a significant reduction in headache frequency in the second and third months. Headache duration also differed significantly at the second and third months (P=0.012 and P=0.001, respectively). Riboflavin decreased disability, as indicated by lower PedMIDAS scores in the riboflavin group compared to the placebo group (26.1 and 34.3, respectively, P= 0.001).

Conclusion Riboflavin effectively decreased migraine frequency, duration and disability in adolescents. **[Paediatr Indones. 2012;52:132-7]**.

Keywords*: riboflavin, preventive, migraine, adolescents*

Headaches are a major cause of human suffering. Approximately 90% of people have had at least one headache attack that disturbed daily activity.[1] Headaches can be classified into two types, primary and secondary. Migraine and tension headaches have unknown pathologic mechanisms and are due to intrinsic processes. Secondary headaches are due to underlying conditions, such as brain tumors, elevated intracranial pressure, intoxication, sinusitis or acute conditions, such as influenza.[2]

Migraine headaches are fairly common in children and peak in adolescence. Prevalence is 3% in 3 to 7 year-olds, 4 - 5% in 7 to 11 year-olds, and 8 - 23% in adolescents. The average age of onset is 7.2 years in boys and 10.9 years in girls. Other study has shown migraine prevalence of 10.6% in 5 to 15 year-olds and 28% in 15 to 19 year-olds. Migraine is the fifth most common disease in children.[3]

The World Federation of Neurology stated that migraine is a familial disorder of recurrent headaches,

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with unilateral pulsating and varied intensity, frequency and duration. It is often accompanied by loss of appetite, nausea, and vomiting, but may be relieved by sleep. In some cases, it is also accompanied by emotional, neurological, visual, and autonomic disorders.[2,3]

Migraine treatment may be pharmacologic or non-pharmacologic. Pharmacologic treatment includes acute (abortive) and preventive (prophylactic) treatments.[4] Acute treatment aims to stop the attack or decrease pain. Preventive treatment is given during a headache-free period, in order to decrease the frequency, duration, and intensity of migraines so that the patient will have improved quality of life and response to acute treatment.[5-7] Both preventive and acute treatment may be given to people with heavy and frequent migraine attacks.[8] Studies on preventive treatment in children have been limited. However, several studies have recommended the use of adult medication in children with an adjusted dose.[8,9]

Beta blockers are generally the first line in preventing migraine, while amitriptyline is the second line. But some studies suggest using riboflavin for migraine prevention. Riboflavin is assumed to influence repair of mitochondrial dysfunction, which takes part in migraine pathophysiology.[10,11] Studies on migraine prevention in children have been limited in Indonesia, especially those pertaining to the administration of riboflavin. Riboflavin is relatively affordable and has minimal side effects (diarrhea and polyuria) compared to other medications. Therefore, we aimed to assess riboflavin effectiveness in prevention of migraine in adolescents.

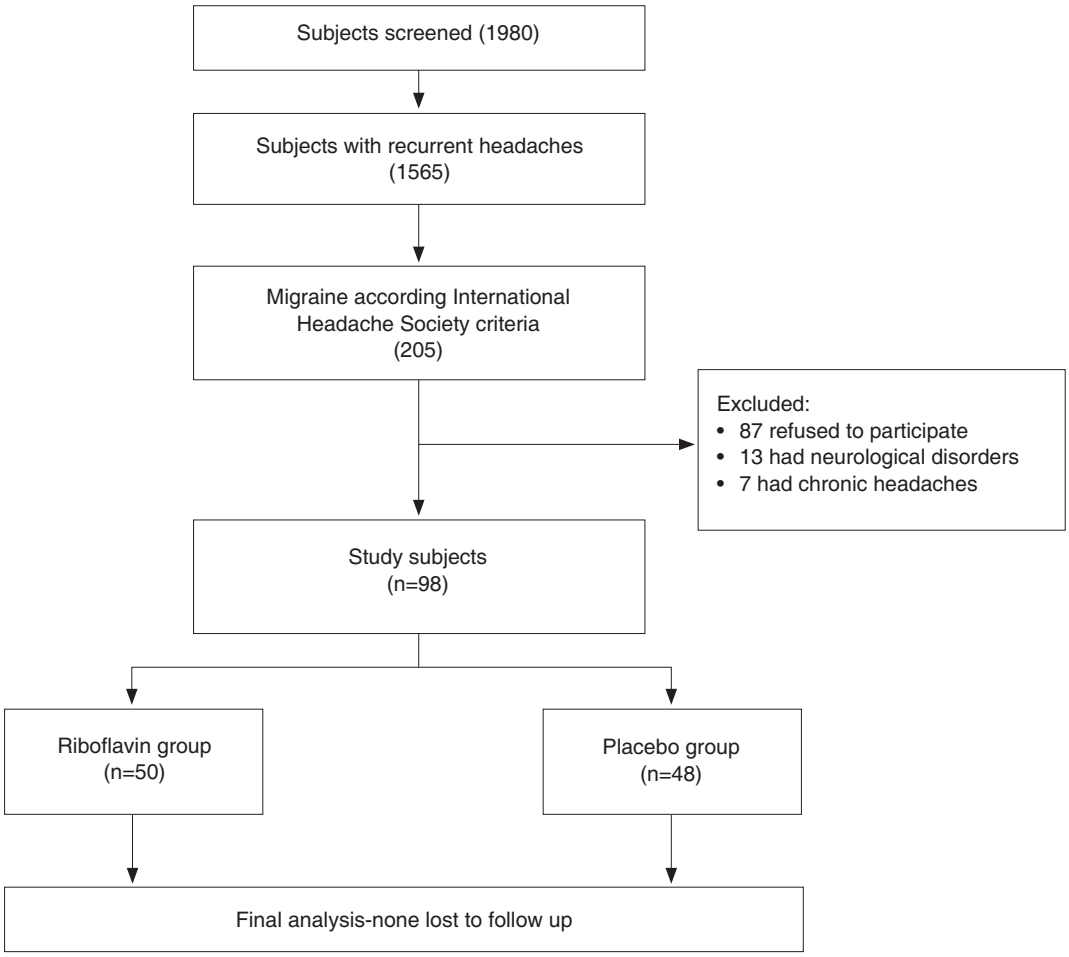

Figure 1. Study flow chart

Methods

We conducted a double-blind, randomized, controlled trial from May to July, 2010 in the Islamic Center of Musthafawiyah Mandailing Natal District, North Sumatera Province. We included adolescents aged 12 to 19 years who had migraine attacks at least three days per month, causing impairment of daily activities, including those with contraindications or unresponsiveness to acute therapy, needing acute therapy more than twice weekly, and those with uncommon migraine, such as hemiplegic migraine or migraine with prolonged aura. We excluded subjects with chronic headaches and other medical conditions, such as neurological and psychiatric disorders, and those who had previously received preventive migraine therapy.

Subjects filled migraine questionnaires. Adolescents meeting the migraine criteria (with or without aura) from the International Headache Society (IHS), were examined before enrollment. We obtained data on frequency, intensity, and duration of migraines at enrollment. We measured subjects' body weight and height.

This study was approved by the Medical Ethics Committee of the University of North Sumatera. Participants were divided by simple randomization into 2 groups. For 3 months, group I received 400 mg/day of riboflavin, while group II received a placebo. Medications were packaged similarly. Subjects were supervised by teachers in taking their medications.

At the beginning of study, we assessed migraine frequency, duration of headache, and disability using the PedMIDAS score, classified into mild disability ($\leq$ 30), moderate disability (31- 50) and severe disability (> 50).

Subjects were given diaries to record frequency and duration of headaches and side effects of medication. We collected diaries monthly. At the end of the third month, frequency, duration, and disability caused by migraine were re-examined by PedMIDAS.

Chi square test was used to examine the association between dependent and independent variables of categorical data. Student's t-test was used for continuous data outcomes. P value was set at < 0.05, with a confidence interval of 95%. The study was an intention-to-treat analysis.

Results

Of 1980 adolescents screened, we found 1565 adolescents with recurrent headaches. Although 205 adolescents met the IHS migraine criteria, only 98 adolescents enrolled in the study (**Figure 1**).

Table 1. Baseline characteristics of subjects

Characteristics	Riboflavin n=50	Placebo n=48
Mean age, years (SD)	14.0 (1.44)	15.5 (1.53)
Sex, n (%)		
Male	21 (42.0)	6 (12.5)
Female	29 (58.0)	42 (87.5)
Mean body weight, kg (SD)	43.9 (7.92)	48.2 (7.38)
Food as inducing factor, n (%)		
Not a factor	9 (18)	15 (31.2)
Induced by caffeine, chocolate meat, dry noodles with preservative, MSG	41 (82)	33 (68.8)
Migraine, n (%)		
Without aura	42 (84.0)	30 (62.5)
With aura	8 (16.0)	18 (37.5)
Mean frequency of migraine, days/month, (SD)	6.4 (2.60)	5.0 (2.80)
Duration of migraine, n (%)		
<1 hour	6 (12)	14 (29)
1-2 hours	23 (46)	24 (50)
> 2 hours	21 (42)	10 (21)
Mean PedMIDAS score, (SD)	35.6 (4.14)	34.6 (3.33)
PedMIDAS grade of disability, n (%)		
mild	11 (22)	7 (15)
moderate	39 (78)	41 (85)
severe	0 (0)	0 (0)

Table 2. Comparison of migraine parameters between the riboflavin and placebo groups

Parameters of migraine	Riboflavin	Placebo	Differences (95% CI)	P
Mean frequency, days (SD)				
1st month	6.4 (2.56)	5.0 (2.85)	-2.463 to -0.295	0.010
2nd month	3.9 (1.15)	4.9 (2.88)	0.151 to 1.924	0.013
3rd month	3.7 (1.28)	4.9 (2.96)	0.104 to 1.891	0.029
Duration, n (%)				
1st month: < 1 hour	9 (18.0)	13 (27.1)	-2.62 to 0.452	0.404
1 – 2 hours	22 (44.0)	22 (45.8)		
> 2 hours	19 (38.0)	13 (27.1)		
2nd month: < 1 hour	23 (46.0)	17 (35.4)	0.001 to 0.03	0.012
1 – 2 hours	25 (50.0)	19 (39.6)		
> 2 hours	2 (4.0)	12 (25.0)		
3rd month: < 1 hour	38 (76.0)	16 (33.3)	0.001 to 0.03	0.001
1 – 2 hours	12 (24.0)	23 (47.9)		
> 2 hours	0 (0)	9 (18.8)		
Mean PedMIDAS score, (SD)	26.1 (3.79)	34.3 (3.37)	6.793 to 9.673	0.001
PedMIDAS grade of disability, n (%)				
mild	47 (94.0)	7 (14.6)		
moderate	3 (6.0)	41 (85.4)	0.001 to 0.03	0.001
severe	0 (0)	0 (0)		
Side effects, n (%)				
None	20 (40.0)	34 (70.8)		
Polyuria	18 (36.0)	10 (20.8)	0.001 to 0.03	0.004
Diarrhea	12 (24.0)	4 (8.4)		

Most participants were female (72.5%) and the most common migraine type (73.5%) was migraine without aura. Food contributed to the occurrence of migraine attacks, such as coffee, chocolate, meat, instant noodles and other foods containing monosodium glutamate was found in 76.5% subjects in both groups. The PedMIDAS mean score was similar in both groups, 35.6 in the placebo group and 34.6 in the riboflavin group, most of whom were classified as having moderate disability (**Table 1**).

Table 2 shows that migraine frequency in the first, second, and third months differed significantly between groups. Mean headache duration was not significantly different between groups in the first month (P=0.404, 95% CI -2.62 to 0.452). However, the duration was significantly shorter in riboflavin group compared to the placebo group at the second (P=0.012) and third (P=0.001) months. Mean PedMIDAS score after three months of riboflavin was significantly lower than that of the placebo group (P= 0.001, 95% CI 6.793 to 9.673). Side effects of riboflavin were polyuria in 18 subjects (36%), and diarrhea in 12 subjects (24.0%). In the placebo group, polyuria was present in 10 subjects (20.8%) and diarrhea in 4 subjects (8.4%).

Discussion

We found a reduction in frequency, duration, and disability of headache after three months of riboflavin treatment compared to the placebo in adolescents with migraine. The reductions in migraine frequency and pain duration were observed at the second and third months. Disability was also reduced after riboflavin treatment, based on PedMIDAS scores at the third month.

Migraine headache is a familial condition with prevalences differing in age groups.[12] The first step in diagnosing migraine is by screening for headache patients, because only 50% of cases seek medical advice.[13] A study in Bangkok, Thailand showed that the prevalence of migraine was 13.8% in adolescents.[14] We also found a high prevalence of migraine in adolescents at 10.4%.

The reported incidence of migraine in school-aged children from 7 to 15 years old is 4%, with girls suffering more frequently during adolescence and boys suffering more at under 10 years of age.[1] Prevalence is reportedly higher in girls (55%) than in boys (45%).[12] We also found more girls than boys with migraines in our study.

The cause of migraines is generally unknown. Only a few risk factors have been identified in children, with genetics thought to be important. Some factors that may lower the migraine threshold in children and adolescents are stress, menstrual periods, and foods such as chocolate and coffee.[1,15] Another study showed that trigger factors cause migraines in 75.6% of children with the condition.[16] In our study, food contributed to the occurrence of migraine attack, with triggers including coffee, chocolate, meat, instant noodles and other foods containing monosodium glutamate (76.5% in both groups).

A study on migraines in Cincinnati showed the incidence of migraine without aura to be 60.6%, migraine with aura 7.9% and the remainder other headache types.[17] A Finnish study showed an increased incidence of migraine with aura from 5.2 per 1000 people in 1974 to 41.3 per 1000 people in 2002. Migraine without aura increased from 14.5 to 91.9 per 1000 people in that period.[18] The majority of participants (73.5%) in our study had migraine without aura.

If migraines occur once or twice monthly, prophylactic therapy is not needed. If migraines occur three or four times monthly, prophylactic therapy may be needed. If migraines occur more than five times monthly, prophylactic therapy is needed.[19] Migraine prophylactic therapy is generally given to patients with frequent and disabling attacks.[5,17] Average migraine duration in children is 2 to 4 hours, while that in adults is 4 to 72 hours.[12] We found the mean duration of migraine in adolescents to be 1 to 2 hours, with a mean frequency of more than four times monthly.

Riboflavin is the precursor of two coenzymes, flavin mononucleotide and flavin adenine dinucleotide. Both are involved in electron transport in oxidation-reduction reactions. Patients with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes showed mitochondrial metabolism energy reduction, causing migraine-like headaches. In those subjects, headache was reduced by riboflavin treatment.[20-22] The first study that evaluated riboflavin efficacy as prophylaxis for migraine in children reported that 50% of patients had a reduced number of migraines within 4 weeks of treatment.[23] We observed the administration of riboflavin over 3 months, revealing a reduction in migraine frequency at the second and third months of riboflavin treatment compared to placebo.

Beta blocker is the first line of migraine prophylactic treatment and amitriptyline is the second line. There have been few, limited studies using riboflavin for migraine prevention. Riboflavin is thought to influence the repairing of mitochondrial dysfunction that occurs in migraine pathophysiology.[10,23] A retrospective study in Italy involving 41 subjects with migraine showed that oral riboflavin at 200 – 400 mg daily for 4 to 6 months had a preventive effect, at low cost and minimal side effects.[23] For this reason, we used riboflavin in our study.

A prospective study in Germany involving 23 migraine patients who received 400 mg of riboflavin daily for 6 months had reduced migraine attacks and decreased use abortive anti-migraine therapy.[20] Another study in Belgium involving 26 migraine patients showed that riboflavin and beta blocker had similar efficacy in preventing migraine. The combination of these medications increased the efficacy.[24] In our study, we found significant reductions in frequency, duration, and disability after three months of riboflavin compared to placebo.

Another trial in Belgium involving 54 subjects divided in two groups (placebo and riboflavin 400 mg) for 3 months showed that riboflavin was well tolerated and effective in preventing migraine, but subjects had diarrhea and polyuria as the side effects.[25] We also found diarrhea and polyuria to be side effects of riboflavin, though none of our subjects dropped out from the study.

PedMIDAS questionnaire is a sensitive, reliable and valid tool to evaluate disability due to headache in children and adolescents, with regards to functioning at school and daily home activities. One study showed a reduction in PedMIDAS mean score to be as much as 22.3 points after prophylactic therapy.[17,26] After riboflavin treatment, we observed a decrease of 9.5 points in the mean PedMIDAS scores, from 35.6 to 26.1 points, the latter categorized as mildly disabled. Migraine frequency and PedMIDAS scores were also reduced in the riboflavin group, but remained the same in the placebo group.

Compared to placebo, riboflavin treatment showed reductions in migraine frequency in the second and third months, but was higher than that of the placebo group in the first month. Migraine duration in the first month was similar in both groups, but in second month, the duration decreased in the riboflavin group compared to that of the placebo group.

We concluded that riboflavin was well-tolerated and effective in reducing migraine frequency, duration, and disability in adolescents. Therefore, riboflavin may be used as migraine preventive therapy in adolescents.

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