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Prophylactic effect of riboflavin on pediatric migraine: a randomized, double-blind, placebo-controlled trial

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Abstract

Background and aim: Riboflavin may have an acceptable effect on migraine among children. This study was carried out to determine the prophylactic effect of riboflavin on migraine in children.

Methods: This randomized clinical trial study was performed at Shahid Beheshti Hospital in Kashan, Iran from December 2012 to February 2015. Ninety children with migraine were allocated randomly into 3 groups (placebo, low-dose and high-dose riboflavin). The outcomes (frequency, intensity and duration of headaches) were measured at baseline and 12 weeks of medication in each group, and the decrease of them were compared. SPSS software version 16 was used for analysis of the data. Descriptive statistics, Chi-square, Fisher's exact and t-test were used for statistical analyses.

Results: There was a significant decrease of migraine frequency (p=0.000) and mean duration (p=0.000) in the high-dose group compared with the placebo group. No significant reduction of frequency and mean duration of attacks were reported in the low-dose group compared to the placebo group (p=0.49 and p=0.69 respectively). There was no significant reduction of migraine intensity in the low-dose and high-dose groups compared to the placebo group (p=0.71 and p=0.74 respectively).

Conclusion: High-dose riboflavin is a safe, well tolerated, cost-effective method of prophylaxis for children with migraine.

Trial registration: The trial was registered at the Iranian Clinical Trial Registry with number IRCT2013020412361N1.

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Keywords: Migraine; Children; Riboflavin; Prophylaxis

1. Introduction

Migraine is a common disorder among children and adolescents, with prevalence of about 3% in early childhood and up to 23% in adolescents (1). Occasionally, frequency and severity of migraine become overwhelming which

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cause disturbance of life quality and can lead to high rates of absenteeism from school and many social problems. In such circumstances, prophylactic therapy is recommended to reduce excessive drug usage and improve the quality of life (2, 3). The safety of many prophylactic drugs in adults with migraine has not been tested completely on children, so symptomatic therapies are preferred for them (1, 4, 5). Despite the use of topiramate as a prophylactic agent for migraine, some studies have indicated marked side effects on cognition (6, 7). Cinnarizine is a calcium channel blocker that has been documented as an effective prophylactic agent for migraine (2). Nevertheless, in spite of various drugs, no Food and Drug Administration (FDA) approved medication is recommended for prophylaxis of migraine in children (8). Riboflavin is involved in the mitochondrial electron transport chain and has been used in some patients with mitochondrial disorders (9-12). Riboflavin is a known co-factor of mitochondrial oxidative phosphorylation and is a precursor of flavin which is needed for transport of electrons in respiratory process of the mitochondria and some investigations have shown a mitochondrial oxidative phosphorylation dysfunction in adults with migraine. So, supraphysiological doses of riboflavin could be beneficial for this impairment (13).There are some studies that suggest the efficacy of high-dose riboflavin (400 mg/day) for migraine prevention in adults (14-16), and doses of 100-400 mg/day of riboflavin in children are concordant with adult studies (1, 12). There is limited evidence for riboflavin use among children (1). A randomized, placebo-controlled trial showed no effect of high-dose riboflavin on migraine prophylaxis in children (13, 17). Another study on 8 to 18-year-old children in Italy indicated decrease of migraine frequency and intensity by riboflavin (1). The side-effects of riboflavin have been shown as minimal, including diarrhea and polyuria (1 out of 43 adults). The most common harmless adverse effect of riboflavin is yellow to orange color change of the urine (13). Due to substantial controversy about the effectiveness of riboflavin in children with migraine and a few side effects of it, we decided to perform a study to determine the effect of low dose and high dose riboflavin on intensity, duration and frequency of migraine

2. Material and Methods

2.1. Study design and participants

This double-blind, randomized clinical trial study was conducted on 5 to 13-year-old children with migraine, from December 2012 to February 2015 in the neurology clinic of Shahid Beheshti Hospital, Kashan, Iran. All cases were diagnosed and examined by a pediatric neurologist. After obtaining the informed consent from parents, questionnaires were filled. The questions covered different areas including age, sex, migraine with and without aura, months passed since onset of migraine, family history of migraine and mean intensity, frequency and duration of headache in the last month preceding our trial. Diagnoses were made based on diagnostic criteria for migraine with or without aura and tension headaches present in the International Classification of Headache Disorders, 2nd edition (ICHD-II) (18). Inclusion criteria were 5 to 13-year-old children with or without aura who had at least two moderate to severe intensity attacks per month. Exclusion criteria were: 1- severe neurologic disorders or epilepsy 2- liver, kidney, gastrointestinal, cardiovascular or metabolic disorders 3- prophylactic drug use during the month prior to the trial 4- less than two attacks per month 5- tension headache 6- mild intensity headache 7- uncooperative parents and children.

2.2. Intervention, randomization and blinding

Following a one-month baseline period, patients were randomized to either receive a capsule of placebo, 100 mg riboflavin (low-dose) or 200 mg riboflavin (high-dose) daily for 12 weeks. No other prophylactic drugs were used during the study and only analgesics were prescribed if needed. Double-blinding was implemented in this trial. Researchers and participants were not aware of group allocation. A pharmacologist supervised the randomization process. For assessment of blinding, the parents were asked which medication their children were receiving (they did not know anything about it). At first, between numbers 1-90, 30 random numbers were chosen from a random number table and allocated to the placebo group and then another 30 random numbers allocated to the low dose group and finally the remaining 30 numbers were allocated to the high dose group (simple random sampling). They were written in a check list which was unseen by researchers and patients. The drugs were numbered from 1 to 90 by a pharmacologist, and the pharmacology staff gave them to patients respectively without any awareness about them. The pharmacologist had the check list and after filling it at the end of the study, the results were analyzed. Patients were instructed to take the capsules at breakfast. The capsules were manufactured by a pharmaceutical company with supervision of a pharmacologist. The drugs were similar according to their shape and taste. Both riboflavin and carotene make yellow/orange urine discoloration. So, to assure a double-blind study was taking place, 100mg carotene was used in placebo capsules. The patients were instructed to improve their sleep quality and increase its duration, stop caffeine intake and decrease the time of computer activity or television watching to a maximum of two hours daily. The parents and children received data concerning childhood migraine (3) and the patients consumed acetaminophen or ibuprofen orally during attacks.

2.3. Outcomes

Severity (intensity) of attacks was evaluated according to the following Likert scale: 1- for mild headaches during which the patient performs the usual activity, 2- for moderate headaches that slow down patient activity without halting it and 3- for severe headaches that stop patient activity (18). Mean duration, intensity and number (frequency) of attacks were assessed two times, the first at the month before starting of riboflavin (baseline or week 0) and the second at the last month of riboflavin prophylaxis (week 8 to 12 or in other word week 12). Duration of attacks was defined as hours and frequency of attacks was based on the number of headache attacks per month (1). The patients' parents were asked to fill a headache diary in two stages (baseline period and the last month of riboflavin prophylaxis) of study including date, intensity and duration of any headache attack. Furthermore, the side-effects of the drugs were noted by the parents. Response was evaluated in the last month of consuming prophylactic medication in each group according to outcome variables. Primary and secondary outcomes were defined as follows: at least 50% drop in the number of headaches (frequency), one degree decrement in intensity and/or lessening of mean headache duration in last month of prophylaxis (last 4 weeks of treatment) regarding to the month before prophylaxis (4 weeks baseline or week 0) (1).

2.4. Statistical analysis

Sample size was estimated according to a study by Condo et al., in which a significant decrease of mean headache frequency in phase 2 compared to baseline (21.7±13.7 vs. 13.2±11.8) in riboflavin group, α =0.05 and power equaled 0.8 (1). Sample size was estimated as 90 for all groups (30 patients in each group). Data were entered into SPSS software version 16 (SPSS, Inc. Chicago, Illinois, USA). Statistical analysis was performed based on intension-to-treat (ITT) method. Continuous data were measured by mean and standard deviation (SD) and categorical data were shown by frequency and percentage. Comparison of riboflavin effect between groups on attack frequency and intensity was evaluated by Chi-square and Fisher's exact tests, and the effect on duration of headaches was conducted by independent-samples t-test. The riboflavin effect on three headache items in each group was determined by paired-samples t-test. All statistical tests were considered significant at $p<0.05$.

2.5. Research ethics

The study was approved by the ethics committee of Kashan University of Medical Sciences with number 29/5/1/4410. All parents and some patients filled the informed consent and the nature of the study was explained to them. The information of participants was kept confidential. No charge was obtained from the patients. They were informed about the side-effects of the drugs and that they could contact the corresponding author regarding them. If any cases at any time decided to exclude themselves from the study, they were free to do so without any recompense. The Iranian Clinical Trial Registry number was IRCT2013020412361N1.

3. Results

In total, 130 patients were enrolled and 40 children were excluded due to not meeting inclusion criteria, presence of exclusion criteria or declined to participate in the study (Figure 1). The 90 remaining children were randomly and equally allocated in each group (placebo, low-dose riboflavin and high-dose riboflavin). Because the study had incorporated an ITT design, after allocation of the patients to the three groups, the lost follow up patients were not excluded from the study and their outcome variable data were reported equally at baseline and the last month of investigation (Figure 1). The baseline characteristics of the three study groups are shown in Table 1 and no confounding factors exist among them. Table 2 shows the mean (SD) frequency, duration and intensity of migraine attacks at baseline and the end of riboflavin prophylaxis and mean decrease of them (baseline - end) in each group. The outcome variables were assessed at the end of the last month of medications. No significant difference was found between placebo and low-dose groups regarding 50% or more reduction of frequency attacks (p=0.49), but there was significant decrease of migraine frequency in the high-dose group compared with the placebo group (p=0.000). Four (13.3%), 6 (20%) and 24 (80%) patients had 50% or more decrease in migraine frequency in the placebo, low dose and high dose groups respectively (p=0.000). There was no significant diminution of migraine intensity in low-dose and high-dose groups in comparison to the placebo group (p=0.71 and p=0.74 in order). No significant difference was found in decline of mean duration of headache attacks in the last month of prophylaxis between the placebo and low-dose riboflavin groups (0.30±1.12 vs. 0.17±1.49) (p=0.69). Meanwhile, there was a dramatic shortening of mean duration of migraine attacks among the high-dose group individuals compared to those in the placebo group (4±3.49 vs. 0.30±1.12) (p=0.000). Also, there was a marked decline in mean duration of migraine attacks in the high-dose group compared with the low-dose group (4±3.49 vs. 0.17±1.49) (p=0.000). A significant decrease in frequency of attacks was reported in the high-dose group in comparison with the low-dose group (p=0.000). No significant reduction of migraine intensity was seen among the high-dose group compared to

the low- dose group (p=0.47). Out of the three groups, 21 (70%), 20 (66.7%) and 7 (23.3%) of placebo, low dose and high dose group patients required analgesic drugs respectively (p=0.000). No noticeable side-effects of the treatment were reported during the study.

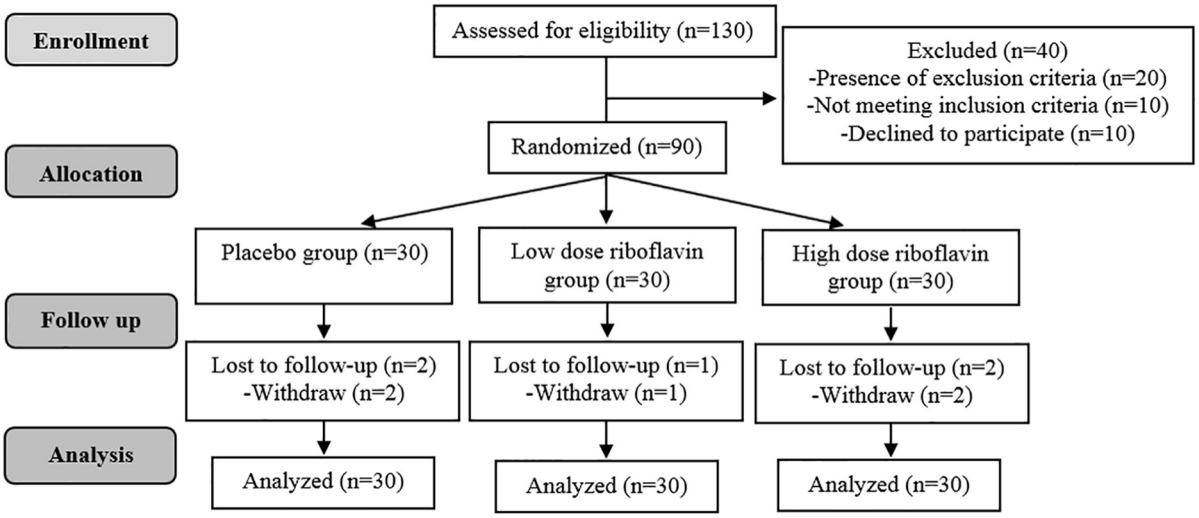

Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) flow chart

Table 1. Baseline characteristics of the study groups

Characteristics	Placebo (n=30)	Low-dose riboflavin (n=30)	High-dose riboflavin (n=30)	p-value
Age in years (mean ± SD)	7.90±2.19	8.47±2.06	8.97±2.21	0.16
Male, n (%)	15 (50)	17 (56.7)	17 (56.7)	0.84
Migraine with aura, n (%)	3 (10)	5 (16.7)	4 (13.3)	0.75
Family history of migraine, n (%)	15 (50)	19 (63.3)	19 (63.3)	0.38
Months since onset of migraine (mean ± SD)	29.33±15.54	25.37±14.69	22.77±12.33	0.21
Frequency of migraine per month (mean ± SD)	8.20±3.25	7.83±3.83	9.27±3.03	0.24
Duration of migraine in hours (mean ± SD)	7.97±2.92	6.97±2.62	7.90±3.03	0.36
Intensity of migraine in degree (Likert scale) (mean ± SD)	2.30±0.47	2.37±0.49	2.40±0.48	0.72

Table 2. Mean (SD) frequency, duration and intensity of migraine attacks at baseline and end of riboflavin prophylaxis and mean decrease of them in each group[a]

Variables	Placebo group (n=30)			p-value	Low dose group (n=30)			p-value	High dose group (n=30)			p-value
	Wk0	Wk12	Decrease		Wk0	Wk12	Decrease		Wk0	Wk12	Decrease	
Frequency	8.20±3.25	8.17±3.97	0.03±2.24	0.94	7.8 3±3.83	7.23±4.17	0.60±4.07	0.43	9.27±3.03	2.87±1.66	6.40±3.98	0.000
Duration	7.87±2.92	7.57±2.91	0.30±1.12	0.15	6.97±2.62	6.80±2.55	0.17±1.49	0.54	7.90±3.03	3.90±2.62	4±3.49	0.000
Intensity	2.30±0.47	2.23±0.63	0.07±0.52	0.49	2.37±0.49	2.30±0.47	0.07±0.37	0.33	2.40±0.49	2.27±0.58	0.13±0.51	0.16

[a] SD, standard deviation; Wk. 0, week 0 (baseline); Wk. 12, week 12 (end); Frequency, frequency (number) of migraine attacks monthly; Duration, mean duration of migraine attacks in hours monthly; Intensity, mean intensity of migraine attacks in degree monthly; Decrease, decrease of headache items (baseline- end); p, p.value decrease of three items of headache in each group between two times (wk. 0 and wk. 12) with paired-samples t-test.

4. Discussion

The present study showed that riboflavin prophylaxis significantly reduces migraine duration and frequency, but not the intensity. These data are in line with Condo et al. regarding frequency, not intensity (1). The probable cause of frequency reduction may be due to high-dose riboflavin use in both studies. During an investigation on 48 Australian children, 200 mg/day riboflavin was not effective on frequency and severity of migraine attacks (17) which is inconsistent with our study, concerning the frequency response. This discrepancy may be due to genetic variation causing differences between distinct populations. On another note, the duration of therapy was three months in the Australian survey (17), whereas in the Condo et al. investigation, the proper duration was proposed to be 4 months (1). This is incongruent with our research, because we used riboflavin for three months. During a trial in the Netherlands on 6 to 13-year-old children, 50 mg/day riboflavin was prescribed for four months and no significant difference in mean duration, frequency and intensity between riboflavin and placebo groups was found (13). These findings are in contrast with our results. The observed difference may be due to the fact that no upper limit (19) for migraine frequency (15 or more attacks per month is indicative of riboflavin resistance) was chosen as exclusion criterion and also, low-dose riboflavin was used (13). The upper limit of eight headache attacks per month was used as an exclusion criterion in a MacLennan et al. study (17). It must be mentioned that we did not determine any upper limit for headache frequency in our study. Condo et al. showed that riboflavin prophylaxis reduced migraine intensity and frequency, and this is compatible with our study according to headache frequency but not intensity (1). Notably, they found a significant reduction of migraine frequency among children less than 12 years of age and a substantial decrease of migraine intensity in males (1). It seems that age and sex may have influence on riboflavin's effect, probably due to various riboflavin serum levels and pharmacokinetics (20). These findings are incompatible with our data that indicate no relationship between age and sex and effect of riboflavin treatment on migraine intensity and frequency. Some adult studies have suggested that riboflavin prophylaxis diminishes migraine frequency but not migraine intensity, and this is congruent with our results (14, 16). Because of a probable high metabolic rate among children, Condo et al. treated patients with 200 mg or 400 mg/day riboflavin, however, no significant differences were detected in intensity and frequency responder rates between the two doses (1), so we decided to choose 200 mg as the high-dose therapy. In a trial by Bruijn et al., cross-over design was performed for placebo and riboflavin (50 mg daily) groups. Nevertheless, no effect was reported on frequency and duration of migraine (13). Probably due to use of low- dose riboflavin, their results were not in line with our research. Based on a recent pharmacogenetic study among adults with migraine, patients with non-haplogroup H human mitochondrial DNA (mtDNA) respond better than those with haplogroup H mtDNA to riboflavin therapy (21). In the present study, no riboflavin side-effects were reported which was consistent with other investigations (1, 17). Half-life of riboflavin is about 1 to 2 hours and its absorption has been indicated to reach saturation rate at 30-50 mg (22). So, riboflavin dose between 100 to 400 mg daily in children with migraine seems to be safe for several months (12).

5. Strengths and limitations of the study

The present study has some strong points: 1- The sample size is larger than some surveys (14, 23, 24). 2- A placebo-controlled, double-blind, randomized study was conducted. 3- Drop-out cases during the study were negligible. 4- Two appropriate doses of riboflavin were compared with the placebo group. To be noted, riboflavin is a low-cost drug without side-effects, so its use could be recommended to parents of children with migraine who have financial restrictions. Some limitations of our investigation include the following: 1- Duration of riboflavin prophylaxis was 3 months, whereas the minimum duration is usually recommended to be about 4 months (1). 2- Upper limit for migraine frequency as an exclusion criterion was not ascertained. 3- Cross-over design was not performed for groups.

6. Conclusions

The present study indicates that high-dose riboflavin decreases the frequency and duration of migraine attacks in children, with no side effects. The practical importance issue is that it can be used instead of other medications. It is recommended that high dose riboflavin be used for migraine prophylaxis among children. Further studies with larger sample sizes and longer duration of riboflavin treatment with cross-over design will be helpful in the future.

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Trial Registration:

The trial was registered at the Iranian Registry of Clinical Trials (IRCT) with ID: IRCT2013020412361N1.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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