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Oral riboflavin versus oral propranolol in migraine prophylaxis: An open label randomized controlled trial

[1]*Natasha J Nambiar *MBBS MD*, [1]*Cuckoo Aiyappa *PhD*, [2]R Srinivasa *MD DM*

[1]Department of pharmacology and [2]Department of Neurology, MS Ramaiah Medical College Bangalore, India
*These authors contributed equally to this work

Abstract

Background: Migraine is a chronic, often debilitating disease. The treatment of migraine with propranolol (80-240 mg/day) is limited by side effects and lack of tolerability. Riboflavin (vitamin B2) is the precursor of flavin mononucleotide and flavin adenine dinucleotide which are involved in mitochondrial transport chain. The use of riboflavin in migraine prophylaxis is based on the hypothesis of a deficient mitochondrial energy reserve as a causal factor in migraine pathogenesis, and on the findings of its safety and effectiveness at high doses (400 mg/day) in the treatment of migraine like headaches in classic mitochondriopathies. *Objectives:* To compare the efficacy of lower dose oral riboflavin at 100 mg/day with oral propranolol 80 mg/day in the reduction of migraine frequency and severity. *Methods:* One hundred patients diagnosed with migraine were randomized to receive either oral riboflavin 100 mg/day or propranolol 80 mg/day for a period of 3 months. Patients were issued a migraine diary and explained how to record the frequency of migraine attacks, headache intensity, duration and to report any side effects. Follow-up was at the end of 3 and 6 months. *Results:* Both study groups showed a reduction of migraine frequency, duration and severity of headache by visual analogue scale (VAS), and disability by migraine disability questionnaire (MIDAS) score at 3 months. No significant difference was seen between the two study groups in most of the measures. Side effects were significantly less in the riboflavin group (P=0.035).
Conclusion: Oral riboflavin 100mg/day is a safe, equally effective and well tolerated alternative in migraine prophylaxis.

INTRODUCTION

Migraine is a chronic, often debilitating disease that affects 12% of the general population[1], 18% of women and 6% of men.[2] WHO cited migraine as the 19th leading cause of years lived with disability among both males and females of all ages combined.[3] The high prevalence, the marked impairment of the sufferer's quality of life culminate in a major societal burden with high medical bills and indirect costs such as unemployment and work productivity loss.[4] The goal of preventive treatment should be to prevent or reduce the frequency of migraine attacks, to improve response to acute medications, to improve patient function and to reduce disability.[5] To maximize compliance, prophylaxis treatment should be safe, well tolerated, and inexpensive.

The theoretical basis for using riboflavin is its ameliorating effect on the mitochondrial dysfunction that might be involved in the pathophysiology of migraine. A previous study of 49 patients treated with 400 mg daily of riboflavin showed a mean global improvement of 68.2%.[6] The dose of 400 mg was chosen in the previous trials because comparable doses were previously used to treat mitochondriopathies, and the lack of toxicity.

Because of its high efficacy, excellent tolerability, and low cost, riboflavin is an interesting option for migraine prophylaxis, and a candidate for a comparative trial with an established prophylactic drug. Since the use of riboflavin as a migraine preventive medication is supported by a few clinical trials which have shown its safety and efficacy, the present study intends to explore the use of the drug in comparison with propanolol, a gold standard prophylactic drug. There is no evidence that riboflavin interacts with abortive medication, as do many other prophylactic agents.[7] It may also be worthwhile for cost reasons to explore the antimigraine effect of lower doses of riboflavin. Furthermore, no such studies have been done

Address correspondence to: Dr.Natasha JB Nambiar, Department of pharmacology, M.S. Ramaiah Medical College, Bangalore-560054, India. E-mail: dr.natasha7@gmail.com

in the Indian population. Therefore, this study is undertaken to investigate the effectiveness of riboflavin in a lower dose of 100mg, and to compare its role as prophylactic agent with propranolol in migraine patients.

METHODS

The study was conducted for a period of one year starting from November 2008 to October 2009 on patients diagnosed with migraine attending Neurology outpatient department at M.S. Ramaiah Medical Teaching Hospital and in M.S. Ramaiah Memorial Hospital, Bangalore. Consent was taken from the subjects before their inclusion in the study. The ethical clearance was obtained from the Institutional Ethical Review Board of the Institute. The inclusion criteria were: (1). History of migraine of more than one year diagnosed according to IHS criteria; (2). Had 2-8 headache attacks per month; (3). Age between 18 to 65 years. The exclusion criteria were: (1). Use of prophylactic medication 3 months prior to the study; (2). Tension type headache more than five days per month; (3). Pregnancy or lactation; (4). Anemia; (5). Use of vitamin supplements; (6). Alcohol abuse; (7). Abnormal liver or renal function tests; (8). Patients diagnosed to have transformed migraine, chronic daily headache, cluster headache or cluster migraine; (9). Any significant cardiovascular, central nervous system, renal or respiratory dysfunction; (10). Patient who refused consent.

Prior to randomization patients were counseled regarding migraine preventive therapy and the need for taking the treatment for at least 3 months. Patients were randomly assigned using computerized randomization table to either of the two groups: Group 1: Tablet propranolol 80mg once daily; Group 2: Tablet riboflavin 100mg once daily.

All patients were issued a migraine diary and explained how to record the number and duration of attacks, severity of migraine headaches according to the visual analogue scale (VAS) and the disability using the migraine disability questionnaire (MIDAS). The patients were asked to come for follow-up at the end of first, third and sixth month. All patients were reminded of the follow-up through telephone. During the follow-up migraine diaries were cross-checked with compliance to the drug. Patients were allowed to use concomitant rescue medication to abort migraine attacks.

Statistical methods

Descriptive statistical analysis was carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. 2x3 Repeated measures Analysis of variance (RANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software SAS 9.0, SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data.

RESULTS

Patients in both the study arms are age and sex matched. The mean age was 31 years with higher preponderance of females. Type of migraine was similar between the two groups with majority having migraine without aura. A positive family history was slightly higher in the riboflavin group. Baseline frequency and duration of headache, VAS and MIDAS scores were also similar in both study groups (Table 1).

Both study groups showed reducetion of frequency of headache at the end of 3 months, and at sixth month follow up. There was a significant reduction in the frequency of migraine headaches in the propanolol relative to the riboflavin group at the end of the first month, but there was no difference in the two groups at the end of the third month and sixth month follow-up (Table 2). As for the duration of migraine headache, both groups showed reduction in the duration of headache at the third month. There was no significant difference between the two study groups at the end of three months of treatment, and follow-up at sixth month (Table 3). As for severity of the headache as measured by the VAS score, both groups showed reduction in the VAS scores at 3 months and at the sixth month follow-up. There was a also significantly lower VAS score in the riboflavin as compared to the propranolol group in the third month of treatment. (Table 4). As for disability as measured by the MIDAS score, both groups showed reduction at 3 months, but there was no significant difference between the two groups (Table 5). As for side effects, overall

Table 1: Baseline demographic and clinical characteristics of study patients

Characteristic	Group 1 Propranolol 80mg/day (n =50)	Group 2 Riboflavin100mg/day (n =50)	P value
Age	31.5±7.9	31.5±7.6	0.990
Female gender n (%)	27(54%)	28(56%)	0.841
Type of migraine n (%)			
With aura	16(32%)	15(30%)	0.829
Without aura	34(68%)	35(70%)	
Duration of migraine in years	6.7±3.0	6.9±3.7	0.789
Positive family history	11(22%)	15(30%)	0.362
Frequency of headaches/month	4.0±0.8	4.0±1.0	0.751
Duration of attack in hours	2.9±1.0	2.8±1.0	0.620
VAS at baseline (0 month)	5.3±1.4	4.9±1.1	0.068
MIDAS at baseline (0 month)	4.7±1.6	4.8±1.5	0.800

VAS: visual analogue score
MIDAS: migraine disability questionnaire

Table 2: The frequency of headache per month in the study period

Frequency of headache	Group 1 Propranolol 80mg/day	Group 2 Riboflavin 100mg/day	P value
Baseline	4.0±0.8	4.0±1.0	NS
1st month	3.3±0.6	3.9±1.0	<0.001
2nd month	2.8±0.9	2.9±0.7	NS
3rd month	2.3±0.7	2.3±0.7	NS
6th month follow up	2.8±0.7	2.9±0.7	NS
% change at 3rd month	42.1%	43.2%	-
% change at 6th month follow up	30.2%	28.1%	-
Repeated measures ANOVA Model up to 3rd month evaluation			
Group effect		F=0.862; P=0.355	
Time effect		F=258.54; P<0.001	
Group*Time effect		F=11.385; P<0.001	

NS: no significance

Table 3: The duration of headache in hour in the study period

Duration of headache	Group 1 Propranolol 80mg/day	Group 2 Riboflavin 100mg/day	P value
Baseline	2.9±1.0	2.8±1.0	NS
1st month	2.9±1.1	2.8±1.0	NS
2nd month	2.4±0.7	2.4±0.6	NS
3rd month	2.0±0.8	2.1±0.7	NS
6th month follow up	2.9±1.0	2.6±0.8	NS
% change at 3rd month	32.2%	26.2%	-
% change at 6th month follow up	2.05%	9.2%	-
Repeated measures ANOVA Model up to 3rd month evaluation			
Group effect	F=0.009; P=0.925		
Time effect	F=106.948; P<0.001		
Group Time effect	F=1.630; P=0.182		

NS: no significance

Table 4: The severity of headache by visual analogue score (VAS) in the study period

VAS score	Group 1 Propranolol 80mg/day	Group 2 Riboflavin 100mg/day	P value
Baseline	5.3±1.4	4.9±1.1	NS
1st month	5.3±1.33	4.9±1.1	NS
2nd month	4.4±1.0	4.2±0.9	NS
3rd month	4.0±1.0	3.6±0.9	0.033
6th month follow up	4.4±1.0	4.3±0.9	NS
% change at 3rd month	25.8%	27.1%	-
% change at 6th month follow up	17.2%	13.1%	-
Repeated measures ANOVA Model up to 3rd month evaluation			
Group effect		F=3.278; P=0.073	
Time effect		F=153.403; P<0.001	
Group Time effect		F=1.428; P=0.243	

NS: no significance

Table 5: The disability of headache by migraine disability questionnaire (MIDAS) score in the study period

MIDAS score	Group 1 Propranolol 80mg/day	Group 2 Riboflavin 100mg/day	P value
Baseline	4.7±1.6	4.8±1.5	NS
3rd month	3.8±1.2	3.8±1.4	NS
% change at 3rd month	18.6%	21.3%	-
Repeated measures ANOVA Model up to 3rd month evaluation			
Group effect		F=0.001; P=0.972	
Time effect		F=209.288; P<0.001	
Group Time effect		F=1.136; P=0.289	

NS: no significance

side effects were significantly less in the riboflavin as compared to the propranolol group. Patients on riboflavin treatment complained of orange discoloration of urine, nausea and diarrhea while in the propranolol group the common side effects reported were fatigue, dizziness and nausea (Table 6).

DISCUSSION

Riboflavin (vitamin B2) is the precursor of flavin mononucleotide and flavin adenine dinucleotide. These are coenzymes required for the activity of flavoenzymes involved in the transfer of electrons in oxidation-reduction reactions and

Table 6: Side effects of the study patients

Side effects	Group 1 Propranolol 80mg/day (n=50)		Group 2 Riboflavin100mg/day (n=50)	
	No	%	No	%
Absent	28	56.0	38	76.0
Present	22	44.0	12	24.0
• Fatigue	12	24.0	0	0.0
• Dizziness	8	16.0	0	0.0
• Orange discoloration of urine	0	0.0	10	20.0
• Vomiting	0	0.0	1	2.0
• Nausea	2	4.0	0	0.0
• Diarrhoea	0	0.0	1	2.0

Side effects are significantly less in Group 2 with P=0.035

in the production of energy in the mitochondria. A beneficial clinical response to riboflavin has been observed in patients with syndrome of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), who experience headaches similar to headaches in migraine.[8,9]

The present study suggests that oral riboflavin in the dose 100 mg/day is comparable with oral propranolol 80 mg/day in reducing the frequency of migraine headaches at the end of 3 months, and at sixth month follow up.,This study is in accordance with a non randomized trial by Sandor *et al* in which 26 patients with migraine received 4 months migraine prophylaxis with either riboflavin or beta blockers. Clinical improvement was seen with both treatments with patients in the riboflavin group demonstrating a reduction from 3.5 to 1.7 attacks/month. Based on auditory evoked cortical potential responses before and after treatment, the authors concluded that β-blockers and riboflavin act through different mechanisms.[10]

Though both study drugs reduced the migraine headache frequency, our study showed that the propranolol group had a faster effect, with significantly greater reduction in the headache frequency by the end of the first month. In an open pilot study conducted by Schoenen *et al*, riboflavin at 400mg/day was superior to placebo in reducing headache attack frequency. The effect of riboflavin was found to set in after 1 month and was maximal after 3 months of treatment.[11,12] In another open label study by Boehnke *et al*, riboflavin 400mg/day significantly reduced the headache frequency from 4 to 2 days/month after 3 and 6 months.[13]

The lag before reduction in headache frequency in the riboflavin group may be because impaired mitochondrial energy metabolism is likely to be only one functional abnormality that predisposes to migraine, and may not be crucial in all patients. It is also conceivable that a clinical effect due to pharmacologic intervention on mitochondrial metabolism builds up more slowly than one brought about by receptor blockade. The efficacy of riboflavin beyond 3 months of treatment is yet to be determined.

Both of our study group patients showed reduction of duration of headache at 3 months, although there was no no significant difference in the reduction between the two groups at the end of 3 months and the sixth month follow-up. In the randomized double blind placebo controlled trial conducted by Schoenen *et al*, there was significant reduction of the migraine headache in the 28 patients on riboflavin 400 mg/day.[11]

Both of our study group patients also showed reduction in severity of headache as measured by the VAS scores at 3 months and at the sixth month follow-up. There was a also significantly lower VAS score in the riboflavin as compared to the propranolol group in the third month of treatment. The percentage reduction of VAS scores at the end of three months and at sixth month follow-up was however similar in both study groups. Schoenen *et al* also found a significant reduction in migraine severity in the riboflavin arm as assessed by a four point scale in their placebo control study.[11] Boenhke *et al* on the other hand, using riboflavin 400 mg/day showed no effect on the migraine severity.[13]

Although there are no human studies, animal studies conducted by Franca *et al* demonstrated a dose dependent analgesic effect of riboflavin against formaldehyde induced nociception. A similar animal study conducted by Granados-Soto *et al* also demonstrated the ability of riboflavin to produce antinociception and anti-inflammatory effect. This was thought due to the activation of K^+ channels or nitric oxide release, but not activation of opioid mechanisms.[14,15] The above observations may explain the effect of riboflavin on migraine severity.

We have shown that both study groups showed reduction at 3 months of disability as measured by the MIDAS score, but there was no significant difference between the two groups So far no studies using riboflavin have assessed this parameter.

The side effects in the present study were significantly less in the riboflavin group with orange discoloration of urine, vomiting and diarrhoea being the most reported. Only 24 % complained of adverse events in the riboflavin group as compared to 44% in the propranolol group. The present study is in accordance with the trial by Schoenen *et al*[11] and Boehnke *et al*, the later using higher dose of riboflavin 400mg/day, with mild adverse effects such as diarrhoea, upper abdominal pain and facial erythema.[13]

This was a prospective study with clear inclusion criteria, statistical analysis plan, closely matched study groups, and the patient follow-up was high. Among the limitations of the study is the open label study design and the relatively small sample size. We believe that the small sample size does not affect the internal validity of this study. Though noninferior, the results are unbiased.

In conclusion, we have demonstrated that oral riboflavin 100mg/day is comparable with oral propranolol 80 mg/day in reducing the frequency, duration and severity of migraine headaches and may be preferred over the latter due to its safety and tolerability.

DISCLOSURE

Disclaimer: None
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