

# AREST Migraine (An Evaluation of Riboflavin 200 mg+Magnesium 200 combination Efficacy and Safety in Migraine Headache)

Harmohan Sahoo<sup>†1</sup>, Anand G Diwan<sup>2</sup>, and Manjusha Patanka<sup>3</sup>

### ABSTRACT

Background: Migraine is a common cause of recurrent headaches. Although drugs for prophylaxis of migraine are effective in reducing the frequency and severity of migraine headaches, less than 13% of patients take prophylactic medications. Often, adverse drug reactions lower the adherence of patients to prophylactic therapies. Riboflavin and magnesium have been demonstrated to be effective agents for prophylaxis of migraine

Methodology: 69 neurologists from across India participated in the study. 699 patients diagnosed with migraine were enrolled in the study. Patients were treated with the combination of Riboflavin 200 mg and Magnesium 200 (One tablet twice a day) for duration of 3 months. The primary endpoint was a reduction in migraine headache frequency per month as per the diary reviewed at follow-up. The secondary endpoint was a reduction in pain intensity as per headache severity score (Wong-Baker Faces Rating Scale) at end of treatment as compared to baseline. The safety of the treatment was assessed by the adverse events reported by the patients during the study.

Results: The mean duration of migraine was 14.29 months  $\pm$  16.48 months. A 3-fold reduction in frequency and pain intensity of migraine was observed after treatment with the combination of magnesium, and riboflavin. 96% of physicians rated the efficacy of the combination of magnesium, and riboflavin treatment as Excellent to good

Conclusion: The need for prophylactic therapy for migraine is increasing since migraine adversely affects work-life balance in patients. Current evidence proves the efficacy and safety of the combination of magnesium and riboflavin in reducing the frequency and severity of migraine attacks. The fixed dose formulation of magnesium and riboflavin has a definite place in the prevention of migraine in the real-world setting.

Keywords: Migraine; Riboflavin; Magnesium

### Introduction

Migraine is a common cause of recurrent headaches and is ranked seventh in terms of causing disability in the patient. Migraine represents a neurovascular syndrome that poses a challenge to treat [1]. Triggers of migraine headaches have been identified and avoidance of the triggers plays a major role in the prevention of recurrent attacks of migraine.

There is a plethora of medications available to address acute migraine headaches and the associated symptoms. Several medications are available for prophylaxis of migraine. Lifestyle modifications play a major role in reducing the frequency and severity of migraine. Yet, there is a substantial subset of patients who continue to have recurrent attacks of migraine which adversely affects their quality of life [2].

Preventive therapy with drugs such as divalproex, topiramate, metoprolol, propranolol, and timolol is indicated in patients who have four or more headaches a month or eight or more headache days a month, or have debilitating headaches, patient preference, or certain migraine subtypes (i.e., hemiplegic migraine; migraine with brainstem aura; migrainous infarction; or frequent, persistent, or uncomfortable aura symptoms) [3]. Although drugs for prophylaxis of migraine are Received: 15-Feb-2024, Manuscript No. IJOCS-24-127654; Editor Assigned: 17-Feb-2024, PreQC No. IJOCS-24-127654(PQ); Reviewed: 22-Feb-2024, QC No. IJOCS-24-127654(Q); Revised: 24-Feb-2024, Manuscript No. IJOCS-24-127654(R); Published: 25-Feb-2024, DOI: 10.37532/1753-0431.2024.18( 2).317

<sup>1</sup>Harmohan Sahoo, Neurophysician, Neurologist Heritage Institute of Medical Sciences Varanasi, India

<sup>&</sup>lt;sup>2</sup>Anand G Diwan, Neurophysician, Neurologist, Narayani Hospital, Nashik, Maharashtra, India

<sup>&</sup>lt;sup>3</sup>Manjusha Patankar -Medical Advisor, Health 'N' U Therapeutics Pvt Ltd. India

<sup>&</sup>lt;sup>†</sup>Author for correspondence: Harmohan Sahoo, Neurophysician, Neurologist Heritage Institute of Medical Sciences Varanasi, India, E-mail- manjusha.patankar114@gmail.com

### Research Article Harmohan S, et al.

effective in reducing the frequency and severity of migraine headaches, less than 13% of patients take prophylactic medications. Often, adverse drug reactions lower the adherence of patients to prophylactic therapies [3].

Non-pharmacologic therapies such as cognitive behaviour therapy also has good evidence to corroborate their use in migraine prevention [3]. Emerging data has corroborated the role of vitamins such as riboflavin and other supplements for the prophylaxis of migraine. Riboflavin which improves energy metabolism is a safe and well-tolerated option for preventing migraine symptoms in adults [4,5].

Magnesium deficiency has been implicated in the pathogenesis of migraine [6,7]. Magnesium has been extensively used in migraine prophylaxis and treatment [8]. Oral magnesium alleviates the frequency and intensity of migraine [9]. In a cohort of pregnant women with migraine, riboflavin and magnesium reduced migraine frequency safety and effectively [10].

Magnesium has been recommended by the European Headache Society for prophylaxis of migraine. The Canadian Headache Society has given a strong recommendation for riboflavin, coenzyme Q10, and magnesium citrate for prophylaxis of migraine [11]. The American Headache Society and American Academy of Neurology have placed both Riboflavin and Magnesium in category-2 therapy of Migraine [12].

The efficacy and safety of the combination of riboflavin 400 mg and magnesium in Indian patients with migraine needs to be evaluated in areal-world setting.

### Methodology

69 neurologists from across India participated in the study. Patients diagnosed with migraine as per the International Classification of Headache Disorders diagnostic criteria for migraine were enrolled in the study. The inclusion criteria were patients with migraine aged 12 years or more. Patients with hypersensitivity to riboflavin or Magnesium were excluded from the study. Patients were treated with the combination of Riboflavin 200 mg + Magnesium 200 mg (One tablet twice a day) for duration of 3 months. The primary endpoint was a reduction in migraine headache frequency per month as per the diary reviewed at follow-up. The secondary endpoint was a reduction in pain intensity as per headache severity score (Wong-Baker Faces Rating Scale) at the end of treatment as compared to baseline [13]. The safety of the treatment was assessed by the adverse events reported by the patients during the study. No other prophylactic drugs for migraine were given to the patients. Patients were asked to keep a dairy for chronicling headache episodes every day for each week of the study Statistical analysis was carried out using the paired t test.

#### Results

699 patients with migraine were enrolled in the study. Of the enrolled subjects, 53.8% were males while 46.13% were females. 269 (38.8%) women were of child-bearing age (18 years-45 years). The mean duration of migraine was 14.29 months  $\pm$  16.48 months. The patients were treated with a fixed dose formulation of Riboflavin (200 mg)+Magnesium (200 mg). A 3-fold reduction in the frequency of migraine was observed after treatment with the combination of magnesium and riboflavin in Figure 1. The patients had almost a 3-fold reduction in the pain intensity after treatment with the combination (Figure 2). (p<0.05) 96% of physicians rated the efficacy of the combination of magnesium and riboflavin treatment as Excellent to good (Figure3). Yellow discoloration of urine and loose stools were reported by 2.28% of patients. No gender differences were observed in the outcomes.





### **Research Article**

AREST Migraine (An Evaluation of Riboflavin 200 mg+Magnesium 200 combination Efficacy and Safety in Migraine Headache)



Figure 2: Reduction in migraine intensity.



Figure 3: Physicians global assessment.

#### Discussion

Migraine is a debilitating disease characterized by recurrent headaches. Patients with recurrent migraine headaches are distressed and have a poor quality of life. Extensive research into the pathogenesis of migraine has revealed that the complex pathophysiology of migraine involves diverse mechanisms involving modulation of central and peripheral pain structures and release of vasoactive peptides [14].

While symptomatic therapy or abortive therapy is used to treat migraine attacks, the toll taken by the attacks on work, and daily life encourages patients to look for preventive therapies. Prophylactic drug treatment of migraine is indicated if the quality of life of the patient is severely impaired when two or more attacks occur per month, or when migraine attacks do not respond to acute drug treatment or in case of intolerance to or side effects due to drugs used to treat acute treatment [15]. Prophylactic drugs are expected to not only reduce the frequency and intensity of migraine but also improve the quality of life (Table 1). Drugs prescribed for prophylaxis of migraine have potential side effects, sometimes of a severe nature. Hence patient adherence to these drugs is low and patients often look for alternative treatment options. Prophylactic treatment in migraine is given for 3 months to 9 months' period till the frequency and intensity of attacks reduce.

Data from studies have indicated that decreased levels of the micronutrients riboflavin, magnesium, and coenzyme occur in the plasma and in the brain of migraine patients [16,17]. Deficiency of these nutrients could play a role in the pathophysiology of migraine such as mitochondrial dysfunction [18]. Riboflavin and magnesium modulate the production of energy in the mitochondria [19]. Magnesium plays a role in diverse physiological processes that influence the pathophysiology of migraine (vasoconstriction, platelet inhibition, and secretion of serotonin). Magnesium also acts as a co-factor for ATP-synthase which produces ATP. Mg is also a physiological antagonist at the NMDA channel which regulates neuronal excitability. Patients with migraine have been observed to have magnesium deficiency which is associated with increased platelet aggregation and consequent release of the vasoconstrictor 5hydroxy tryptamine in Figure 4 [20-22].

Riboflavin is a precursor for Flavin-Mononucleotide (FMN) and Flavin-Adenine-Dinucleotide (FAD). Both are involved in electron transport in the mitochondrial membrane. Based on these observations, it seems rational that replenishing these micronutrients in migraine patients could help prevents or reduce the intensity of migraine attacks, reduce recurrent migraine attacks, and may be preferred in patients with adverse reactions to drugs [23].

Riboflavin and magnesium have a level B recommendation as prophylactic drugs for migraine. The UK guidelines for the management of headaches advise that riboflavin at a dose of 400mg daily may be effective in reducing migraine frequency and intensity for some patients [24].

In the study by Nambiar et al, riboflavin was compared with propranolol in 100 patients with 2-8 migraine attacks per month. The efficacy of riboflavin in reducing the frequency and intensity of migraine attacks was comparable to propranolol [25].

## **Research Article** Harmohan S, et al.

Table 1: Goals of migraine prevention.	
1	Decrease attack frequency (by 50%), severity and duration
2	Improve responsiveness to acute treatment
3	Improve function and decrease disability
4	Improve the Quality of life (HRQoL)
5	Prevent disease progression
6	Prevent overuse, CDH and reduce cost

Our patients had more than 60% reduction in migraine frequency and intensity of pain. 96% of physicians rated the treatment of Riboflavin+Magnesium as good to excellent in terms of reducing migraine frequency and intensity while improving the quality of life of the patients. All patients tolerated the FDC well. The FDC of Riboflavin+Magnesium was well tolerated and this was associated with excellent patient adherence to therapy was high. This was ratified by the high physician rating score.

The chief limitations of the study were the non-comparative study design. Future comparative studies need to be undertaken to compare the efficacy of the combination of Riboflavin+magnesium, with standard of care in the real world setting. Further studies including a control group would make the observations of his study more robust.



Figure 3: Role of deficiency of magnesium in migraine

### Conclusion

The need for prophylactic therapy for migraine is increasing since migraine adversely affects work-life balance in patients. Current evidence proves the efficacy and safety of the combination of magnesium, and riboflavin in reducing the frequency and severity of migraine attacks. The FDC was well tolerated and had high patient adherence to therapy. The fixed-dose formulation of magnesium, riboflavin has a definite place in the prevention of migraine in the real-world setting. AREST Migraine (An Evaluation of Riboflavin 200 mg+Magnesium 200 combination Efficacy and Safety in Migraine Headache)

### **Research Article**

#### References

- Bianchi, A., Salomone, S., Caraci, F., et al. Role of magnesium, coenzyme Q~ 1~0, riboflavin, and vitamin B~ 1~2 in migraine prophylaxis. Vitam Horm. 69, 297-312(2004).
- Sun-Edelstein, C., & Mauskop, A. Foods and supplements in the management of migraine headaches. Clin J Pain. 25, 446-452(2009).
- Ha H, Gonzalez A. Migraine Headache Prophylaxis. Am Fam Physician. 1; 99:17-24(2019).
- Namazi, N., Heshmati, J., & Tarighat-Esfanjani, A. Supplementation with Riboflavin (Vitamin B). Int J Vitam Nutr Res. 85, 79-87(2015).
- Sândor, P. S., Di Clemente, L., Coppola, G., et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology. 64, 713-715(2005).
- Domitrz, I., & Cegielska, J. Magnesium as an Important Factor in the Pathogenesis and Treatment of Migraine—From Theory to Practice. Nutr. 14, 1089(2022).
- Fila, M., Chojnacki, C., Chojnacki, J., et al. Nutrients to improve mitochondrial function to reduce brain energy deficit and oxidative stress in migraine. Nutr. 13, 4433(2021).
- Dolati, S., Rikhtegar, R., Mehdizadeh, A., et al. The role of magnesium in pathophysiology and migraine treatment. Biol Trace Elem Res. 196, 375-383(2020).
- Chiu, H. Y., Yeh, T. H., Yin-Cheng, H., et al. Effects of intravenous and oral magnesium on reducing migraine: a meta-analysis of randomized controlled trials. Pain Physician. 19, E97(2016).
- Parohan, M., Sarraf, P., Javanbakht, M. H., et al. Effect of coenzyme Q10 supplementation on clinical features of migraine: A systematic review and dose-response meta-analysis of

randomized controlled trials. Nutr Neurosci. 23, 868-875(2020).

- 11. Pringsheim, T., Davenport, W., Mackie, G., et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 39, S1-59(2012).
- Silberstein, S. D., Holland, S., Freitag, F., et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 78, 1337-1345(2012).
- Garra, G., Singer, A. J., Domingo, A., et al. The Wong-Baker pain FACES scale measures pain, not fear. Paediatr Emerg Care. 29, 17-20(2013).
- 14. Gaul, C., Eismann, R., Schmidt, T., et al. Use of complementary and alternative medicine in patients suffering from primary headache disorders. Cephalalgia. 29, 1069-1078(2009).
- 15. Silberstein, S. D. Preventive migraine treatment. Contin: Lifelong Learn Neurol. 21, 973-989(2015).
- Hershey, A. D., Powers, S. W., Benntti, A. L., et al. Chronic daily headaches (CDH) in children: characteristics and treatment response. Headache. 39, 358(1999).
- Mauskop, A., & Altura, B. M. Role of magnesium in the pathogenesis and treatment of migraines. Clin Neurosci. 5, 24-27(1998).
- Sparaco, M., Feleppa, M., Lipton, R. B., et al. Mitochondrial dysfunction and migraine: evidence and hypotheses. Cephalalgia. 26, 361-372(2006).
- Lodi, R., lotti, S., Cortelli, P., et al. Deficient energy metabolism is associated with low free magnesium in the brains of patients with migraine

and cluster headache. Brain Res Bull. 54, 437-441(2001).

- Karimi, N., Razian, A., & Heidari, M. The efficacy of magnesium oxide and sodium valproate in prevention of migraine headache: a randomized, controlled, double-blind, crossover study. Acta Neurol Belg. 121, 167-17(2021).
- Khani, S., Hejazi, S. A., Yaghoubi, M., et al. Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium valproate therapy in the prevention of migraine headaches: a randomized controlled double-blind trial. J Headache Pain. 22, 1-10(2021).
- 22. Maier, J. A., Pickering, G., Giacomoni, E., et al. Headaches and magnesium: Mechanisms, bioavailability, therapeutic efficacy and potential advantage of magnesium pidolate. Nutrients. 12, 2660(2020).
- Gaul, C., Diener, H. C., Danesch, U., et al. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebocontrolled, double-blind, multicenter trial. J Headache Pain. 16, 1-8(2015).
- 24. The UK guidelines for headache.
- Nambiar, N., Aiyappa, C., & Srinivasa, R. Oral riboflavin versus oral propranolol in migraine prophylaxis: An open label randomized controlled trial. Neurol Asia. 16, 223–229(2011).