THE EFFICACY OF DIFFERENT ORAL MAGNESIUM SUPPLEMENTS FOR MIGRAINE PREVENTION: A LITERATURE REVIEW

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Submitted: 17-04-2016

Revised: 22-06-2016

Accepted: 20-08-2016

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ABSTRACT

No study was conducted to evaluate the efficacy of particular oral magnesium supplement over another in preventing migraine. Different magnesium supplements have different oral absorption and bioavailability. The objective was to identify the efficacy of different oral magnesium supplements in migraine prophylaxis. A literature review using MEDLINE, Scopus, Cochrane library, and EMBASE was conducted during the period from November 1, 2015 until December 30, 2015. Magnesium citrate was used as single oral migraine prophylactic supplement in most of the published trials. Migraine attack frequency and intensity were significantly lower in magnesium citrate group compared to placebo with 41.6-64% and 43-59% reduction in migraine attack frequency and severity frequently. Magnesium oxide was used in combination with magnesium citrate in 2 randomized clinical trials (RCTs), and used alone in one RCT in adults and children. No different in migraine frequency or severity between Mg-oxide and placebo in RCT conducted in children while Only Mg-oxide containing groups showed significant reduction in migraine days when compared to control ($p < 0.006$) in RCT conducted in adults. Magnesium chloride had never introduced as migraine prophylactic agent in clinical trials. Magnesium citrate seems to be the preferred oral magnesium supplement for migraine prevention; however, further studies comparing the efficacy of different oral magnesium supplements are needed.

Key words: magnesium, migraine, prophylaxis, efficacy, oral supplements

INTRODUCTION

Magnesium is an important cation in the body that involves in various cellular functions, and plays vital role in maintaining the proper function of skeletal and cardiac muscle (Sun-Edelstein *et al.*, 2009). Magnesium is also essential mineral in regulating bone metabolism, nerve conduction, muscular contraction, and blood pressure. Deficiency in magnesium level may cause apathy, depression, delirium, seizure, tremors, leg cramps, premenstrual symptoms, and dysarrhythmias.

Although migraine pathogenesis is not completely understood, hypomagnesaemia may lead to increase the frequency of migraine attacks by several mechanisms (Bianchi A *et al.*, 2004). It's believed that migraine pathogenesis is triggered by serotonin receptors, nitric oxide

production, and various inflammatory mediators. Magnesium has significant impact on these triggers. A study found that approximately 50% of patients had low level of intracellular magnesium during their migraine attack (Mauskop *et al.*, 1998). As result, oral magnesium supplements have been introduced as an effective pharmacological intervention for migraine prevention (Guerrera *et al.*, 2009).

Many clinical trials were conducted to evaluate the efficacy of oral magnesium supplements (Facchinetti *et al.*, 1991; Peikert *et al.*, 1996; Pfaffenrath *et al.*, 1996; Demirkaya *et al.*, 2001; Wang *et al.*, 2003; Maizels *et al.*, 2004; Köseoglu *et al.*, 2008; Tarighat *et al.*, 2012; Gaul *et al.*, 2015). Most of these trials showed positive outcomes; however, few studies concluded no difference between oral

Figure 1. Flowchart of literature review of oral magnesium supplements for migraine prophylaxis

magnesium supplements and placebo. Different salt forms of magnesium forms were used in these studies. Different magnesium supplements have different oral absorption, and therefore different bioavailability. Chemically, the bioavailability of magnesium oxide versus magnesium citrate in healthy individuals is still controversial. Clinically, no study has been conducted to evaluate the efficacy of particular oral magnesium supplement over another in preventing migraine. Therefore, a literature review was conducted to identify the efficacy of different oral magnesium supplements in migraine prophylaxis.

MATERIAL AND METHODS

A literature review using MEDLINE, Scopus, Cochrane library, and EMBASE was conducted during the period from November 1, 2015 until December 30, 2015. Keywords included migraine, prophylaxis, and magnesium. The search was limited to clinical trials conducted in human subjects, and available in English language. Any experimental human study published thru the period from 1985 till 2015 and evaluated the efficacy of oral magnesium supplements in prevention of

migraine attack was included in the review. Studies were excluded if the salt form of magnesium supplement was not mentioned in the study. The quality of randomized clinical trials (RCTs) included in this review was assessed using Jadad score that ranges from 0 to 5 scores. High quality RCTs score 3-5 points on Jadad score while low quality RCTs score 0-2 points.

RESULTS AND DISCUSSIONS

A total of 13 articles were screened after removing the duplicated and non-related studies (Figure 1). Eleven articles met the inclusion criteria, and full-text articles were reviewed. Of the reviewed articles, two articles were excluded due to missing naming the magnesium salt, and therefore, 9 RCTs were included in the study. A summary of these RCTs (Table I). Overall quality of the included RCTs was high, having Jadad score of 5 points in 2 trials and 3 points in 5 trials. Only two RCTs score 2 on Jadad score.

Two RCTs compared the efficacy of magnesium supplements in combination with other supplements to placebo, and two RCTs compared the efficacy of magnesium supplement to active medications and to placebo.

Table IA. Controlled trials of oral magnesium supplements in migraine prevention.

Trial and methods (score)	Subjects and designa	Diagnosis & duration of symptoms
Facchinetti <i>et al.</i> , 1991 ⁵ (3)	n= 35 adults (age 28 -36 years) RSBPC	Menstrual migraine for 2 – 9 years
Peikert <i>et al.</i> , 1996 ⁶ (3)	n= 81 adults (age 18 -65 years) RSBPC	Migraine with or without aura (as defined by IHS)
Pfaffenrath <i>et al.</i> , 1996 ⁷ (3)	n= 69 adults (age 18 -60 years) RDBPC	Migraine without aura for at least 2 years (as defined by HIS)
Demirkaya <i>et al.</i> , 2000 ⁸ (3)	n= 87 adults (age 20 -54 years) RDBPC	Migraine with or without aura (as defined by IHS)
Wang <i>et al.</i> , 2003 ⁹ (5)	n= 86 children (age 3 - 17 years) RDBPC	Headache for at least ≥ 4 weeks accompanied with anorexia/ nausea, vomiting, photophobia, sonophobia, a pulsatile or throbbing quality
Maizels <i>et al.</i> , 2004 ¹⁰ (3)	n= 57 adults (age 18 -65 years) RDBPC	Migraine with or without aura for at least 1 year (as defined by IHS)
Köseoglu <i>et al.</i> , 2008 ¹¹ (2)	n= 40 adults (age 20 -55 years) RDBPC	Migraine without aura for at least 2 years (as defined by IHS)
Esfanjani <i>et al.</i> , 2012 ¹² (2)	n= 133 adults (age 18 -55 years) RSBPC	Migraine without aura (as defined by HIS)
Gaul <i>et al.</i> , 2015 ¹³ (5)	n= 130 adults (age 18 -65 years) RDBPC	Migraine with or without aura for at least 1 year (as defined by IHS)

The remaining RCTs discussed the effectiveness of magnesium supplement compared to placebo in migraine prophylaxis. All included RCTs were conducted in adults except one RCT that was studied in pediatric population. Different endpoints and follow-up periods were used; however, a three months follow-up of migraine frequency and intensity was the most common used endpoint. Although different doses of magnesium supplements were used in the included RCTs, the 600mg dose per day seems the common oral dose of magnesium supplement.

Magnesium Citrate

Magnesium citrate was studied as single prophylactic supplement of migraine with or without aura over 3 months period in adult population in 3 RCTs; 2 of which compared

magnesium citrate to placebo and one compared magnesium citrate to placebo and active medications (Peikert *et al.*, 1996; Demirkaya *et al.*, 2001; Köseoglu *et al.*, 2008). Migraine attack frequency and intensity were significantly lower in magnesium citrate group compared to placebo in these RCTs; however, on difference has been shown between magnesium citrate and flunarizine or amitriptyline. Two different doses of magnesium citrate were used; 1830 mg and 600mg per day. The daily dose of 1830 mg magnesium citrate reduced the migraine attack frequency and severity by 64% and 59% compared to 12% and 7% with placebo respectively (Demirkaya *et al.*, 2001). The daily dose of 600 mg magnesium citrate reduced the migraine attack frequency by 41.6% compared to 15.85% in placebo with no difference in

Table IB Controlled trials of oral magnesium supplements in migraine prevention.

Trial and methods (score)	Treatment drug (Mg supplement)	Control treatment (comparative drugs)
Facchinetti <i>et al.</i> , 1991 ⁵ (3)	MPCA 360 mg daily	Placebo (participants received MPCA & placebo for the first 2 months, but all received MPCA in the second 2 months)
Peikert <i>et al.</i> , 1996 ⁶ (3)	Mg citrate 600mg daily (inform of trimagnesium dicitrate)	Placebo
Pfaffenrath <i>et al.</i> , 1996 ⁷ (3)	MAH 486 mg daily	Placebo
Demirkaya <i>et al.</i> , 2000 ⁸ (3)	Mg citrate 1830 mg daily	3 comparative groups: 1- Flunarizine 10 mg daily at night; 2- Amitriptyline 10 mg daily; 3- Placebo
Wang <i>et al.</i> , 2003 ⁹ (5)	Mg Oxide 9 mg/kg daily	Placebo
Maizels <i>et al.</i> , 2004 ¹⁰ (3)	Combination of 300 mg Mg oxide & citrate (ratio 1:1) + 400 mg riboflavin + 100 mg feverfew daily	Placebo (because riboflavin may cause urine discoloration ,only 25 mg riboflavin was added to placebo to confirm blindness)
Köseoglu <i>et al.</i> , 2008 ¹¹ (2)	Mg citrate 600 mg daily	Placebo
Esfanjani <i>et al.</i> , 2012 ¹² (2)	3 active groups: 1- Mg oxide 500 mg daily; 2- L-carnitine 500 mg daily; 3- Mg oxide 500 mg + L-carnitine 500 mg daily	Placebo
Gaul <i>et al.</i> , 2015 ¹³ (5)	Migravent® (in Germany) or Dolovent® (in the USA) + multivitamins/tracers - Migravent® (contains 600 mg Mg citrate & oxide, 400 mg riboflavin, 150 coenzyme Q10) - Dolovent® (contains 600 mg Mg oxide, 400 mg riboflavin, 150 coenzyme Q10)	Placebo

migraine severity or duration in a study conducted by Peikert *et al.* Similar results were shown by Köseoglu *et al.* who found that the pre/post ratios of migraine attack frequency and severity were 0.55 (45% reduction) and 0.57 (43% reduction) in patients who received 600mg magnesium citrate (Köseoglu *et al.*, 2008).

Magnesium citrate was studied in combination with other supplements to prevent migraine in adults population in 2 RCTs (Maizels *et al.*, 2004; Gaul *et al.*, 2015). In a study conducted by Maizels *et al.*, 300 mg magnesium (1:1 ratio of magnesium citrate and oxide) in combination with riboflavin and

feverfew did not show significant difference in reducing the number of migraine attacks over 3 months compared to placebo (Maizels *et al.*, 2004). Similar trial by Gaul *et al.* who used Migravent® (contains 600 mg Mg citrate & oxide, 400 mg riboflavin, 150 coenzyme Q10) in Germany centers and Dolovent® (contains 600mg Mg oxide, 400 mg riboflavin, 150 coenzyme Q10) in the United States centers versus placebo found no difference in the migraine days between the treatment and placebo groups; however, the intensity of migraine was lower in Migravent® and Dolovent® compared to placebo. The intensity of migraine was lower in the treatment group

Table IC. Controlled trials of oral magnesium supplements in migraine prevention.

Trial and methods (score)	Outcome measure (follow-up)
Facchinetti <i>et al.</i> , 1991 (3)	At the end of first 2 months: (1) Duration and intensity of migraine using PTI; (2) number of migraine days; (3) incidence of premenstrual symptoms using MDQ. At the end of second 2 months: (1) Duration and intensity of migraine using PTI; (2) incidence of premenstrual symptoms using MDQ
Peikert <i>et al.</i> , 1996 (3)	Migraine attack frequency, number of migraine days, migraine severity using VAS and duration of migraine (12 weeks)
Pfaffenrath <i>et al.</i> , 1996 (3)	≥ 50% reduction in the duration of migraine in hours or in the intensity of migraine using VAS (12 weeks)
Demirkaya <i>et al.</i> , 2000 (3)	Migraine attack frequency and intensity using pain scale from 0 "no pain" to 3 "severe pain" (3 months)
Wang <i>et al.</i> , 2003 (5)	The number of headache days reported during the eight 2-week intervals of the study (16 weeks)
Maizels <i>et al.</i> , 2004 (3)	≥ 50% reduction in the number of migraine attacks (3 months)
Köseoglu <i>et al.</i> , 2008 (2)	Comparison of 1 month pre-treatment vs. 3 months post-treatment in: A- the frequency & intensity of migraine attack using VAS in: (1) Mg group, (2) Placebo group; B- VEP amplitude & frequency: (1) Mg group (2) Placebo group; - Comparison of ratio means of pre/post-treatment in clinical and VEP parameters between Mg group and placebo group
Esfanjeni <i>et al.</i> , 2012 (2)	- Comparison of 1 month pre-treatment vs. 12 weeks post-treatment in the mean number of migraine attack/month, mean number of migraine days, migraine severity using pain scale from 0 "no pain" to 3 "severe pain" and index; - Comparison of changes of migraine frequency, severity, or index between different study groups
Gaul <i>et al.</i> , 2015 (5)	Comparing the days with migraine and migraine pain (using HIT-6 validated questionnaire and 3-point pain intensity scale) to a 4 week baseline period (3 months). HIT-6 questionnaire included the following items (with their points): never (6 points), rare (8 points), sometimes (10 points), very often (11 points) and always (13 points). Headache impact on this scale ranges from 36 (no headache) to 78 (very severe headache); 3-point pain intensity scale is rated by patient as mild, moderate, severe for each migraine day

compared to placebo with 4.8 points versus 2 points reduction from baseline to the end of the 3 months-therapy in HIT-6 questionnaire ($p=0.01$), and with 0.24 points versus 0.06 points reduction from baseline to the end of the 3 months-therapy in 3-point pain intensity scale ($p=0.03$) (Gaul *et al.*, 2015).

Magnesium Oxide

Magnesium oxide was studied as single prophylactic supplement of migraine in 2 RCTs (Wang *et al.*, 2003; Tarighat *et al.*, 2012). A study conducted by Wang *et al.* in pediatric population (age 3-17 years) over 16 weeks found no difference in the number of headache

days between magnesium group (magnesium oxide 9mg/kg/day) and placebo group; however, the frequency of headache was significantly lower in magnesium group over time (Wang *et al.*, 2003).

Another trial by Esfanjeni *et al.* compared the efficacy of magnesium oxide (500mg/day), L-carnitine (500mg/day), and combination of magnesium oxide and L-carnitine to placebo in prevention of migraine attack in adult population over 12 weeks. The first endpoint was to compare 1 month pre-treatment versus 12 weeks post-treatment for each study group individually in the followings: (1) the mean number of migraine

Table ID. Controlled trials of oral magnesium supplements in migraine prevention.

Trial and methods (score)	Results: drug vs. control
Facchinetti <i>et al.</i> , 1991 (3)	- At the end of first 2 months: PTI lower in MPCA group ($p < 0.03$); Significant reduction in migraine days in MPCA group ($p < 0.01$); Significant decrease in MDQ in MPCA group ($p < 0.05$); - At the end of second 2 months: Significant decrease in PTI & MDQ since all participants received MPCA during this period
Peikert <i>et al.</i> , 1996 (3)	- Frequency of attack reduced by 41.6% in Mg group vs. 15.8% in placebo group ($p < 0.05$); - Number of days with migraine reduced by 50.3% in Mg group vs. 21.2% in placebo group ($p < 0.05$); - No sig differences in migraine severity or duration
Pfaffenrath <i>et al.</i> , 1996 (3)	10 (28.6%) vs. 10 (29.4%). P value = 0.6599
Demirkaya <i>et al.</i> , 2000 (3)	Mg citrate, flunarizine and amitriptyline were all superior to placebo ($p < 0.001$) in reducing both attack frequency and severity; neither drug was superior to the other
Wang <i>et al.</i> , 2003 (5)	The headache frequency over time was significantly lower in Mg group ($P = 0.037$) than in placebo ($P = 0.086$), but no difference between Mg & placebo at the end of the study ($P = 0.88$)
Maizels <i>et al.</i> , 2004 (3)	10 (42%) vs. 11 (44%). P value = 0.87
Köseoglu <i>et al.</i> , 2008 (2)	- A(1) frequency 3 vs. 2 ($p < 0.001$); intensity 7.57 vs. 4 ($p < 0.001$); - A(2) frequency 3 vs. 3.5 ($p < 0.05$); intensity not significant ($p > 0.05$); - B(1) & (2) Only VEP amplitude was sig lower in Mg group 5.98 vs. 5.62 ($p < 0.05$); - All ratios were sig lower in Mg group ($p < 0.05$), except with VEP latency ($p > 0.05$)
Esfanjani <i>et al.</i> , 2012 (2)	All 4 study groups showed significant decrease in the number of migraine attacks and days, severity and index before & after treatment ($p < 0.05$); All 4 study groups showed significant reduction in the number of migraine attack only ($p = 0.008$). Only Mg groups showed significant reduction in migraine days when compared to control ($p < 0.006$)
Gaul <i>et al.</i> , 2015 (5)	Migraine reduced by 1.8 days/month in treatment group and by one day/month in the placebo group ($p = 0.23$); The intensity of migraine was lower in the treatment group compared to placebo with 4.8 points versus 2 points reduction from baseline to the end of the 3 months-therapy in HIT-6 questionnaire ($p = 0.01$), and with 0.24 points versus 0.06 points reduction from baseline to the end of the 3 months-therapy in 3-point pain intensity scale ($p = 0.03$)

HIT= headache impact test; IHS= international headache society; MAH= magnesium aspartate hydrochloride; MDQ= Moos Menstrual Distress Questionnaire; Mg = magnesium; MPCA = Magnesium pyrrolidone carboxylic acid; PTI = Pain Total Index; RDBPC= randomized double blind placebo controlled; VAS= visual analog scale; VEP= visual evoked potential study

attack per month; (2) the mean number of migraine days per month; (3) severity using pain scale from 0 "no pain" to 3 "severe pain" and index; and (4) serum level of magnesium and L-carnitine determine. The second objective was to compare changes of migraine attacks or days per month, severity, or index between different study groups. All the four study groups showed

significant decrease in the number of migraine attacks and days, severity and index before & after treatment ($p < 0.05$). Also all the four study groups showed significant reduction in the number of migraine attack only ($p = 0.008$), but only Mg groups showed significant reduction in migraine days when compared to control ($p < 0.006$), but not in migraine severity or index.

Other oral magnesium supplements

Pfaffenrath *et al.* evaluated the efficacy of 486 mg magnesium aspartate hydrochloride (MAH) in reducing the duration or intensity of migraine compared to placebo in adult population over 12 weeks (Pfaffenrath *et al.*, 1996). No difference between the MAH and placebo in the primary endpoints. Magnesium pyrrolidone carboxylic acid (MPCA) is another magnesium supplement used in trial conducted by Facchinetti *et al.* in women with menstrual migraine.^[5] Participants were given either 360 mg of MPCA per day or placebo for the first 2 months, and all participants then received MPCA for the second 2 months. The primary endpoints were intensity and duration of migraine using Pain Total Index (PTI), number of migraine days, and incidence of premenstrual symptoms using Moos Menstrual Distress Questionnaire (MDQ) at the end of the first 2 months. Both MPCA and placebo showed a significant reduction in PTI ($p < 0.03$); however, only MPCA showed a significant reduction in MDQ ($p < 0.05$) at the end of the first 2 months. Also, MPCA group was associated with lower migraine days with significant reduction in number of migraine days from 4.7 ± 3.1 to 2.4 ± 2.2 ($p < 0.01$).

Although the clinical superiority of a particular oral magnesium supplement in prevention of migraine is not determined yet, the absorption and bioavailability of three forms of magnesium (citrate, oxide, and amino acid chelate), each contains 300 mg elemental magnesium, were compared to placebo by Walker *et al.* in RCT including healthy participants for 2 months (Walker *et al.*, 2003). Any participant with disease, condition, or medication that may alter the absorption of magnesium was excluded. After 2 months of the study, magnesium citrate showed a significant increase in urine excretion ($p = 0.033$), saliva concentration ($p = 0.027$), and plasma concentration ($p = 0.006$) compared to magnesium oxide or placebo, but no difference in red blood cell magnesium concentration between the three forms. As result, magnesium citrate was concluded to be more bioavailable than other magnesium preparations. In contrast, magnesium oxide showed significant increase in intracellular magnesium concentration ($p < 0.001$) and significant

decrease in LDL cholesterol ($p = 0.042$) compared with magnesium citrate in a cross-over RCT conducted by Shechter *et al.* in healthy individuals (Shechter *et al.*, 2012).

Clinically, there is no clinical trial compared the efficacy of particular oral magnesium supplement against another in prevention of migraine, instead different magnesium supplements were studied against placebo. Magnesium citrate seems to be the effective choice in preventing migraine in adult population based on the reviewed articles. In addition, the results of Taubert's RCT (article in Germany) showed a significant reduction in migraine attack after administering his subjects 600mg magnesium citrate (in form of trimagnesium dicitrate) (Taubert, 1994). However, neither magnesium citrate nor magnesium oxide were able to improve blood pressure, fasting glucose or H₁Ac level in diabetic patients (Song *et al.*, 2006).

Magnesium chloride was claimed to be more bioavailable than other commercial magnesium preparations, even though it had never been studied as migraine prophylactic agent (Firoz *et al.*, 2001). However; magnesium chloride showed a significant reduction in blood pressure compared to placebo in 2 RCTs (Guerrero-Romero *et al.*, 2009; Shafique *et al.*, 1993).

Many of the included studies are old and thereby quality of these articles is questionable; however, the literature review was conducted to answer very specific question that necessitates the exclusion of some studies. Another limitation is the usage of different outcome measures for migraine frequency or severity. Furthermore, there is inconsistency in the usage doses of particular oral magnesium supplement and in migraine characteristics.

Gaps between guidelines and practice

Although of the low quality evidence, Canadian Headache Society strongly recommends magnesium citrate 600 mg per day as migraine prophylactic agent (Hui *et al.*, 2003). It's the only organization that recommends particular magnesium supplement and its dose. The other organizations such as the American Academy of Neurology and the American Headache Society did not specify the type of oral magnesium supplement; however, they

relied on the same trials that Canadian Headache Society used for their recommendations (Silberstein *et al.*, 2012). In the practice, the available magnesium supplement, regardless of the type of its salt, is introduced as migraine prophylactic agent.

CONCLUSION

Magnesium citrate was used as single oral migraine prophylactic supplement in most of the published trials. Magnesium oxide was used in combination with magnesium citrate in 2 RCTs, and used alone in one RCT in adults and pediatric population. Magnesium chloride had never been introduced as migraine prophylactic agent in the clinical trials. Therefore, Magnesium citrate seems to be the preferred oral magnesium supplement for migraine prevention at the mean time; however, further studies comparing the efficacy of different oral magnesium supplements are needed to identify the gap between guidelines and practice regarding the use of oral magnesium supplements for migraine prevention.

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