SHOULD MAGNESIUM BE GIVEN TO EVERY MIGRAINEUR? YES

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Many studies have documented magnesium deficiency in a significant proportion of migraine patients. These studies have included those measuring whole brain magnesium content using NMR spectroscopy, intracellular levels, serum ionized levels, and magnesium loading test. There is a clear understanding of the role of magnesium in a large number of intracellular metabolic processes, function of various receptors and neurotransmitters, cortical excitability, and vascular tone. Some of these studies indicate that up to 50% of migraine sufferers may have a magnesium deficiency. Commonly available serum magnesium level of magnesium is highly unreliable because only 1% of magnesium is extracellular, while 99% is intracellular or bound within bones. Measurement of red blood cell magnesium levels is somewhat more accurate and is performed by many clinical laboratories, but is fairly expensive – in the US it costs $85 plus $11 for blood drawing. Considering that oral magnesium supplementation is extremely inexpensive (less than a dollar a month) and very safe, it is prudent to recommend a trial of magnesium supplementation to all migraine sufferers.

Treatment with Oral Magnesium: Two double-blind, placebo controlled trials showed therapeutic efficacy of Mg^{2+} supplementation in headache patients. The first one was a double-blind, placebo-controlled study of oral magnesium supplementation in 24 women with menstrual migraine which yielded positive results [Facchinetti, 1991]. The supplement consisted of 360 mg of magnesium pyrrolidone carboxylic acid taken in 3 divided doses. Women received 2 cycles of study medication, taken daily from ovulation to the first day of flow. In addition to a significant reduction of the number of days with headache ($p<0.1$) and the total pain index ($p>0.03$), patients receiving active treatment also showed improvement of the Menstrual Distress Questionnaire score.

A larger double-blind, placebo-controlled, randomized study involving 81 patients with migraine headaches also showed significant improvement in patients on active therapy with 600 mg of trimagnesium dicitrate in a water-soluble granular powder [Peikert, 1996]. Attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group. Diarrhea was present in 18.6% and gastric irritation in 4.7% of patients in the active group; three patients dropped out of the study.

A third placebo-controlled, double blind trial showed no effect of oral magnesium on migraine [Pfaffenrath, 1996]. This negative result has been attributed to the use of a poorly absorbed magnesium salt, since diarrhea occurred in almost half of patients in the treatment group.

Most recently, the prophylactic effects of 600 mg/day oral magnesium citrate supplementation in patients with migraine without aura were assessed in a randomized, double-blind, placebo-controlled study [Koseoglu, 2008]. Treatment with 600 mg of oral magnesium citrate resulted in a significant decrease in migraine attack frequency.

In a randomized, double-blind, placebo-controlled trial [Wang, 2003] with children and adolescents ages 3 to 17 years, a statistically significant downward trend in headache frequency was noted in the magnesium oxide group but the slopes of the 2 lines were not statistically different from each other.

Treatment with Intravenous Magnesium: In a pilot study [Mauskop, 1995], 40 patients received intravenous magnesium sulfate after a blood sample was drawn to measure ionized magnesium (IMg^{2+}) levels. An 85% correlation between the clinical response and the levels of serum IMg^{2+} was found ($p<0.01$). Of the patients who had serum IMg^{2+} levels below 0.54 mmol/L, 86% had relief of pain and associated symptoms that was sustained over 24 hours. In contrast, of the patients who had serum IMg^{2+} levels greater than 0.54 mmol/L, only 16% experienced a similar degree of relief. Though the study was not double-blinded or placebo-controlled, both the researchers and subjects were blinded to the IMg^{2+} levels, since the clinical evaluation and treatment were done well before the lab results were known. Later, another study [17] showed that 1 gram of magnesium sulfate resulted in rapid headache relief in patients with low serum IMg^{2+} levels.

In another randomized, single-blind, placebo-controlled trial [Demirkaya, 2001], 30 patients with moderate to severe migraine attacks received either 1 gram intravenous magnesium sulfate or 10 mL of saline intravenously. Patients in the placebo group who continued to have pain, nausea, or vomiting after 30 minutes were then given 1 g magnesium sulfate. Treatment was superior to placebo in terms of both response rate (100% for magnesium sulfate vs. 7% for placebo) and pain-free rate (87% for magnesium

sulfate and 0% for placebo). 87% had mild side effects including flushing and a burning sensation in the face and neck. No subjects reported headache recurrence during the 24 hours after treatment.

The efficacy of 1 gram of magnesium sulfate on the pain and associated symptoms in patients with migraine without aura and migraine with aura were assessed in a randomized, double-blind, placebo-controlled study [Bigal, 2002]. Pain relief was assessed with 7 analgesic parameters and an analogue scale was used to measure nausea, photophobia, and phonophobia. There were no significant differences in pain relief or nausea between treatment and placebo in patients with migraine without aura, although a significant lower intensity of photophobia and phonophobia in patients receiving magnesium sulfate was noted. However, patients with migraine with aura who received magnesium sulfate showed a statistically significant improvement in pain and all the associated symptoms when compared to those who received placebo.

Two studies have been conducted in an emergency room setting. In the first, a randomized, double-blind, placebo-controlled study [Corbo, 2001], 44 subjects with acute migraine (42 of whom were women) received either 20 mg of metoclopramide plus 2 grams of intravenous magnesium sulfate or 20 mg of metoclopramide plus placebo at 15 minute intervals for up to 3 doses, or until pain relief occurred. Pain intensity was recorded using a standard visual analog scale (VAS) at 0, 15, 30, and 45 minutes. Results were surprising in that although both groups experienced more than 50 mm improvement in the VAS score after treatment, the improvement was smaller in the magnesium group for the primary endpoint, which was the between-group difference in pain improvement when the initial and final VAS scores were compared. Results also favored the placebo group when comparing the proportion of patients with normal functional status at the final rating. The authors suggested that adding magnesium to metoclopramide might somehow diminish the efficacy of metoclopramide in decreasing migraine pain. The second emergency room study, also randomized, double-blind, and placebo-controlled, compared the effectiveness of intravenous magnesium sulfate and intravenous metoclopramide to placebo [Cete, 2005]. Patients received either 10 mg of metoclopramide, 2 grams of intravenous magnesium sulfate, or normal saline, and then rated their pain using VAS scores at 0, 15, and 30 minutes. Subjects were subsequently followed up by telephone over the next 24 hours to assess for headache recurrence. Each group showed more than a 25 mm improvement in the VAS score at 30 minutes, which was the study's primary endpoint. Nonetheless, there was no significant difference in the mean changes in VAS scores for pain, although the need for additional rescue medication was higher in the placebo group. Recurrence rates within 24 hours were similar between the groups.

Intravenous magnesium may also be effective in the treatment of episodic cluster headache. One study [Mauskop, 1995], in which 22 cluster headache patients were treated with 1 g magnesium sulfate, showed that 41% reported "meaningful relief" after treatment. "Meaningful relief" was defined as either a complete cessation of attacks or relief for more than 3 days.