

Cochrane Corner



What is the role of magnesium for skeletal muscle cramps? A Cochrane Review summary with commentary

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The aim of this commentary is to discuss from a rehabilitation perspective the published Cochrane Review "Magnesium for skeletal muscle cramps"¹ by Garrison et al.^a, under the direct supervision of the Cochrane Neuromuscular Group. This Cochrane Corner is produced in agreement with the Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation.

Background

Muscle cramp is a sudden, painful, and sustained contraction of skeletal muscle fibers. Muscle cramps commonly occur as an isolated phenomenon (idiopathic) or may be disease-associated. Pathogenic mechanisms of muscle cramps are poorly known, but a neurogenic origin has been hypothesized based on the occurrence of cramps in some neuromuscular diseases, such as poliomyelitis and polyneuropathies, radiculopathies and nerve root compression². However, cramps are associated with many other systemic disorders, including metabolic derangements associated with liver and/or kidney failure, thyroid and parathyroid disorders; usually cramps are associated with electrolyte imbalance, including

hypomagnesaemia³⁻⁵. Magnesium is one of the minerals required by human body for nerve transmission⁶ and muscle contraction⁷, with putative benefits for musculoskeletal health⁸, and its oral supplementation is marketed as over-the-counter prophylaxis for muscle cramp. From a functional perspective, experimental studies suggest that magnesium administration might enhance glucose uptake and limit lactate accumulation in skeletal muscle thus improving exercise performance⁹. However, the role of magnesium supplementation for preventing and/or treating muscle cramps remains unclear.

Magnesium for skeletal muscle cramps

(Garrison SR, Korownyk CS, Kolber MR, Allan GM, Musini VM, Sekhon RK, Dugré N, 2020)

What is the aim of this Cochrane review?

The aim of this Cochrane Review was to investigate the efficacy and safety of magnesium supplementation in people with skeletal muscle cramps.

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The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.



What was studied in the Cochrane review?

The population addressed in this review was people with idiopathic or disease-associated skeletal muscle cramps in any body region and of any age.

The intervention studied was oral or parenteral (IM or IV) supplementation with magnesium salts at any dose.

The comparators were no intervention, placebo or other therapies targeting muscle cramps, such as drugs (quinine, calcium channel blockers, sodium channel blockers), electrolyte supplements or hydration, or stretching. Studies including combination of magnesium salts with other active substances were not considered.

The primary outcome studied was cramp frequency, measured as the percent change from baseline in the number of cramps per week at 4 weeks. The same measure, at 12 weeks, was a secondary outcome. Frequency was also measured as the percentage of patients with at least 25% reduction from baseline in cramp frequency (responders), defined by authors¹ as the minimum clinically important difference, at both 4- and 12-week follow-ups. Other secondary outcomes include painful cramp intensity measured on a three-point scale from mild (1 point) to severe (3 points) at both 4- and 12-weeks follow-up and as the number of patients rating their cramps as moderate (2 points) or severe (3 points). Also, the number of patients experiencing the majority of cramps lasting at least 1 minute, as well as treatment withdrawals because of minor (not requiring therapy) or major adverse events (death, hospitalization, or symptoms requiring therapy) were assessed.

Search methodology of the Cochrane review?

The review authors searched for studies that had been published up to September 2019 in several databases, including Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies, Cochrane Central Register of Controlled Trials (CENTRAL) via the CRS Web, MEDLINE, Embase, AMED, LILACS, CINAHL, SPORTDiscus, US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov), World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP; apps.who.int/trialsearch). Authors searched for open-label, single-blind, or double-blind randomized controlled trials (RCTs) without excluding studies based on language or publication status.

This is an update of the Cochrane Systematic Review (CSR) published in 2012¹⁰.

What are the main results of the Cochrane review?

The review included 11 trials, of which four were newly identified compared to the original CSR¹⁰, for a total of 735 patients, with a sample size ranging from 29 to 120 patients for all studies. Participants were healthy people, particularly older adults (5 studies), except one study that included

patients with liver cirrhosis, or pregnant women (5 studies).

The review shows that oral (100-520 mg elemental magnesium daily) or intravenous (5 days consecutive 4-hour IV infusions of 250 ml 5% dextrose in water with 20 mmol of magnesium sulphate corresponding to 486 mg elemental Mg) magnesium supplementation compared to placebo for treating idiopathic rest cramps:

- Did not significantly reduce cramp frequency measured in terms of percentage change from baseline at 1 month (mean difference, MD, -9.59%, 95% CI -23.12 to 3.97; 3 studies) neither cramp frequency measured in terms of mean number of cramps per week on treatment at the same follow-up (MD -0.18, 95% CI -0.84 to 0.49; 5 studies) (moderate certainty of the evidence)
- Did not significantly increase responders (25% or better reduction) at 1 month (risk ratio, RR, 1.04, 95% CI 0.84-1.29; 3 studies, high certainty of the evidence)
- Did not significantly reduce cramp intensity (RR 1.33, 95% CI 0.81-2.21; 2 studies, moderate certainty of the evidence) nor cramp duration (RR 1.83, 95% CI 0.74-4.53; 1 study, low certainty of the evidence) at 1 month
- Did not significantly increase the risk of major (RR 0.68, 95% CI 0.14-3.31; 3 studies, very low certainty of the evidence) or minor adverse events (RR 1.51, 95% CI 0.98-2.33; 4 studies, low certainty of the evidence). Gastrointestinal adverse events, particularly diarrhea, were reported by 11% to 37% of participants receiving oral magnesium, whereas a burning sensation at the site of infusion was reported by half of patients receiving IV magnesium.

Very low certainty of evidence is available for the effects of oral supplementation of magnesium compared to placebo for pregnancy-associated leg cramps in terms of cramp frequency. No studies investigating cramp intensity and duration for this indication and comparison were found.

How did the authors conclude?

The authors concluded that it is unlikely that magnesium supplementation is effective for idiopathic skeletal muscle cramps at any of the dosages and administration route used. Moreover, evidence about the role of magnesium administration in pregnancy-associated muscle cramps is conflicting, while that about the same intervention for exercise- or disease-related muscle cramps is not reliable.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Most people have experienced a muscle cramp. Cramps can sometimes be severe and disabling, requiring medical attention¹¹. Cramps occur in altered physiologic states, such as pregnancy and exercise, in metabolic and neurologic diseases as well as during therapy with some medications, such as diuretics and inhaled β_2 -agonists³. Epidemiological data suggest that muscle cramps are commonly observed

in older people, pregnant women, and athletes^{12,13}. Large populations have inadequate intakes of several key nutrients for musculoskeletal health, including vitamin D¹⁴, choline¹⁵ and magnesium⁸, and the use of dietary supplements may improve the intake of these substances¹⁶. However, findings reported by this CSR demonstrated that magnesium supplementation probably makes little or no difference in reducing frequency of muscle cramps and makes little or no difference in term of treatment response, largely in older adults. On the other hand, it is uncertain whether oral magnesium supplementation reduces pregnancy-associated rest cramps as well as the safety profile of this intervention.

However, the main limitation of this CSR is the lack of investigation about the effects of magnesium supplementation on specific functional outcomes, such as muscle performance, mobility, or limitations in activities of daily living (ADL). Other issues of interest for rehabilitation field that should be addressed are the relevance of muscle cramps and/or myalgia in limiting the participation of patients to rehabilitative interventions. The population included in this CSR consists mainly of healthy people and it is important to investigate the effects of magnesium supplementation for the management of muscle cramps and/or myalgia in patients affected by neuromuscular^{17,18} or musculoskeletal diseases¹⁹ who might be undergoing a rehabilitation program.

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