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The Effect of Magnesium Infusion on Rest Cramps: Randomized Controlled Trial

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Background. Rest cramps (also known as nocturnal leg cramps) are very common in a geriatric population. Oral magnesium supplements are marketed for prophylaxis of such cramps but clinical trials exploring the efficacy of oral magnesium conflict. A therapeutic trial of intravenous magnesium overcomes the limited oral bioavailability of magnesium and better assesses its therapeutic potential.

Methods. A double blind, placebo controlled randomized controlled trial was conducted on 46 community-dwelling older adult (69.3 ± 7.7 years) rest cramp sufferers to determine whether 5 consecutive days infusion of 20-mmol (5 g) magnesium sulfate would reduce the frequency of leg cramps per week in the 30 days immediately pre and post infusions. It was also determined whether the response to treatment varied with the extent to which infused magnesium was retained (as measured by 24-hour urinary magnesium excretion).

Results. The study population averaged 8.0 cramps per week at baseline. The mean change in number of cramps per week, magnesium versus placebo arms, was −2.4 versus −1.7, $p = .51$, 95% confidence interval of the difference −3.1 to 1.7. Magnesium retention did not correlate with treatment response.

Conclusions. Intravenous magnesium infusion did not reduce the frequency of leg cramps in a group of older adult rest cramp sufferers regardless of the extent to which infused magnesium was retained. Although oral magnesium is widely marketed to older adults for the prophylaxis of leg cramps, our data suggest that magnesium therapy is not indicated for the treatment of rest cramps in a geriatric population.

Key Words: Magnesium—Rest cramps—Nocturnal leg cramps—Randomized—Controlled trial.

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REST cramps (also known as nocturnal leg cramps) are painful muscle contractions, typically in the legs or feet, that occur during prolonged periods of rest—most often while in bed at night. Such cramps are especially common in the elderly. Within a UK general practice population, almost one third of men and women more than the age of 50 reported experiencing a rest cramp during the preceding 2 months. Of those who experienced such cramps, 40% cramped three or more times per week and 6% cramped nightly (1). Oral magnesium (Mg) is marketed worldwide as a nonprescription cramp prophylactic to older adults—it is also promoted as a preventive measure for muscle cramps in pregnancy. Although a Cochrane systematic review of rest cramps in pregnancy supports its use in that population (2), the only two randomized controlled trials of oral Mg in older adults have come to conflicting conclusions (3,4). One potential explanation for the discrepancy between pregnant and older adult populations is that bioavailability of oral Mg is both limited and age related. The rate of Mg absorption falls with age (5), varies among supplements (6), and has a saturable component that results in the percent absorption falling as dosage increases (7,8). For example, increasing dietary Mg intake 2.5 times above normal only increases the amount of Mg absorbed by 33% (7). We hypothesized that if the limited effectiveness of Mg as a cramp prophylactic in older adults resulted from the limited bioavailability of oral Mg, then intravenous (IV) magnesium should provide an effective treatment for rest cramps in older people.

To determine whether Mg therapy provided rest cramp prophylaxis in nonpregnant adults, we performed a randomized controlled trial of parenteral (IV) Mg versus placebo. Our secondary aim was to determine whether Mg retention predicted treatment response. Measuring Mg retention was important because it has been used as a tool to predict total body Mg deficiency (9–13). Also, there is a strong positive correlation between the total amount of IV Mg retained during replacement therapy and the rise in intracellular Mg on skeletal muscle biopsy (13).

Methods

Institutional review and approval of the study protocol and written informed consent used in this trial was obtained from the Health Canada Therapeutic Products Directorate and from the University of British Columbia's Clinical Research Ethics Board.

Participants

Forty-six independent community-dwelling older adults were recruited by means of waiting room posters and pamphlets in the offices of 21 Richmond British Columbia family physicians and by community newspaper advertisement within the Greater Vancouver area. All assessed individuals were volunteers who called our contact number inquiring about the study after having learned about it from one of these sources. The only prescreening consisted of asking, at the time of that initial phone call, if the caller had two or more cramps per week and was free of heart and kidney disease. Anyone answering yes to these questions was given an appointment for assessment. Adult crampers were eligible for the study if they could competently complete a run-in diary showing 8 or more cramps in 30 days. They were excluded if on history, physical exam, or screening laboratory evaluation they had estimated glomerular filtration rate (eGFR) less than 50 mL/min; atrioventricular nodal heart block or heart rate less than 54 beats per minute without a pacemaker; previous myocardial infarction; congestive heart failure; digoxin use; significant neurologic disease (eg, stroke, multiple sclerosis, amyotrophic lateral sclerosis, visible fasciculation, upper motor neuron signs); pregnancy, Addison's disease; chronic hepatitis; or significant abnormalities of serum calcium, sodium, potassium, chloride, bicarbonate, thyroid-stimulating hormone, alanine aminotransferase, or prothrombin time.

Participants had an average age of 69.3 ± 7.7 years, 70% of them were female and the mean duration of episodic cramping was 16 ± 14 years. Participants had a normal serum Mg of 0.81 ± 0.09 mmol/L (except for two individuals who were slightly below the normal range) and good renal function overall (eGFR 78.0 ± 16.4 mL/min). Quinine was used by 20% of participants and oral Mg by 35% (taken largely as a combined calcium and magnesium supplement intended for bone health rather than for cramp prophylaxis).

Study Design and Intervention

After completing the first 30 days of their cramp diary, participants were referred to the Richmond Hospital ambulatory care department where they were randomized to one of two possible sets of 4-hour infusions on 5 consecutive days (Monday to Friday). The infusions consisted of 250-mL D5W either with (active arm) or without (placebo arm) 20-mmol (5 g) magnesium sulfate added. The specific magnesium preparation was Health Canada DIN #00602264 Magnesium Sulfate INJ 50% USP 10-ml vial = 5 g per vial (Sandoz, Boucherville, Quebec, Canada). Active and placebo solutions were indistinguishably clear and colorless. Randomization, using a computer-generated random allocation sequence without any blocking or stratification, was carried out by the hospital pharmacist dispensing the study drugs according to a series of opaque allocation envelopes kept in the pharmacy. All investigators, study nurses, and participants were blinded as to treatment allocation.

Recruitment, infusions, and all follow-up occurred between January 2007 and October 2008. Participants were co-located in the ambulatory care during treatment (no more than four participants for any given week) but instructed not to discuss cramps that occurred during the infusion week. They were permitted to use any cramp treatments that were being employed in the run-in period; however, they were requested to stop oral Mg a few days before and during infusion week, and not to start oral Mg if they had not been on it during the preinfusion run-in.

The period of time between reviewing the first 30 days of the diary (to assess eligibility) and the infusion week was variable (2–4 weeks typically), but participants were instructed not to stop recording cramps in their diaries. It was the 30 days immediately prior to infusions that served as the baseline for cramp rate. Participants were requested to continue recording cramps for 90 days following completion of infusions. Each cramp was recorded along with its severity (on a 1–10 pain scale) and duration (broken down into less than 1, 1–5, or greater than 5 minutes). Only cramps occurring below the waist were recorded.

All participants received all of their allocated treatments —with the exception of one Mg participant who felt lightheaded on the evening after the fourth infusion and had her fifth infusion withheld. The first 30 days of the 90-day post infusion cramp recording were used in calculating the primary end point, and all participants had a complete diary for this period. One placebo participant stopped recording on day 31 because of a stroke and two participants (one each from the Mg and placebo arms) stopped recording short of 90 days (days 62 and 78, respectively). Another participant mistakenly stopped recording her cramps during the interval between run-in diary and the start of infusions. In this case, the 30-day run-in diary was used as the cramp baseline instead of the 30 days immediately prior to infusions.

Assessment of Mg Retention

On days 1 and 5 of the infusion week, concurrent with the start of infusions and after voiding, a 24-hour urine for Mg collected in plastic bottles and acidified with 5-ml 10% hydrochloric acid was begun to determine the percent Mg retention on the first and last day of infusions, respectively. The percent retention of that day's infused 20-mmol Mg load was calculated as 100 × (20 mmol – 24-hour urinary excreted Mg)/20 mmol. It was the percent retention of the

first day's infusion that was the main measure of Mg retention. The urines on day 5 were used to assess change in Mg retention over the infusion week, as well as to assess for adequacy of collection on day 1 by comparing the 24-hour urinary creatinine excretion on day 1 and day 5 (day 1 urine creatinine expected to be at least two third of day 5 if adequate collection). To avoid compromising the blind, all participants underwent urine collection identically, and results of urine testing (along with baseline serum Mg) were sequestered from investigators until trial completion. The pharmacist maintaining the study blind communicated directly with the laboratory courier to indicate which specimens to process for Mg retention and which to discard.

One participant had substantially lower 24-hour creatinine in her day 1 specimen than on day 5 (as well as low urine Mg) and was excluded from assessment of Mg retention because of what was assumed an incomplete catch. All 24 active treatment participants submitted 24-hour urines for day 1, but three of these participants did not have a corresponding day 5 urine either because they did not receive the fifth infusion or the laboratory did not process their specimens (in one case because it was not properly acidified, in the other because the specimen was discarded by mistake). All three had day 1 urinary creatinine excretions judged appropriate for their body size/gender and were included in the analysis.

Statistical Analysis

The primary objective of the trial was to compare the effectiveness of IV Mg infusions versus IV placebo infusions in reducing the frequency of rest cramps in older adults—with the primary outcome being the change in the frequency of rest cramps per week (active versus placebo arms) over the 30 days immediately pre and post infusions. The secondary objective was to determine the percent Mg retention in rest cramp sufferers and to determine if Mg retention correlates with treatment response.

A target sample size of 44 (22 per group) provided 90% power to detect a difference in the mean change in number of cramps per week between groups of one standard deviation magnitude when applying a two sample *t* test with a two-tailed significance level of .05. In choosing this sample size, we were predicting and specifying a baseline of eight cramps per week, a 20% placebo response, a minimal detectable difference between groups of 50%, and a four cramp per week standard deviation for the primary outcome.

Graphical analysis of the primary outcome suggested a normal distribution, and a Welch modified two-sample *t* test of the difference between two means of unequal variances was employed to assess the statistical significance of the observed differences. The primary analysis of the change in cramps per week was by intention-to-treat and includes all participants ($n = 46$).

Table 1. Baseline Characteristics of Rest Cramp Sufferers

Variables	Placebo ($n = 22$)	Magnesium ($n = 24$)
Women	13 (59%)*	19 (79%)
Mean age (years)	70.1 (8.7)	68.6 (6.9)
eGFR (mL/min)†	76.5 (18.1)	79.4 (15.0)
Serum Mg (mmol/L)‡	0.82 (0.08)	0.81 (0.10)
Oral Mg use	8 (36%)	8 (33%)
Quinine use	5 (23%)	4 (17%)
Median # of years cramping	14 (9–28)	10 (6–23)
Median # cramps per wk	6.2 (3.9–10.5)	5.8 (4.4–8.0)
Median # cramps per wk lasting >1 min	2.3 (0.6–4.0)	3.7 (1.2–5.0)
Mean cramp pain (1–10)	4.1 (1.8)	3.6 (1.8)

*Data are *M* (*SD*), *n* (%), or medians (interquartile range).
†Estimated glomerular filtration rate (eGFR)—normal ≥60 mL/min.
‡Serum Mg—normal range 0.65–0.95 mmol/L.

Sensitivity analyses for confounding of the primary outcome by baseline differences in gender and cramp rate were performed by multiple linear regression using, as independent variables, group allocation and either gender or baseline cramp rate—along with an interaction term. Sensitivity analysis for baseline cramp rate was further explored by recalculating the primary end point after removing two placebo-assigned high-frequency cramp outliers. As clinicians often think in terms of percent reductions, we also analyzed (without exclusions) the percent change in cramps between groups.

The effect of Mg retention on treatment response was assessed within Mg recipients using linear regression to search for correlation between percent retention of Mg and change in cramp rate. A median split of Mg recipients by degree of Mg retention was also carried out and differences in the change in cramp rate between groups determined by Welch modified two-sample *t* test of the difference between two means of unequal variances.

Results

Baseline demographics are shown in Table 1. Participants were well matched for age, eGFR, serum Mg, oral Mg use, and quinine use. More men were allocated to placebo (41% versus 21%), and the mean baseline cramp rate was higher in the placebo group (8.6 versus 7.5 cramps per week) due to two outlying crampers (each averaging close to 29 cramps per week) being allocated to placebo.

Figure 1 shows the flow of participants through the trial. Of 139 assessed individuals, 93 were excluded. Twenty-four of those (mostly respondents to newspaper ads) were excluded because they did not have rest cramps. They had exertion or posture-related (rather than rest) muscle cramps [8], restless leg syndrome [5], arterial insufficiency [3], neuropathic pain [3], myalgia [2], nocturnal myocolonus [2], and tarsal arthritis. Exclusion for too few cramps (<8 cramps in 30 days) occurred in 18 potential participants and 17 declined enrollment. Concurrent neurologic abnormalities excluded 14 participants and included diagnoses of

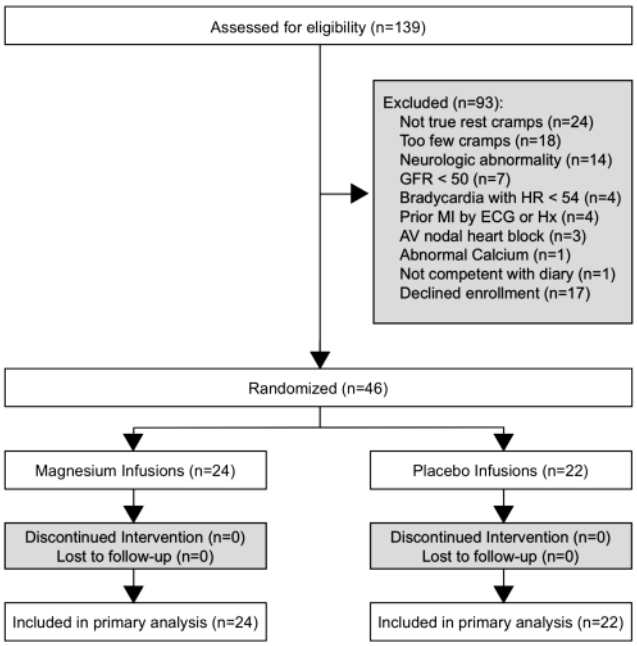

Figure 1. Flow of participants through trial.

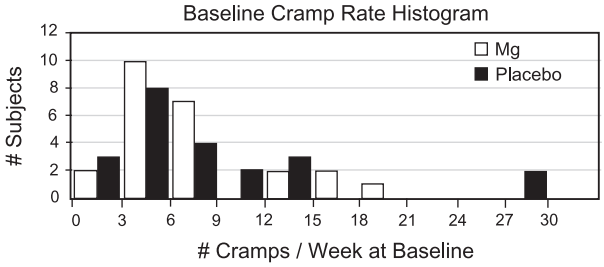

Figure 2. Histogram of baseline cramp rate for Mg and placebo groups.

spinal stenosis [3], radiculopathy [3], ALS, postpolio syndrome, myelopathy not yet diagnosed, multiple sclerosis, complex regional pain syndrome, Parkinson's disease, benign fasciculation syndrome, and progressive weakness not yet diagnosed. A further 20 participants were excluded by various criteria including eGFR less than 50 [7], bradycardia [4], history or electrocardiogram evidence of myocardial infarction [4], heart block [3], hypocalcemia [1], and being unable to satisfactorily complete a baseline diary [1]. This left 46 participants to be randomized, 24 allocated to the Mg treatment group and 22 to placebo. The baseline cramp rate averaged 8.0 cramps per week, and its distribution was skewed to the right (Figure 2) with a median of 5.8 and interquartile range 4.4–9.0 cramps per week. The mean change in number of cramps per week was normally distributed and, Mg versus placebo arms, was -2.4 ± 4.4 versus -1.7 ± 3.3 cramps per week, $p = .51$, 95% confidence interval (CI) of the difference −3.1 to 1.7.

Sensitivity analysis for gender confounding of the primary outcome using multiple linear regression with group, gender, and an interaction term as independent variables shows the gender – treatment group interaction to be not significant (−2.0 cramps per week in treated men, $p = .46$, 95% CI −7.3 to 3.35).

Sensitivity analysis for confounding by differences in baseline cramp rate obtained by excluding the two placebo-assigned high cramp rate outliers provides a mean change in number of cramps per week, Mg versus placebo arms, of −2.4 versus −1.6, $p = 0.47$, 95% CI of the difference −3.2 to 1.5, that is virtually identical to the results before the outliers were removed. Regressing the primary outcome against group, baseline cramp rate, and an interaction term, however, did show a significant interaction between treatment and baseline cramp rate (−0.53 cramps per week per baseline cramp in treated participants, $p = .0039$, 95% CI −0.88 to −0.18). This difference was no longer significant when the two placebo assigned outliers were removed (−0.31 cramps per week per baseline cramp in treated participants, $p = .19$, 95% CI −0.78 to 0.16).

Percentage change in cramps, Mg versus placebo, was −26.8% versus −21.3%, $p = .71$, 95% CI difference −35.0 to 23.9. We suggest that the threshold for a clinically meaningful reduction in cramps between groups would be 25%. Using a one-sided t test and assuming a true difference of 25% in favor of the intervention (rather than no difference) as the null hypothesis, we find a p value of .09. This means that, if the true difference in treatment effect is a 25% reduction in favor of Mg, the probability of observing a reduction in cramp rate of 5.5% or less (as we have done) is only 9%.

No difference was evident in degree of pain, duration of cramps, or cramp rate during either the 5 days of infusions or the full 90-day follow-up interval. Mg retention did not predict treatment response, baseline cramp rate, or the change in cramp rate during the infusion week (when serum Mg would be highest). Using a median split for Mg retention (median retention = 15%) shows the change in cramp rate for retainers of greater than 15% versus retainers of less than 15% of the initial Mg load to be −2.4 versus −2.5 cramps per week, $p = 0.94$—see Figure 3. No correlation exists between percent retention of Mg and change in cramp rate for the Mg treatment group as a whole using linear regression ($R^2 = .0087$)—see Figure 4. The same is true looking only within the group of greater than 15% Mg retainers.

Mean 24-hour urinary Mg excretion in Mg recipients at baseline (day 1 of infusions) was 17.5 ± 3.3 mmol and rose on day 5 to 20.2 ± 3.1 mmol. A statistically significant positive correlation existed ($p = .03$, $r = .46$) between urine Mg excretion at baseline and eGFR—that is consistent either with other work suggesting that low intracellular Mg may impair GFR (14,15) or with the possibility that lower glomerular filtration of Mg itself leads to lower excretion rates.

Within the Mg treatment group, mean urinary Mg excretion in oral Mg users versus nonusers was 18.3 versus 17.0 mmol/L, $p = .36$. Nonusers of oral Mg trended (nonsignificantly) toward a greater reduction in cramps per week when given Mg (−3.2 vs. −0.93 cramps per week, $p = .13$) but this

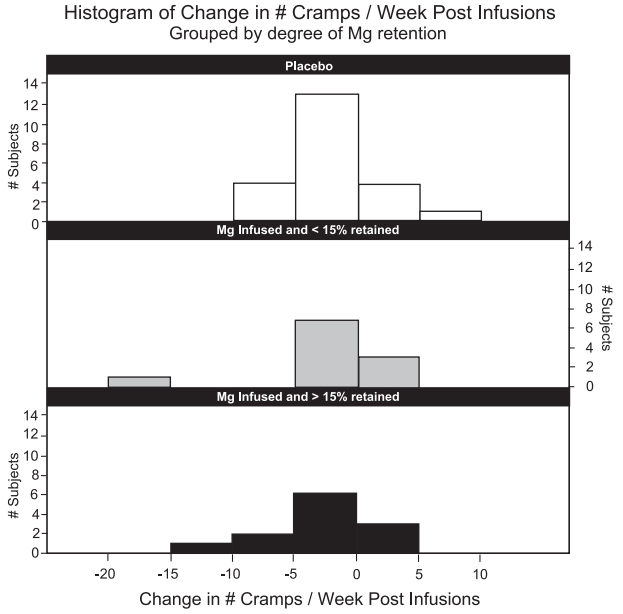

Figure 3. Histogram of change in number of cramps per week postinfusions (grouped by degree of Mg retention).

appeared driven solely by the 10 highest rate crampers—none of whom took oral Mg, and who trended nonsignificantly to a greater response to treatment. Comparing percent reduction in cramp rate instead of change in number of cramps per week shows no significant difference between nonusers and users of oral Mg (−29.6% vs. −21.6%, $p = .64$).

The only major adverse event was a stroke on day 31 post infusions in one placebo recipient. Asymptomatic hypotension was reported by the study nurse in 3/24 Mg versus 0/22 placebo participants during infusions. Facial flushing was noted in 9/24 Mg and 7/22 placebo recipients but was generally not complained of by participants. Two Mg recipients noted transient lightheadedness several hours after the infusions on day 3 and day 4 and more Mg recipients noted burning of the IV site (12/24 vs. 0/22) with 5/24 Mg participants receiving some piggybacked extra dilution of the IV solution with normal saline to improve tolerability.

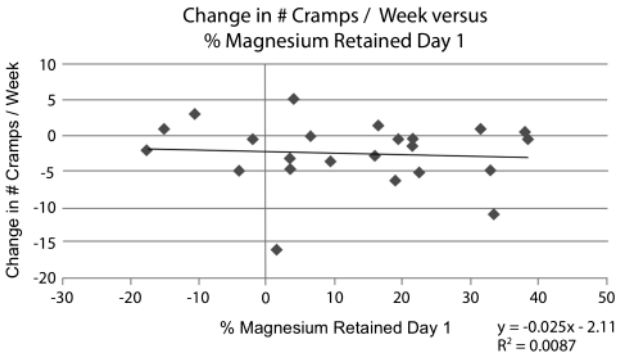

Figure 4. Change in number of cramps per week versus percent Mg retained on first day of infusions.

Participants had been told that IV site discomfort was possible with both placebo and Mg infusions. Although generally it was considered that blinding was reasonable, the sensation of burning at the IV site, coupled with the additional saline dilution in some Mg participants, could have compromised the blind to some extent (presumably favoring the intervention).

Discussion

We observed a 2.4-cramp per week (−26.8%) reduction in the Mg treatment group compared with a 1.7 (−21.3%) cramp per week reduction in placebo recipients. The difference of 0.7 cramps per week (5.5% reduction) between groups is neither statistically significant nor clinically significant if it were the true difference. We would consider a 25% reduction in cramp rate between groups to be at the lower end of clinical significance for this therapy. If the true difference between therapies is a 25% reduction in favor of Mg, the chance of observing a difference in favor of Mg of 5.5% or less (as we have found) is only 9%. Hence, it is unlikely that Mg provides a clinically significant benefit in this population of cramp sufferers.

There was no relationship between the degree of Mg retention at baseline and the change in cramp rate following Mg therapy. This is important because the degree of retention of infused Mg is believed to reflect Mg status (9–12), and has been shown to correlate very strongly with the extent of intracellular Mg increase following a series of Mg infusions (assessed via skeletal muscle biopsy) (13). On its own, the observation that there was no greater reduction in cramps following Mg infusion in retainers of Mg argues strongly against a therapeutic value for Mg in cramp prophylaxis.

Two previous randomized controlled trials ($n = 42$ and $n = 46$ included in analysis) have assessed oral Mg in older adult rest crampers (3,4). Both employed a cross-over design. The first found no difference between oral Mg and placebo (4), and the second suggested a trend to benefit ($p = .07$) (3). Both studies used magnesium citrate. However, the study finding no benefit gave it in pill form, whereas the study suggesting benefit gave it as a powder dissolved in water. In this study, the placebo powder (provided by the manufacturer and sponsor of the trial) consisted of vehicle/flavoring without Mg citrate added. Bias in this cross-over trial may have been introduced both by unsuccessful blinding and by a very high (37%) dropout rate.

Our results differ from those of the single study ($n = 73$ parallel design) that reported a benefit from oral Mg in the rest cramps of pregnancy (16). This population is metabolically very distinct from the older adults we studied, and it would not be surprising if the rest cramps of aging and pregnancy prove to have different underlying etiologies.

Participants for our trial were recruited roughly equally from participating Richmond family practices and from self-referral following newspaper advertisement in the Vancouver

area. Ad responders were much more likely to have leg complaints that were not truly cramps, and to have associated neurologic conditions that disqualified them. We were very careful in screening out anyone who did not appear to have typical rest cramps, and we believe our results can be generalized to both a primary care and referral geriatric population.

Conceivably, we could have missed a meaningful reduction in cramps because of the slow equilibration of Mg within different tissue compartments (17) preventing adequate Mg replacement during the 5 days of infusions. However, the mean urinary Mg excretion rose from 17.5 mmol on day 1 to 20.2 mmol on day 5 with the percentage of those with greater than 15% retention falling from 48% (11/23) day 1 to 10% (2/21) day 5—that is consistent with adequate replacement. Additionally, both human studies of experimental Mg deficiency and case reports of muscle cramping in established Mg deficiency have all shown resolution of cramps following infusions of substantially less Mg than the 100-mmol total Mg infused in this study (18–20).

It is possible that a clinically distinct subset of crampers (eg, nonusers of oral Mg with very high cramp rates) can be defined that might still benefit from Mg, but studies with larger numbers of those subsets would be needed to determine benefit. If a true reduction in rest cramp frequency can be attributed to Mg supplementation in an older adult population, it would appear to be restricted either to a minority subgroup or, if the majority benefit, to a relatively small magnitude of effect.

Conclusions

Although oral Mg has demonstrated efficacy only in the setting of pregnancy associated rest cramps, it is marketed over-the-counter worldwide to the elderly—who constitute the majority of rest cramp sufferers. We have found no benefit to Mg therapy in older adults despite a highly reliable (IV) delivery method and have additionally shown that treatment response does not vary with the degree of Mg retention. Collectively, these findings suggest that Mg therapy is unlikely to be beneficial for cramp prophylaxis in a geriatric population.

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