Magnesium for the Treatment of Nocturnal Leg Cramps
A Crossover Randomized Trial

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BACKGROUND. Nocturnal leg cramps are a common health problem in the ambulatory setting. Our objective was to evaluate the efficacy of magnesium in the treatment of nocturnal leg cramps.

METHODS. Our study was a crossover randomized double-blind placebo-controlled trial. We included patients from a large university-based ambulatory clinic in Buenos Aires, Argentina, with at least 6 cramps during the previous month. A total of 93 subjects took part in a 4-week washout period with placebo. Those who were still eligible (n = 45) were randomized to receive either (1) an oral dose of 900 mg magnesium citrate twice daily for 1 month, followed by a matching placebo for 1 month, or (2) the placebo first, followed by magnesium. Both groups had a 4-week washout period with placebo between each treatment month. Forty-two patients completed the 4-month study. The main outcome was the number of nocturnal leg cramps, and the secondary outcomes were duration, severity, and sleep disorders caused by those cramps.

RESULTS. There were no significant differences between magnesium and placebo in any of the evaluated outcomes. The mean number of cramps was 11.1 (standard deviation [SD] ± 7.3) for placebo versus 11.8 (SD ± 7.6) for magnesium (P = .59). We observed a significant period-effect bias: All patients improved over time regardless of the treatment sequence they received.

CONCLUSIONS. Magnesium was not effective for the treatment of nocturnal leg cramps. The period-effect bias probably occurred because of a combination of the natural history of this condition, a regression to the mean, and a true placebo effect.

KEY WORDS. Magnesium, muscle cramp, clinical trials. *(J Fam Pract 1999; 48:868-871)*

Nocturnal leg cramps are a common health problem. The elderly are often affected; in one survey, 70% of the people older than 50 years had experienced at least one cramp in their lives.[1] Different treatments have been proposed to relieve nocturnal leg cramps, including stretching, massage, or walking,[2] and many pharmacologic interventions have been suggested, such as diphenhidranymine, verapamil,[3] vitamin E,[4,5] or quinine sulfate.[6-10]

Quinine sulfate has been prescribed for decades for the treatment of nocturnal leg cramps, but clinical trials have only recently been performed. This is the only drug that has shown efficacy for this problem.[3,6,7,9,21] Given the risks of serious side effects, this treatment has to be carefully evaluated to weigh the benefits against potential risks, such as cinchonism (nausea, vomiting, tinnitus, and deafness),[11] thrombocytopenia,[12] and visual impairment.[13] Magnesium plays a central role in metabolism and muscle function by participating in many of the biochemical reactions that take place in the body, particularly in those processes involving the formation and use of adenosin triphosphate (ATP).[14] Approximately two thirds of all enzymatic reactions in the body requiring metals as cofactors and all enzymatic reactions that involve ATP require magnesium.[15]

In pharmacologic doses, magnesium has a curariform action on the neuromuscular junction. It interferes with the release of acetylcholine from motor nerve terminals. Magnesium depletion leads to increased neuronal excitability and enhanced neuromuscular transmission[16] with symptoms that include muscle tremor, ataxia, tetany, and cramps.[17]

Although magnesium therapy has shown positive results for the treatment of nocturnal leg cramps in pregnant women,[18] the elderly,[19] and patients with type 1 diabetes,[20] only the study performed on pregnant women was a double-blind randomized controlled clinical trial. Despite the lack of strong evidence, the use of magnesium salts to relieve nocturnal leg cramps is a common practice in some countries in Europe and Latin America. In addition, magnesium is a safe and affordable drug.

METHODS

We instructed family physicians at a large university-based ambulatory clinic to refer patients with nocturnal

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leg cramps for admission to the study. To increase recruitment, we delivered information about this study to all patients visiting the clinic.

We conducted a double-blind placebo-controlled crossover randomized trial. Cramps were defined as painful involuntary skeletal muscle contractions that occurred in the thigh, foot, or lower part of the leg when the patient was in bed or resting.

The entry criteria were: men and women presenting with 6 or more cramps in the previous month; experiencing the same number of cramps after a 4-week of washout period with placebo; aged older than 18 years; normal neurologic examination results of both legs; and a signed informed consent form. The exclusion criteria were: alcohol abuse; psychiatric diseases; terminal disease; type 1 diabetes mellitus; renal failure; pregnancy; arteriopathy or neuropathy of one or both legs; hypocalcemia, hyponatremia, or hypokalemia; not speaking Spanish or not having a telephone; inability to stop taking medications that contained magnesium; and low compliance or having less than 6 cramps after the first washout.

Patients who fit the entry criteria were given a physical examination and a questionnaire about physical activity, tobacco or illegal drug use, occupation, and leg cramps characteristics. To rule out other causes of cramps, we measured serum and urine magnesium, calcium, electrolytes, creatinine, glycemia, albumin, and acid-base status. Magnesuria was measured at the end of each period to evaluate compliance.

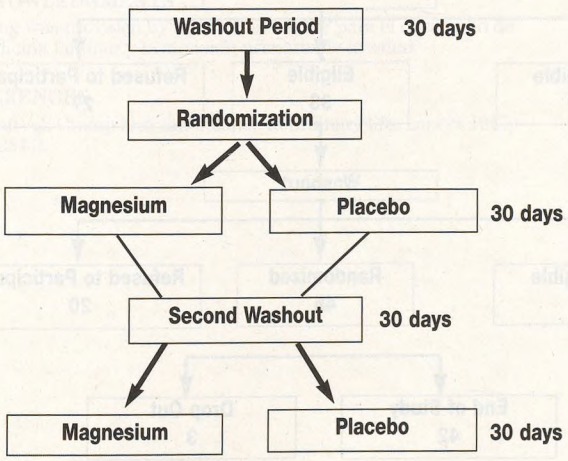
Randomization

Patients were enrolled consecutively as they met the entry criteria. We started with a first washout period of 4 weeks. During this period, patients stopped any treatment with magnesium and started taking placebo while recording the number of cramps, their severity and duration, and any sleep disturbance in a daily log. At the end of this period, those who still reported 6 or more cramps were randomized.

Patients randomly received magnesium or placebo in the first drug period, switching to the one not previously used in the second drug period. A second washout period was scheduled between the 2 drug periods (Figure 1). Each pill contained 900 mg of magnesium citrate or matched placebo (same appearance and taste). Patients were instructed to take one pill in the morning and another at bedtime. We determined the amount of magnesium citrate from recommended maximum doses. All the pills were obtained in the same pharmacy and were packaged and dispensed in the same place. Each packet contained 63 pills (56 pills for the 28 days of treatment and 7 to assess compliance) and was labeled with 3 letters: A and B for the drug periods and P for the washout periods. The codes were inside a sealed envelope opened at the end of the analysis.

FIGURE 1

Our Crossover Study Design.



Outcome Measures

The primary outcome measure was the number of muscle cramps, and the secondary outcomes were the duration and severity of cramps and any sleeping disturbance caused by the cramps.

Each patient had a daily log for each period, in which they recorded the outcome measures. Patients were instructed to record in the log each morning. The number and the severity of cramps were recorded on an analog numerical scale, and their duration was measured in intervals of 0 to 5 minutes, 5 to10 minutes, 10 to 30 minutes, and more than 30 minutes. For the evaluation of sleep disturbance, we used a numerical scale of 1 to 10, where 0 was "no sleep disturbance" and 10 was "could not sleep because of the cramps."

All patients were contacted by telephone each week to assess compliance and to detect any problem with the treatment. Once a month, subjects were contacted personally to receive the new medication and the new daily log. Patients' compliance with the treatment was evaluated by counting the number of pills that were left in the package, by phone calls to the participants, and by measurement of urinary magnesium at the end of each period.

Statistical Analysis

We analyzed the primary outcome measures using the Wilcoxon test and the Student t test for dependent variables. We estimated that a sample size of 42 patients was necessary to obtain a difference of at least 25% in the number of cramps between the 2 groups (α = 0.05; power = 90%; expected dropout rate = 15%).

TABLE 1

Patients' Characteristics (n = 45)

Characteristic	Mean
Age, years	61.6*
	Percent
Women	73
Exercise	52
Education†	69
Married	52
No known disease	43
Hypertension	43
Varicose veins	19
Type 2 diabetes	5
Smoking	24
Diuretic use	10

*Range = 28 to 87 years.
†More than 7 years.

RESULTS

The baseline characteristics of randomized patients are listed in Table 1, and we show the sampling and eligibility process in Figure 2. From March 1996 to March 1997, we interviewed 309 patients. Only 93 met the entry criteria. After the first washout, we randomized 45 eligible patients, and 42 patients finished the study. None of the randomized patients had hypomagnesemia, hyponatremia, or hypokalemia in the initial laboratory determinations.

Twenty patients refused to participate after the first washout period because of diarrhea (4), family problems (5), abdominal pain (5), lack of time (2), complaint of weight gain (2), major surgery (1), and change of medical insurance (1). Twenty-eight patients were not eligible after the first washout period because they did not meet the criteria to continue. Three patients dropped out after randomization because of lack of time (2) or a change of medical insurance (1).

All studied end points are showed in Table 2. The mean number of cramps with placebo was 11.1 (SD ± 7.3) and with magnesium was 11.8 (SD ± 7.6). No statistical differences between placebo and magnesium were found.

We observed no differences in the percentage of common side effects (diarrhea, nausea, vomiting) between magnesium (10.7%) and placebo (10.1%).

We observed a significant decrease in the number of cramps between the first and second treatment months (Table 3). This was probably because of a period-effect bias, because regardless of the treatment they received, the patients in the second round of treatment had fewer cramps than those in the first round.

DISCUSSION

Magnesium is commonly prescribed for treating nocturnal leg cramps in many Latin American and some European countries. Only one previous randomized double-blind controlled trial[20] had been conducted to evaluate magnesium efficacy, and that study was performed on pregnant women. In that study, patients improved with magnesium treatment (a combination of citrate and lactate). We designed our study to evaluate if magnesium was effective in men and nonpregnant women. Our study was a controlled trial with a randomized crossover design similar to the study by Connolly and colleagues.[21] This design allowed us to control for each patient's personal confounding bias (every patient is his own control), but leaves the chance for a period effect. Although magnesium was not effective in relieving nocturnal leg cramps, we observed a period-effect bias, as all patients improved over time, regardless of the sequence of treatment they received. This finding was statistically significant. The effect may be explained by a combination of: (1) the nat-

FIGURE 2

The Sampling and Elegibility Process.

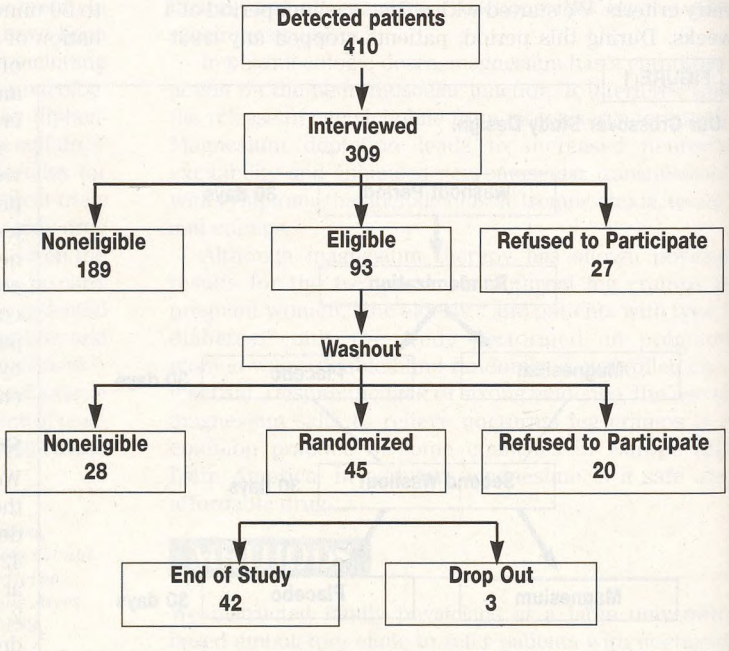


TABLE 2

Outcomes Results, Mean and Median

Outcome	Placebo		Magnesium		P
	Mean ± SD	Median	Mean ± SD	Median	
Number of cramps	11.1 ± 7.3	5	11.8 ± 7.6	4.5	.59
Severity	2.07 ± 2	1.25	2.01 ± 1.73	1.41	.84
Duration*	2.2 ± 0.72	2	2.5 ± 0.69	2	.44
Sleep disturbance	1.47 ± 2.35	0	1.89 ± 2.62	0	.39

SD denotes standard deviation.
*In minutes.

TABLE 3

Evaluation of the Period Effect

Outcome	1st Treatment Period		2nd Treatment Period		P
	Mean	Median	Mean	Median	
Number of cramps	13.02	6.5	9.9	4	.027
Severity	2.25	1.2	1.83	1.5	.16
Duration*	2.0	1	1.8	1	.58
Sleep disturbance	2.1	0.5	1.25	0	.07

*In minutes.

ural variability of the symptom, (2) regression to the mean, and (3) a true placebo effect.

CONCLUSIONS

We cannot explain why magnesium was effective in pregnant women,[18] but the physiopathology may be different in this subset of women. On the basis of our findings, we do not support the use of magnesium citrate for the treatment of nocturnal leg cramps.

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