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Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Nocturnal leg cramps are common and distressing. The only treatment of proven effectiveness is quinine, but this has a number of side effects. Magnesium salts have been shown to reduce leg cramp distress in pregnancy. This study tests whether magnesium citrate is effective in the treatment of leg cramps in non-pregnant individuals by conducting in a randomised, double-blind, cross-over placebo-controlled trial.

Material/Methods: Volunteers suffering regular leg cramps were recruited. Magnesium citrate equivalent to 300 mg magnesium and matching placebo were given for 6 weeks each. The number of cramps recorded in the cramp diary during the final 4 weeks of magnesium and placebo treatment, severity and duration of cramps and the participants' subjective assessment of effectiveness were analysed.

Results: In subjects who started with placebo (n=29) the median (95% CI) number of cramps was 9 (6-17) on placebo and 5 (4-8) on magnesium. For the group starting with magnesium (n=17) the median no of cramps was 9 (5-13) on magnesium and 8 (4-14) on placebo. There was no significant carry-over effect (p=0.88), but a highly significant period effect (p=0.008). There was a trend towards less cramps on magnesium (p=0.07). There was no difference in cramp severity and duration between the groups. Significantly more subjects thought that the treatment had helped after magnesium than after placebo 36 (78%) and 25 (54%) respectively, (p=0.03). Diarrhoea was recorded as a side effect of magnesium.

Conclusion: The results suggest that magnesium may be effective in treatment of nocturnal leg cramps. Further evaluation is recommended.

key words: **muscle cramps • magnesium • magnesium citrate • trace elements**

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BACKGROUND

Chronic, persistent leg cramps are a common and distressing problem. Their prevalence increases with age, affecting 30% of over sixty year olds and 50% over the age of eighty [1,2]. Cramps may be precipitated by changes in water and electrolyte homoeostasis or by drugs such as diuretics, laxatives, beta2-agonists, cimetidine, and phenothiazines.

Correction of the underlying cause is often the only treatment required [3,4]. If this fails, the only drug of proven benefit is quinine sulphate. A meta-analysis of published and unpublished trials including 659 patients showed that quinine treatment was associated with a reduction of 3.6 (95% CI 2.15–5.05) cramps in a 4-week period compared with placebo [5]. Even at therapeutic doses side effects such as tinnitus, headache, nausea, visual disturbances, photosensitivity, hyperglycaemia and cardiac arrhythmias can occur, especially in patients with impaired renal function or on multiple drug treatments [6].

Magnesium salts have been shown to be effective in the treatment of pregnancy-associated leg cramps [7]. Apart from diarrhoea, which can be avoided by building up the dose gradually, and nausea, there are no known side effects with oral treatment at therapeutic dosage in patients with normal renal function [8–11].

The purpose of this study is to assess whether magnesium citrate is effective in the treatment of chronic persistent leg cramps in non-pregnant individuals.

MATERIAL AND METHODS

Subjects were recruited by advertisements in local papers, in pharmacies and at bus stops. A leg cramp was defined as a painful contraction of any muscle group in the leg, which was either precipitated by certain movements, aborted by procedures involving stretch of the affected muscle or which was associated with a palpable hardening of the muscle. The cramp had to have a defined onset and successive improvement. This definition was used to distinguish leg cramps form other causes of leg discomfort such as restless leg syndrome, arthritis or ischaemic pain. To qualify for trial inclusion, subjects had to have a stable pattern of two or more cramps per week for three months. Subjects with unstable medical conditions known to affect cramp frequency, renal failure, pregnancy and terminal illness were excluded. Patients taking medications which could affect cramp frequency such as quinine, diuretics, laxatives or beta-agonists were only included if their drug treatment had not been changed within 4 weeks of trial entry. Patients on quinine were only enrolled if in spite of this treatment they fitted the above mentioned entry criteria. They were advised to continue their quinine tablets during the trial.

The protocol was approved by the local Research Ethics Committee. Written informed consent was obtained from all participants.

Treatment allocation was randomised, double-blind, placebo-controlled and consisted of magnesium 300 mg (12 mmol) given as sachets of magnesium citrate (trimagnesium dicitrate 1830 mg) dissolved in water or matching placebo each night with cross-over after six weeks.

Randomisation was performed in blocks of 10 by Protina GMBH, Germany. The randomisation code was not known to the investigators who gave out the sachets. The code remained concealed from everyone except the pharmacist who prepared the sachets and, for safety purposes, the hospital pharmacy, until data collection was complete.

Each individual was seen three times by the investigator: at enrolment, at the end of trial phase 1 and at the end of trial phase 2. At the end of each treatment phase leg cramps (see below), magnesium levels, adverse events and changes in drug treatment were recorded. Left-over treatment sachets were collected and counted. The definition of a leg cramp was discussed with each subject at trial entry. Every cramp was recorded in a diary with date, time, duration (short, medium, long) and severity (mild, moderate, severe). In addition volunteers were asked after each phase whether they felt that the treatment was effective.

To establish potential longer term changes in cramp frequency all participants were sent questionnaires three months after completion of the trial medication enquiring how often they were then then disturbed at night by cramps, and whether this was the same, better or worse than before trial entry.

Outcome indicators

The primary outcome of the trial was the difference in the number of cramps between the two treatments during the final 4 weeks of each treatment period (to allow for run-in and/or wash-out). Further outcomes were the severity and duration of cramps and the subjects' opinion whether the treatment was effective. A sample size of 58 was calculated to detect a 25% difference in cramp frequency with 80% power at a significance level of $p<0.05$.

Statistical analysis

The main outcome data were tested for carry-over effects, treatment effects and period effects [12]. Non-parametric tests (Mann-Whitney U test) were used for non-normal data. Results are given as medians with 95% confidence intervals (CI). In figure 1 the number of cramps per participant is given as the mean because this enables comparisons to be made with other published material in this area, which is usually presented as means [5,13]. Approximately normally distributed data are described as means and standard deviations. Other statistical tests used include Student's t-tests for continuous normally distributed data and Chi Square tests for categorical data. are stated with the results. The computer program used for data analysis was MINITAB Data Analysis

Table 1. Reasons for trial abandonment by the participant.

Reasons for discontinuation of the trial drug	Drop out on placebo only	Drop out on magnesium only	Participants who started and stopped both
Diarrhoea	1	4	1
Abdominal pains, indigestion	1	1	1
Constipation	1	0	0
Rash	1	0	0
Non-specifically unwell	1	0	0
Sore throat	1	0	0
Intercurrent illness	2 ('flu', stroke)	0	0
Arms and legs jumpy	1	0	0
No reason given	1	2	0
Reasons unrelated to trial drugs	1 (diary lost)	1 (poor memory) 1 (routine operation)	0
Lack of therapeutic effect	2	0	0

Some of the participants had more than one reason for trial abandonment.

Table 2. Baseline characteristics of subjects who completed the study.

	Placebo start (n=29)	Magnesium start (n=17)
Age in years (mean, SD)	64±10	61±11
Male sex	15 (52%)	6 (35%)
Cramps per week prior to study entry (mean, SD)	4.1±1.9	3.8±1.5
Magnesium [mmol/l] (mean, SD)	0.80±0.07	0.82±0.05
Calcium [mmol/l] (mean, SD)	2.3±0.1	2.3±0.1
Urea [mmol/l] (mean, SD)	6.1±1.6	6.1±1.9
Creatinine [mmol/l] (mean, SD)	90±20	90±22
Number of prescribed drugs (mean, SD)	3.7±2.6	3.2±2.5
Taking quinine	21%	35%
Taking a diuretic	14%	12%
Taking beta$_2$ antagonists	28%	35%
Taking laxatives	10%	12%
Taking cimetidine	0%	0%
Peripheral vascular disease	17%	6%
Varicose veins	45%	41%
Ankle oedema	7%	6%
Arthritis	62%	59%
Smokers	24%	29%
≥28 units alcohol per week	10%	6%
≥6 cups of coffee/mugs of tea per day	45%	41%

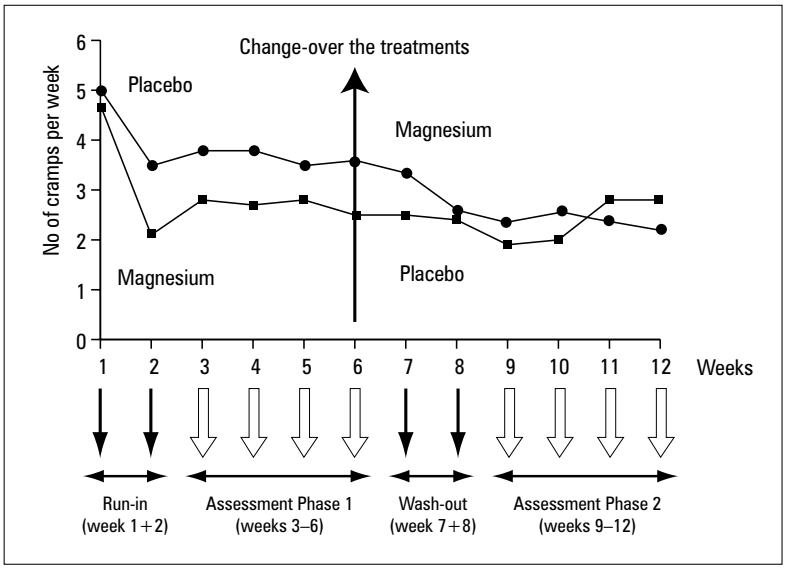

Figure 1. Time course of leg cramps over the 12 week trial period. This figure shows the mean number of cramps per week for each of the 12 weeks of the trial for subjects starting with magnesium or placebo. In both groups there was a sharp decline in cramp frequency during the 2 week run-in period at the start of the first phase. Thereafter cramp counts remained steady to the end of phase 1. In phase 2 cramps fell further in participants on magnesium. In subjects taking placebo in phase 2 there appeared to be a rise of cramps towards the end of phase 2.

Software. For testing differences where data are sparse, a specialist program called Stat Xact Turbo was used.

RESULTS

Of 94 volunteers interested in the study 73 matched the inclusion criteria and were recruited. Five abandoned the trial without starting the treatment. Of the remaining 68, 21 dropped out before study completion (11 on magnesium, 8 on placebo and 2 started and abandoned both). Reasons for trial abandonment are shown in table 1. Forty-seven participants completed the study. One subject was excluded retrospectively because of a routine hip operation. Baseline characteristics of the 46 subjects included in the main analysis are shown in table 2.

Out of 49 magnesium/placebo sachets supplied for each 6 week treatment period (7 sachets more than required), a mean of 8.3 SD 3.1 were returned after the placebo and 7.8 SD 3.8 after the magnesium phase (p=0.4 by Student's t-test).

There was a small increase in plasma magnesium on active treatment (0.82 SD 0.08 mmol/l versus 0.80 SD 0.06 mmol/l after placebo p=0.005 by Student's t-test). The highest magnesium levels were 1.0 mmol/l after magnesium and 0.93 mmol/l after placebo respectively.

The mean number of cramps per week during the 12 weeks of the trial for the two treatment groups is shown in figure 1. During each of the 4 weeks observation periods there were a median (95% CI) of 9 (5–13) cramps in phase 1 (placebo) and 5 (4–8) cramps in phase 2 (magnesium) in participants starting on placebo (n=29). In the group starting with magnesium (n=17) there was a median (95% CI) of 9 (5–13) cramps in phase 1 (magnesium) and 8 (4–14) cramps in phase 2 (placebo). The median of the paired differences (placebo minus magnesium) was 3 for individuals starting on placebo and 0 for those starting on active treatment. Overall there were less cramps during the magnesium phases than during placebo, but the difference was not statistically significant (p=0.07). There was a strong period effect (p=0.008) with more cramps in the first treatment phase than in the second irrespective of which treatment was given. A carry-over effect could not be demonstrated (p=0.88). Magnesium did not reduce the severity or the duration of individual cramps. To exclude any bias, results were also analysed on an intention to treat basis for all participants who had completed both phases of the study (n=47). Inclusion of the retrospectively excluded subject reduced the p-value for the treatment effect to 0.05.

Analysis of phase 1 data only excludes any possible carry-over effect and yields similar results. The results are robust and not changed by the type of analysis performed.

Thirty-six (78%) of the subjects thought that the treatment had helped after the magnesium phase and 25 (54%) after the placebo phase (p=0.03, Fisher's Exact Test). As shown in table 1 two volunteers abandoned the study because of ineffectiveness of the treatment while on placebo. There were no study discontinuations for ineffectiveness in the magnesium group.

The main side effect was diarrhoea (14 subjects (30%) on magnesium and 8 (17%) on placebo, p=0.1) with new onset diarrhoea in 12 (26%) and 5 (11%) respectively (p=0.047). Constipation was reported in 6 subjects (13%) on magnesium and 11 (24%) on placebo (p=0.2). Other side effects were nausea, indigestion or flatulence 2 (4%) on magnesium and 4 (9%) on placebo, p=0.6), skin peeling (1 on magnesium), bruising (1 on placebo) and headaches (1 on placebo). No other side effects were reported. All p-values in this section were calculated using Chi Square Tests (Stat Xact Turbo).

Three-month follow-up

Forty subjects returned the questionnaires, 39 completed all the questions. The median number of nights disturbed by cramp over 4 weeks was reduced from 16 before trial enrolment to 4 three months after completion of the trial. The median of the paired difference (before-after) was 8 (95% CI 5-10). Sixty-seven percent of respondents had less cramps, 39% had no cramps and 3% reported an increase. Cramps were considered to be 'better' in 78%, 'the same' in 19% and 'worse' in 3% (p<0.0001 Chi Square Test).

DISCUSSION

In this study significantly more participants reported that the treatment had helped while on magnesium than on placebo. This subjective impression was supported by cramp diaries, which showed a trend towards less cramps with magnesium than with placebo (p=0.07). There is one previous study of magnesium citrate for the treatment of leg cramps [13]. Trial design, study size, and magnesium dose were similar to that in our study, but there was no treatment effect with difference in the incidence (11.1 SD 7.3 cramps on magnesium and 11.8 SD 7.6 cramps on placebo, p=0.59). Treatment periods in that study were, however, shorter than ours, and no information was available on magnesium levels or compliance with treatment.

Differences between magnesium and placebo may have been reduced by carry-over effects. Even with a two-week wash-out period continued therapeutic effect after cross-over is a theoretical possibility, since magnesium is stored intracellularly and by absorption to bone, and thus eliminated slowly. This is supported by the rise of leg cramps in weeks 11 and 12 in subjects receiving magnesium in the first treatment phase (figure 1), but formal statistical tests did not demonstrate evidence of carry- over. This may have been due to the non-linear trend in cramp frequency and the study size. If the run-in and wash-out periods were slower than expected, as we hypothesise, then differences between the two treatment groups would be more significant if the run-in and wash-out periods were extended to 4 weeks. We therefore did a reanalysis of the data using only the last two weeks of each treatment phase. The median number of cramps for this 2-week period was 3 (95% CI 3-7) for patients during the magnesium phase and 5 (95% CI 5-10) for patients during the placebo phase (p=0.003). This supports our contention that the run-in and wash-out periods may be longer than expected when the trial was designed, but it is important not to overemphasise this result, since this was not one of the pre-specified end points and the analysis was retrospective and post hoc.

A higher dose of magnesium might have proved more effective. However, since the incidence of leg cramps increases with age, volunteers were expected to be older adults, and thus the lower end of the dosage range recommended by the manufacturer (300–600 mg/day) was chosen for this trial. Compliance with treatment was good, and the increase in plasma magnesium levels on active treatment shows that a significant amount of the drug was absorbed. Only one per cent of total body magnesium is extracellular [14], and a small increase in plasma levels therefore reflects larger changes in total body stores.

Magnesium citrate was well tolerated. Apart from diarrhoea, there were few side effects. As would be expected, fewer participants complained of constipation on magnesium than on placebo.

A further interesting outcome of this trial is that 39% of study participants reported no cramps within 3 months

of discontinuation of the trial medication. It is unlikely that such an effect is due to persistent changes of body magnesium stores achieved by the trial medication. Statistical analysis of cramp frequency within the 12 weeks of the trial has shown that the period effect was highly significant, with a rapid fall in the number of cramps during the first two weeks of the study, irrespective of treatment allocation. In their study of the effect of quinine in the treatment of leg cramps, Jansen et al have shown a similar reduction of cramp frequency with time [15]. While a placebo effect cannot be excluded, another conceivable reason for the reduction in cramp frequency with time is that, although a stable pattern of cramps was a major inclusion criterion for the trial, volunteers are more likely to enrol into a study at a time when their leg cramps are particularly troublesome, which means that with the passage of time cramps frequency fall to their previous baseline with or without treatment [16].

CONCLUSIONS

The results of this study suggest that magnesium may be effective in the treatment of leg cramps outside pregnancy. Our findings should be confirmed in a larger study without cross-over design to avoid confounding by period and carry over effects. Furthermore, subjects enrolled in a study of leg cramps appear to reap benefits from volunteering well beyond the therapeutic effect of the drugs.

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