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Effect of Magnesium Oxide Supplementation on Nocturnal Leg Cramps
A Randomized Clinical Trial

Noga Roguin Maor, MD; Mordechai Alperin, MD; Elena Shturman, MD; Hassan Khairaldeen, MD; Moran Friedman, MD; Khaled Karkabi, MD; Uzi Milman, MD

IMPORTANCE Magnesium supplements are widely marketed for prophylaxis of nocturnal leg cramps (NLC) despite no evidence of significant benefit.

OBJECTIVE To determine whether magnesium oxide is better than placebo for NLC prophylaxis.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled clinical trial of 2 weeks eligibility screening followed by 4 weeks of treatment was conducted in northern Israel, from February to October 2013. An intention-to-treat data analysis was performed from March 22, 2014, to April 17, 2016. We used a volunteer sample of community-dwelling individuals experiencing NLC, 21 years or older, with 4 or more documented episodes of NLC during 2 weeks of screening.

INTERVENTIONS Capsules containing either magnesium oxide or a similar-looking placebo to be taken orally, once daily at bedtime for a period of 4 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the difference in the mean number of NLC per week between the screening and treatment phases. Secondary outcomes included severity and duration of NLC, quality of life, and quality of sleep.

RESULTS Of the 166 volunteers, 72 (43%) were excluded, of whom 15 declined to participate and 57 did not meet the inclusion criteria. Of the 94 individuals (39% male; mean [SD] age, 64.9 [11.1] years) randomly assigned to magnesium oxide (48) or placebo (46), 6 did not complete the study protocol (3 in each group). Mean (SD) change of NLC was −3.41 (4.05) (from 7.84 [5.68] to 4.44 [5.66]) and −3.03 (4.53) (from 8.51 [5.20] to 5.48 [4.93]) per week in the magnesium oxide and placebo groups, respectively, a difference between groups of 0.38 (0.48) NLC per week (P = .67 in an intention-to-treat analysis). There were no between-group differences in the severity and duration of NLC, quality of life, or quality of sleep.

CONCLUSIONS AND RELEVANCE Oral magnesium oxide was not superior to placebo for older adults experiencing NLC. The decrease in the mean number of NLC per week, from the screening to the treatment phase in both groups, is probably a placebo effect that may explain the wide use of magnesium for NLC.

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Supplemental content

Author Affiliations: Clinical Research Unit, Clalit Health Services, Haifa and Western Galilee District, Israel (Roguin Maor, Alperin, Shturman, Khairaldeen, Friedman, Karkabi, Milman); Department of Family Medicine, Technion–Israel Institute of Technology, Haifa, Israel (Roguin Maor, Alperin, Shturman, Khairaldeen, Friedman, Karkabi, Milman).

Corresponding Author: Uzi Milman, MD, Clinical Research Unit, Clalit Health Services, PO Box 134, Shlomi, Israel 2283202 (uzimy@netvision.net).

Nocturnal leg cramps (NLC) are painful, involuntary contractions of muscles occurring at rest, mostly at night, and causing a palpable knot in the muscle.[1] Up to 60% of adults report having NLC.[2] In a survey of 490 veterans who were asked about leg symptoms, 276 (56%) reported experiencing NLC, among them 67 (24%) having cramps 1 to 4 times a week.[3] Frequent NLC may cause significant distress and nighttime disturbance.[4,5] Most NLC occurring in adults seem to be idiopathic. Potential predisposing factors include hemodialysis, electrolyte imbalance, and neurologic, endocrine, metabolic, vascular, medication-related, toxic, and congenital conditions.[4] Quinine is the only treatment with moderate-quality evidence of significantly reducing the frequency and intensity of muscle cramps.[6] However, the US Food and Drug Administration issued a warning in 2010 against the use of quinine for treating NLC due to the risk of serious and life-threatening reactions and its unfavorable risk-to-benefit ratio.[7,8]

Magnesium is a commonly used remediation for NLC, particularly in Latin America and Europe.[4] Its effectiveness in treating NLC was first demonstrated in a double-blind, randomized, placebo-controlled study of pregnant women.[9] Subsequent trials—2 crossover studies[10,11] and a placebo-controlled trial of magnesium infusion[12]—did not show significant benefit by magnesium citrate supplements for NLC in older adults.[13] However, none of the published studies investigated oral magnesium oxide. Magnesium is an intracellular cation, and its serum concentrations (only about 1% of total body magnesium) may not accurately mirror magnesium status.[14] A recent study investigated the effect of supplemental oral magnesium oxide, vs magnesium citrate, on intracellular magnesium levels in healthy subjects.[15] Oral magnesium oxide significantly increased intracellular magnesium levels compared with magnesium citrate. On the basis of this observation, we initiated a prospective clinical trial to test the hypothesis that magnesium oxide supplementation may reduce the frequency and severity of NLC and subsequently improve quality of life and quality of sleep of older adults.

Key Points

Question Is magnesium oxide significantly more effective than placebo in reducing the frequency of nocturnal leg cramps?

Findings In this randomized clinical trial that included 94 adults, the mean number of nocturnal leg cramps per week decreased significantly in both the magnesium oxide and placebo groups, with no significant difference between the groups.

Meaning This trial suggests that magnesium oxide is not significantly better than placebo for alleviating nocturnal leg cramps.

Methods

Design Overview

This randomized, double-blind, placebo-controlled trial investigated the effect of magnesium oxide supplementation on NLC. Initially, participants underwent 2 weeks of eligibility screening without treatment, during which they documented all episodes of NLC, followed by 4 weeks of treatment. The primary end point was the effect of magnesium oxide supplementation on the frequency of NLC. Secondary objectives were severity and duration of NLC, quality of sleep, and quality of life.

Setting and Participants

The study took place at community clinics of Clalit Health Services (CHS) in northern Israel, from February to October 2013. We used advertisements in CHS clinics, the local media, and pharmacies to invite individuals suffering from NLC to participate in the trial. Initially, study stuff interviewed interested patients who had called to determine their eligibility. We informed respondents who were currently taking magnesium supplements and expressed interest in participating that they could enroll if they agreed to stop taking the supplements at least 10 days before enrollment. Thereafter, at an in-person, baseline evaluation visit we provided a comprehensive description of the study rationale and process. After confirming that each candidate experienced NLC, described as a painful, involuntary contraction of muscles occurring at rest, mostly at night, and causing a palpable knot in the muscle, the participant signed an informed consent.

Inclusion criteria were community-dwelling individuals, age older than 21 years, 4 or more documented episodes of NLC during the 2-week screening phase, and insurance with CHS. Exclusion criteria were pregnancy, current treatment with quinine, concurrent intake of a magnesium supplement, renal failure (defined as serum creatinine level >2 mg/dL [to convert to micromoles per liter, multiply by 88.4]), and major neurological diseases such as amyotrophic lateral sclerosis, multiple sclerosis, paraplegia, or quadriplegia.

Randomization and Intervention

We randomly allocated participants in a 1:1 ratio to receive either magnesium oxide (inorganic granular magnesium complex, composed of magnesium oxide and magnesium oxide monohydrate 865 mg, providing 520 mg of free elemental Mg^{2+} [magnesium]) or a similar-looking placebo to be taken orally, once daily at bedtime for a period of 4 weeks.

Identical-looking capsules, containing either magnesium oxide or placebo, were prepacked in identical bottles and consecutively numbered prior to the study initiation. We generated a randomization schedule, derived from a computer-generated randomization procedure of numbers from 1 to 220, in blocks of 10. The randomization scheme was generated by using the website Randomization.com (http://www.randomization.com). We assigned eligible participants sequential numbers according to the randomization schedule, and they received the corresponding numbered bottle of capsules. Both patients and researchers were blind to the treatment allocation. The manufacturer provided the study participants reimbursement of travel expenses (of up to the equivalent of $50) that was given to each participant at the final meeting after retrieving the medication bottle.

Outcomes and Follow-up

The primary outcome was the mean difference in effect of magnesium oxide, compared with placebo, on the frequency of NLC. Secondary objectives were severity and duration of NLC, quality of sleep, and quality of life.

We measured the primary outcome by comparing the change in the mean number of episodes of NLC per week, during the 2-week screening and the 4-week treatment phases, between the magnesium oxide and placebo groups. Secondary outcomes were changes in the severity and duration of NLC, in quality of life, and in quality of sleep. We collected patients' demographic and clinical characteristics at their baseline visit through self-report questionnaires.

Outcome Measurement Tools

We measured the number, severity, and duration of NLC as recorded daily by the study participants in a designated, structured sleep diary. The Nocturnal Cramps Sleep Diary (NCSD) (eAppendix in Supplement 1) is a combined adaptation of the "assessment, Espie diary form,"[16] which is based mainly on Espie's book,[17(p17)] and the Two Week Sleep Diary,[18] designed for the purpose of the present study. Throughout this 6-week period, participating individuals documented daily all episodes of NLC in the NCSD. They reported every morning in the diary the frequency (ie, the absolute number), duration, and severity of NLC. The severity of pain experienced during NLC was recorded in the diary on a numbered scale of 0 to 10 (0 = no pain, 10 = intolerable pain). Participant assessed and reported the duration of each cramp in minutes.

The Short Form (36) Health Survey (SF-36) measured quality of life.[19] This 36-question survey yields an 8-scale profile of functional health and well-being, as well as psychometrically based physical and mental health summary measures and a preference-based health utility index. This generic measure has demonstrated effectiveness in surveys of general and specific populations, in comparing the relative burden of diseases and in differentiating the health benefits produced by a wide range of different treatments.[20] It has been validated in Hebrew.[21]

We used the Pittsburgh Sleep Quality Index (PSQI) to measure quality of sleep.[22] The PSQI is a standardized self-administered questionnaire that assesses subjective sleep quality over the previous month. The PSQI comprises 19 self-rated questions grouped into 7 component scores. Each score weighs equally on a 0 to 3 point scale. The 7 component scores are totaled to provide a global PSQI score. The global score ranges from 0 to 21. A global score of 5 or more indicates poor sleep quality: the higher the score, the worse the quality of sleep. The PSQI has been validated in Hebrew.[23] We measured quality of life and quality of sleep twice: at enrollment and within 1 week after the end of the treatment period of each participant.

Outcomes and Adherence Ascertainment

During the screening and treatment phases of the study (2 and 4 weeks, respectively), the study participants filled in the NCSD daily, at home. To increase adherence and proper monitoring and documentation of sleep and NLC events, a daily text message reminder was delivered every morning to each participant (all of them had a mobile telephone). Additionally, twice a week we made a telephone call to each study participant inquiring about possible adverse events and encouraging them to take the study treatment and to fill in the diary every evening and morning.

We intentionally placed 32 capsules in each medication bottle, 4 more than the needed 28 capsules for the 4 weeks of the intervention. On the final visit, we asked all participants to bring the study medication bottles, with the remaining capsules, and counted them. We instructed all participants to avoid consumption of vitamin and mineral supplements during the study.

Interim Analysis and Guidelines for Study Termination

The study protocol (Supplement 2) included a preplanned blinded interim analysis of efficacy or futility when outcome results were available for approximately half of the anticipated number of participants. We submitted this analysis to an appointed independent data reviewing and monitoring committee that reviewed the interim results. The committee's role was to monitor the primary outcome, ensure the safety of patients, make recommendations to continue or alter the study design, and determine the necessity of early termination of the trial due to efficacy, harm, or futility.

Ethical Issues

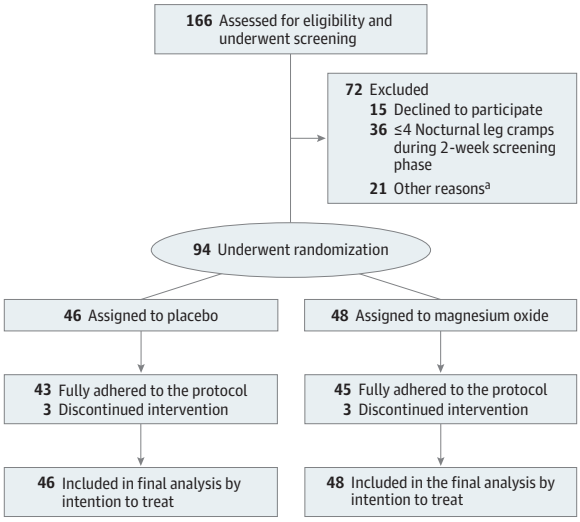
The study medication is a freely available, over-the-counter food supplement. We also recruited individuals who were taking magnesium supplements before enrollment if they wanted to participate and freely agreed to stop taking them. This was possible because they stopped taking the supplement at least 10 days before enrollment. The Community Independent Review Board of CHS approved the study. All participants provided written informed consent prior to any study procedure.

Statistical Analysis

We estimated that 110 participants would be needed in each group to achieve 80% power to detect a treatment difference at a 2-sided .05 significance level if the true difference between treatments is 1 (difference in mean change between treatment groups) NLC per week. This was based on the assumption, and the results reported by Roffe et al,[11] that the standard deviation of the mean number of NLC per week is 3.[24]

We performed all data analyses according to the intention-to-treat principle, and the analysis, data collection, and processing were blinded with respect to treatment group assignment. Randomized participants who did not complete the study were included in their assigned study groups for the primary analysis. We used multiple imputations from the screening values of each participating individual to replace missing values during the treatment phase. Treatment effects for primary and secondary outcome variables in the study were evaluated using a repeated-measure analysis, comparing the individual differences between treatment groups by treatment phase (interaction effect). Thus, we defined the trial outcome as the difference in the mean change from the

Figure 1. Study Flow Diagram



[a] Other reasons include incomplete documentation of nocturnal leg cramps during screening phase or failure to attend scheduled appointments,[14] serum creatinine level greater than 2 mg/dL,[3] concurrent illness,[3] and physicians' instructions.[1]

SI conversion factor: To convert serum creatinine level to micromoles per liter, multiply by 88.4.

screening to the treatment phase in the number of NLC between the treatment groups, that is, magnesium oxide vs placebo. We performed a similar comparison with the data on severity and duration of NLC. We measured quality of life and quality of sleep twice: at enrollment and within 1 week after the end of the treatment period of each participant.

We used the Bonferroni approach[25] as an adjustment for multiple comparisons for the SF-36 subscale measures, resulting in a critical *P* value of .006 (according to the formula of desired *P* value [.05] divided by the number of comparisons [8]). Additionally, we conducted a 2-way (group over time) trend analysis for the primary outcome, examining for possible trends in treatment effects across time.

We compared baseline characteristics between the groups using the χ^2 test for categorical variables and the *t* test for continuous variables. Models evaluating possible modification effects of baseline characteristics on outcomes were conducted by including terms of interactions between the 2 groups and by examining the effect of each of these variables on the study outcomes using 2-way analysis of covariance.

We conducted all analyses using SPSS software, version 21 (IBM SPSS Statistics for Windows). Both patients and researchers were blind to the treatment allocation throughout the study until the decision on early termination.

Results

From February through October 2013, 166 individuals responded to the advertisements and were screened for eligibility for the study. Of these 166 candidates, 94 (56.6%) individuals fulfilled the study's inclusion criteria and underwent randomization. The study protocol was completed fully by 88 (93.6%) of the randomized individuals (**Figure 1**). Baseline characteristics of the participating individuals were similar between the treatment groups (**Table 1**). The characteristics of those who completed the study protocol did not differ significantly from the characteristics of those who did not.

The mean numbers of NLC per week during the 2-week screening period were similar between the groups (**Table 2**). The mean (SD) number of NLC per week decreased significantly from the screening to the treatment phase, by 48.4% (41.2%) and 29.5% (64.8%) for the magnesium oxide and placebo groups, respectively ($P < .001$ for the change within each group). However, there was no statistically significant difference in the primary outcome of change in mean (SD) NLC frequency per week between the magnesium oxide and placebo groups: −3.41 (4.05) and −3.03 (4.53), respectively, a difference between the groups of −0.38 (0.48) NLC per week ($P = .67$). A sensitivity analysis to assess the possible effect of missing data yielded results that were essentially identical to those presented in Table 2. We observed similar results in the analysis of the secondary outcomes, as presented in Table 2. The effect on severity and duration of NLC was also not significant ($P = .38$ and $P = .30$, respectively). Furthermore, no statistically significant differences were observed between the treatment groups in the changes in scores from enrollment to the end of the treatment period, in the total SF-36 score, the scores of any of its components, and in the PSQI global score (Table 2). Additionally, to allow the combination of our results in the meta-analysis, we calculated the minimum clinically important difference (ie, the number of people obtaining 25% reduction in NLC) and obtained 75% (n = 36) and 63% (n = 29) in the magnesium oxide and placebo groups, respectively, a nonsignificant difference ($P = .21$).

We tested for interaction terms and found no interaction effect between any of the baseline characteristics of the participants examined and any of the outcomes. Additionally, we conducted a repeated-measures analysis of variance for trend analysis with specific contrasts that compared the differences in mean values of outcome variables during the screening and treatment periods (5 points of time). The analysis examines the trend of change over time for the entire sample and within each group, while controlling the cumulative statistical error of correlated comparisons ($P = .86$ for trend) (**Figure 2**). We conducted a pill count in the 88 participants who completed the study protocol fully. The number of capsules in the retrieved bottles ranged from 2 to 6 (mean of 4.1 per participant) and was explained by the participants to be due to forgetfulness (twice in 4 cases and once in 3) and continuation for an additional 2 days (1 participant).

Adverse Events

Six serious adverse events (hospitalization) occurred during the study period, 2 during the screening phase and 4 during the treatment phase, 2 in each treatment group. All hospitalizations were for concurrent medical problems that are frequent in elderly individuals. None was assessed to be related to the

study medication use. Additionally, minor adverse effects, mostly gastrointestinal, occurred in 14 and 13 participants in the magnesium oxide and placebo groups, respectively.

Study Termination

On April 1, 2014, we submitted the results of 94 participants (43% of the 220 planned) for a blinded interim analysis. The results showed that magnesium for the treatment of NLC is safe but probably not more effective than placebo. With 43% of the study population recruited, the chances that the differences between the groups in the outcomes assessed would change and become significant were low; thus, at this stage the committee recommended that the study be discontinued due to lack of efficacy.

Discussion

This randomized clinical trial did not confirm our hypothesis that magnesium oxide supplementation is more effective than placebo in reducing NLC in community-dwelling individuals. To our knowledge, this is the first study in which magnesium oxide, rather than magnesium citrate, was tested as prophylaxis for NLC. Despite the recent evidence of improved intracellular absorption,[15] magnesium oxide supplementation was not significantly better than placebo. There was no evidence that the effect of treatment was dependent on demographic or clinical characteristics of the participants, including the use of magnesium supplements before enrollment.

Table 1. Baseline Characteristics of All Randomized Participants

Characteristic	Magnesium Oxide (n = 48)	Placebo (n = 46)	Total (N = 94)
Male sex, No. (%)	17 (35)	20 (43)	37 (39)
Age, mean (SD), y	63.1 (12.4)	66.7 (9.3)	64.9 (11.1)
Height, mean (SD), cm	168 (0.09)	166 (0.08)	167 (0.08)
Weight, mean (SD), kg	78.4 (15.0)	77.3 (14.6)	77.8 (14.7)
Hypertension, No. (%)	18 (38)	24 (52)	42 (45)
Heart disease, No. (%)	7 (15)	8 (17)	15 (16)
Diabetes, No. (%)	16 (33)	13 (28)	29 (31)
Serum creatinine, mean (SD), mg/dL	0.84 (0.26)	0.85 (0.19)	0.84 (0.23)
Use of magnesium supplements before enrollment, No. (%)	6 (13)	3 (7)	9 (10)

SI conversion factor: To convert serum creatinine to micromoles per liter, multiply by 88.4.

Table 2. Study Outcomes

	Mean (SD)						*P* Value for Change
	Magnesium Oxide (n = 48)			Placebo (n = 46)			
	Screening Phase	Treatment Phase	Change[a]	Screening Phase	Treatment Phase	Change[a]	
Primary Outcome[b]							
No. of NLC/wk	7.84 (5.68)	4.44 (5.66)	−3.41 (4.05)	8.51 (5.20)	5.48 (4.93)	−3.03 (4.53)	.67
Secondary Outcomes[b]							
Severity of NLC	4.97 (2.28)	4.58 (1.91)	−0.38 (1.27)	5.12 (2.22)	4.51 (2.21)	−0.62 (1.46)	.38
Duration of NLC, min	6.68 (8.02)	7.54 (9.96)	0.93 (7.86)	5.73 (5.64)	5.44 (5.25)	−0.61 (1.89)	.30
	Enrollment	Posttreatment	Change[c]	Enrollment	Posttreatment	Change[c]	
Quality of life; Short Form (36) score by category[d]							
Physical functioning	61.41 (29.56)	65.71 (27.60)	−4.3 (15.06)	60.18 (31.73)	66.33 (30.84)	−6.15 (16.56)	.60
Role							
Physical	54.17 (39.39)	61.11 (39.44)	−6.94 (27.47)	51.45 (43.51)	67.03 (39.98)	−15.58 (28.79)	.14
Emotional	58.33 (43.22)	71.18 (35.85)	−12.85 (30.80)	68.12 (40.95)	78.99 (34.68)	−10.87 (23.36)	.75
Vitality	53.96 (25.49)	57.47 (23.80)	−3.51 (18.73)	53.48 (26.85)	61.56 (24.96)	−8.08 (20.22)	.22
Mental health	67.19 (22.42)	66.00 (23.99)	1.19 (14.77)	69.63 (23.83)	74.87 (20.81)	−5.24 (16.26)	.02
Social functioning	72.14 (29.88)	82.61 (26.67)	−6.51 (25.65)	73.91 (27.36)	82.61 (25.34)	−8.70 (19.87)	.48
Bodily pain	51.87 (25.15)	62.76 (24.99)	−10.89 (26.87)	49.84 (25.13)	60.92 (26.26)	−11.09 (20.73)	.88
General health	56.87 (25.61)	59.27 (25.16)	−2.40 (17.11)	60.07 (23.98)	61.41 (22.45)	−1.34 (15.18)	.94
Pittsburgh Sleep Quality Index Global score	8.85 (3.57)	6.73 (3.11)	2.13 (2.46)	9.22 (3.81)	7.57 (3.59)	1.65 (2.99)	.23

Abbreviation: NLC, nocturnal leg cramps.

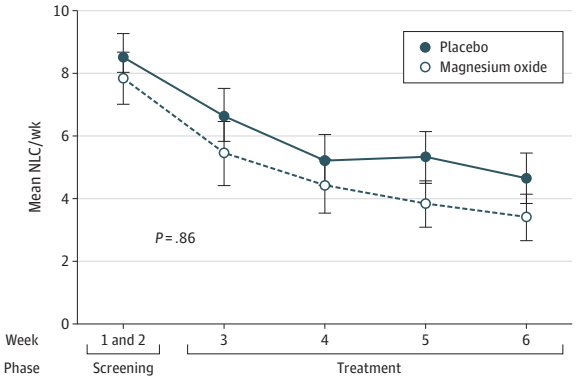
[a] Change denotes the difference in the mean number of NLC/wk between the screening and treatment phases of the study.

[b] Significance was tested using analysis of covariance, adjusted for screening values as covariates, and treatment group (magnesium vs placebo) as the independent variable.

[c] The difference between the scores at enrollment and at posttreatment; negative values reflect an improvement in the relevant category.

[d] Using the Bonferroni approach (see Methods).

Figure 2. Frequency of Nocturnal Leg Cramps (NLC) per Week by Treatment Group During the Entire Study



Values at screening phase refer to the mean number of nocturnal leg cramps per week during the 2 weeks of screening; error bars represent standard errors.

Magnesium plays an important role in hundreds of metabolic reactions and in muscle function.[26]

Magnesium deficiency can result from various etiologies, and elderly people are particularly at risk because of the combination of chronic diseases, poor nutrition, decreased absorption of magnesium, and increased renal exertion.[27] As magnesium deficiency is associated with neuronal excitability and enhances neuromuscular transmission,[4,28,29] and because its substitution has been shown to be effective in eclampsia-related seizures,[30,31] a number of researchers have suggested a possible beneficial role of magnesium supplementation in NLC. Some effectiveness was indeed demonstrated in a study of pregnant women.[9] However, subsequent trials in nonpregnant individuals did not demonstrate effectiveness of magnesium supplementation as prophylaxis for NLC in the general population.[13,32]

The present study is based on self-reported outcomes. The prospective nature and the conduct of a 2-week screening period, during which individuals were instructed to record data daily, in a diary, helped mitigate recall bias and screened for participants who would not adhere to the study protocol. Telephone calls and text messages during the screening and treatment phases presumably contributed to the adherence to the study protocol and the consumption of the study medication, as was reflected in the pill count and the low dropout rate.

Limitations

Limitations of the study include the modest number of participants, who were mostly elderly individuals, and the intervention period of only 4 weeks. Participants were self-selected individuals who volunteered to participate, introducing certain selection bias. However, all reported trials were smaller or of similar size and duration. Given the intensive follow-up and meticulous event adjudication, coupled with the patient-centered approach, it seems unlikely that a significant beneficial effect was missed. This led the independent data reviewing and monitoring committee to recommend early termination of the study after 94 participants due to lack of efficacy.

Conclusions

Previous research shows inconclusive results concerning the efficacy of magnesium therapy in the treatment of NLC in general populations due to the relatively low methodological qualities of the trials.[32] Nevertheless, magnesium supplements are widely marketed, and purchased, worldwide as a preventive treatment for muscle cramps. The statistically significant decrease in the frequency of NLC following treatment with both magnesium and placebo may explain the perceived benefit experienced by magnesium users. However, this randomized clinical trial suggests that magnesium oxide supplementation is no better than placebo for NLC. It appears unlikely that older adults with NLC will significantly benefit from magnesium supplementation.

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Study concept and design: Roguin Maor, Alperin, Khairaldeen, Karkabi, Milman.
Acquisition, analysis, or interpretation of data: Roguin Maor, Alperin, Shturman, Friedman, Milman.
Drafting of the manuscript: Roguin Maor, Alperin, Khairaldeen, Milman.
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