The effect of oral magnesium substitution on pregnancy-induced leg cramps

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OBJECTIVE: Our purpose was to determine whether women with pregnancy-related leg cramps would benefit from oral magnesium supplementation.

STUDY DESIGN: Seventy-three women with pregnancy-related leg cramps were interviewed about their symptoms in a prospective, double-blind, randomized trial. Initial serum magnesium levels and diurnal magnesium excretion was determined in 50% of the patients. Oral magnesium or placebo was given for 3 weeks, after which new interviews and laboratory analyses were performed.

RESULTS: Serum magnesium levels in these patients were at or below the lower reference limit, as is also often the case in healthy pregnant patients. Oral magnesium substitution decreased leg cramp distress ($p < 0.05$ compared with the placebo group, $p < 0.001$ compared with initial complaints), but did not significantly increase serum magnesium levels, excess magnesium being excreted as measured by an increase in urinary magnesium levels ($p < 0.002$).

CONCLUSION: Oral magnesium supplementation seems to be a valuable therapeutic tool in the treatment of pregnancy-related leg cramps. (Am J Obstet Gynecol 1995;173:175-80.)

Key words: Human pregnancy, magnesium deficiency, leg cramps, magnesium substitution therapy

Magnesium acts as a necessary activator of some 300 different enzymes and plays a central role in metabolism and muscle function. Magnesium deficiency can therefore be expected to cause secondary biochemical and physiologic changes.[1-3] Pregnancy and lactation are among those processes that may be associated with a secondary magnesium deficiency.[2, 4, 5] Magnesium action in many conditions has been correlated with its role as a physiologic synergist or antagonist to calcium, and muscular symptoms of magnesium deficiency include muscle tremor, ataxia, tetany, and cramps.[2]

Studies on leg cramps have included investigations of both magnesium and calcium. Magnesium therapy as treatment for nightly leg cramps has, for example, been studied in elderly men and women[6] and in type I diabetics with good results.[7] Leg cramps are reported to occur in 5% to 30% of all pregnant women, most often during the later months of pregnancy and without relationship to other complications or to unfavorable fetal outcome.[8-10] We have, as others before us, previously studied, with inconclusive results, the effect of oral calcium substitution for nightly leg cramps in pregnant women.[8, 11-13] We have also previously found low serum magnesium levels in pregnant women with leg cramps,[14] whereas an open uncontrolled therapeutic trial with oral magnesium substitution indicated a positive effect but did not take placebo effect into account.[10]

The aim of the current study was to determine whether low levels of serum magnesium occur in women with pregnancy-related leg cramps and whether the symptoms can be alleviated by oral magnesium substitution.

Material and methods

Patients. Seventy-three pregnant women complaining of leg cramps during pregnancy were referred from prenatal care units for admission to the study. Thirty-eight women were included in Linköping, and 35 in Jönköping after they gave informed consent. All participants were in good health with no other pregnancy complications or intercurrent medical problems. Mean length of pregnancy was 29 weeks (range 22 to 36 weeks), mean weight gain was 8.7 kg (range 3 to 18.5 kg), and mean parity was 0.7 (range 0 to 4 pregnancies) with 53% primigravid women. No previous treatment had been given for leg cramps in the current pregnancy.

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Table I. Frequency and diurnal distribution of leg cramps before and after treatment (number of patients)

	Magnesium (n = 34)		*Placebo (n = 35)*	
	Before	*After*	*Before*	*After*
Cramp frequency				
Daily	9	7	10	6
Every other day	17	3	18	7
Twice a week	7	4	7	14
Once a week	1	9	0	6
Never	0	11	0	2
Time of day				
Nighttime only	29	20	32	28
Days and nights	5	2	3	3
Daytime only	0	1	0	2
Free of symptoms	0	11	0	2
Persisting symptoms day after nightly cramps				
Always	8	2	14	9
Sometimes	11	4	12	7
Never	15	17	9	17

Table II. Patient evaluation of treatment effect (number of patients)

Patient opinion	*Magnesium (n = 34)*	*Placebo (n = 35)*
Entirely free of symptoms	10	3
Considerably improved	17	11
Unchanged	7	16
Worsened	0	5
Considerably worsened	0	0
TOTAL	34	35

The study was approved by the Ethical Committee of the University of Linköping.

Questionnaire and interviews. The study was initiated by a structured interview regarding the pregnancy in general and the leg cramps in particular. Background questions were asked about previous parity, leg cramps in earlier pregnancies, weight gain, length of pregnancy, ankle and leg swelling, and intake of medications, including vitamins and iron supplements. Current pregnancy complications were noted.

First-visit questions about the leg cramps concerned symptom duration, frequency of cramps during the last 2 to 3 weeks, diurnal variation, and whether nocturnal cramps persisted the following day. Subjective evaluation of distress was noted by the woman on a 100 mm visual analog scale, where 0 = insignificant and 100 = extremely painful. The blood pressure was measured on the right arm after 10 minutes of rest with the patient lying on the left side. The patients were then randomly allocated to either magnesium or placebo.

Second-visit questions at the end of the 3-week treatment period were the same as at the first visit. The patient was also asked whether her condition had improved, deteriorated, or remained unchanged and about side effects. The tablets remaining in the bottle were counted as a measure of compliance.

Magnesium tablet and placebo construction. A magnesium-placebo tablet batch of 90 numbered bottles was prepared by ACO Läkemedel (Stockholm). Each bottle contained chewable tablets consisting of either magnesium 5 mmol (primarily magnesium lactate, magnesium citrate) or placebo (primarily sorbitol, fructose-dextrose), permitting blinded statistical analysis at the end of the study. Dosage was "One tablet to be chewed each morning, and two each evening for leg cramps."

Laboratory data. Laboratory tests were for practical reasons not performed at the referral center in Jönköping.

All patients referred to the Linköping center (n = 38 initially) had blood sampled to determine serum levels of total magnesium and ionized calcium before starting and on completing treatment. Twenty-four-hour urine specimens were collected before and after treatment for measurement of the excretion of magnesium, calcium, and creatinine. Ionized calcium was analyzed with an ion-selective electrode instrument (ICA, Radiometer A/S, Copenhagen).[15] Calcium and magnesium levels in urine and total magnesium in serum was determined by a conventional atomic absorption technique.[16] Creatinine was determined with a routine Jaffé method.

Statistical analysis. Paired Student t test (parametric test) was used when appropriate. The Mann-Whitney U test (nonparametric test) was used in comparing data with nonnormal distributions.

Results

Four of the patients in the Linköping group did not complete the study and were excluded (one because of acid spillage from urine bottle, one because of hospital admission for other reasons, one because of failure to attend second visit, one because of admission for pre-

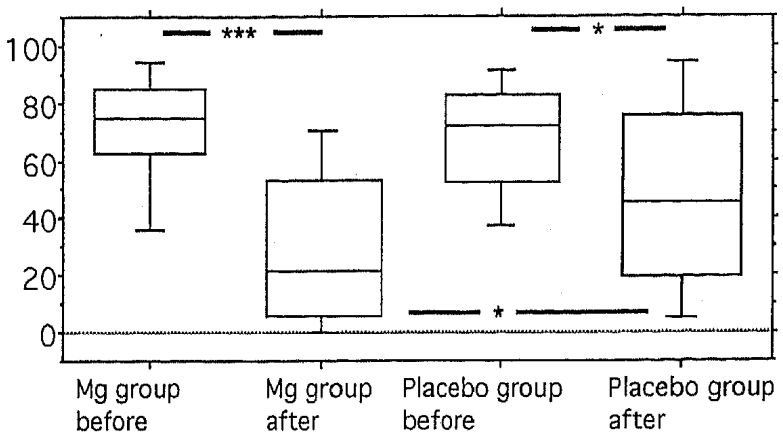

Fig. 1. Leg cramp symptom intensity as measured by visual analog scale before and after treatment with magnesium *(Mg)* (n = 34) or placebo (n = 35). Symptoms by visual analog scale: 0 to 100 mm (0, insignificant; 100, extremely painful). Symptom intensity decreased significantly after treatment in the magnesium group, compared with both initial complaints and results after placebo treatment. *Box plot center line,* Median; *box boundaries,* 25% to 75% interval; *hooks,* 10% to 90% interval; *asterisk,* $p < 0.05$; *three asterisks,* $p < 0.001$.

mature labor). All Jönköping patients completed the study.

The groups proved to be statistically well matched on background factors such as distribution of treatment month (peak in warmer summer months), parity, weight gain, and length of pregnancy. The groups were also well matched regarding the frequency of ankle or leg swelling (~15%); use of vitamins, iron supplements, or other medications; and infrequent occurrence of contractions with or without sick leave. The multigravid subgroups were well matched as to percentage reporting leg cramps in previous pregnancy (~68%) and percentage having received treatment for these in the form of calcium supplement (~8%). None had received other forms of treatment for leg cramps in previous pregnancies. Distribution of attending physicians between the two groups was also well matched, as was the time lapse between the first and second visit (mean 21.3 days).

Initial leg cramp symptoms. The groups proved to be well matched regarding the description of leg cramp symptoms at the initial interview. The mean symptom duration in both groups was 8.1 weeks (3 to 25 weeks), median frequency of leg cramps was every other day, and both groups had the same distribution of nocturnal cramps (88% nights only, 12% nights and days, 0% daytime only), with the same distribution of persisting symptoms the following day (Table I). The mean evaluation of symptoms according to the visual analog scale at the initial interview was 69 mm (range 25 to 100 mm) on the 100 mm scale.

Symptoms at second visit. Statistical analysis showed a clear difference between the groups in symptoms reported after 3 weeks of treatment. Both treatment groups showed a decrease in frequency of symptoms from the initial average of every other day, to every 3 days in the placebo group and one to two times a week in the magnesium group ($p < 0.05$, Table I). The diurnal distribution of symptoms was, as before treatment, primarily nightly (Table I). In the magnesium group, however, only 25% of the patients with nightly cramps sometimes or always had persisting symptoms the following day, which was significantly less ($p < 0.05$) than the 50% in the placebo group. Subjectively experienced distress according to the visual analog scale was reduced from 68.2 mm before to 47.8 mm after treatment ($p < 0.05$) in the placebo group and from 70.4 mm to 30.3 mm ($p < 0.001$) in the magnesium group. The reduction of distress in the magnesium group was significantly greater ($p < 0.05$) than in the placebo group (Fig. 1). Finally, the patients' overall grading of treatment effect in the magnesium group indicated that they had to a significantly greater extent "improved considerably" or "become asymptomatic" compared with the placebo group ($p = 0.0002$, Table II). Every third woman in the magnesium group was totally free of symptoms at the second visit, compared with only three of 35 in the placebo group (Table II).

Correlation between visual analog scale improvement (Δ VAS = VAS 1 − VAS 2) depicted in Fig. 1 and patient grading of treatment effect as noted in Table III was high, which also validates the visual analog scale as a relevant method in this study (Fig. 2).

There was no significant change in blood pressure during treatment (mean 101/57 mm Hg first visit, 102/59 mm Hg second visit). Patient compliance showed no significant difference between the groups (mean number of omitted tablets in the magnesium group was 3.8 compared with 8.1 in the placebo group). Side effects were infrequent in both groups, consisting

Table III. Laboratory results from Linköping patients (mean values for magnesium and placebo control group)

Laboratory test performed	*Mean laboratory values (mean ± SD)*				*Reference values*
	Before treatment		*After treatment*		
	Magnesium (n = 18)	*Placebo (n = 15)*	*Magnesium (n = 18)*	*Placebo (n = 15)*	
Blood tests					
Serum magnesium (total) (mmol/L)	0.70 ± 0.06	0.67 ± 0.07	0.68 ± 0.06	0.65 ± 0.06	0.70-1.20
Serum calcium (ionized) (mmol/L)	1.24 ± 0.04	1.24 ± 0.03	1.23 ± 0.03	1.24 ± 0.02	1.18-1.34
24 hr urine collection					
Urine volume (ml/24 hr)	1394 ± 622	1662 ± 1034	1552 ± 816	1362 ± 576	
Urinary magnesium (total) (mmol/24 hr)	4.3 ± 1.4	4.9 ± 1.1	6.3 ± 1.8*	4.2 ± 1.7	>3.0
Urinary calcium (total) (mmol/24 hr)	6.7 ± 3.2	8.4 ± 2.9	7.4 ± 3.7	6.8 ± 3.5	<7.5
Urinary creatinine (total) (mmol/24 hr)	9.5 ± 2.7	10.4 ± 1.8	9.3 ± 2.5	9.4 ± 3.3	4-14 (women)

*Only significant change was increase in urinary magnesium after magnesium treatment, $p < 0.002$).

primarily of slight or initial nausea. One patient in the placebo group aborted treatment because of severe, persisting nausea.

Possible significance of vitamin or iron supplements. Statistical subgroup analysis indicated no adverse effects of simultaneous oral vitamin and iron supplements. The extent of this intake throughout the study was, however, not defined in sufficient detail to permit any statistical conclusions regarding the possibility of positive interactions. The subgroups consisted of patients taking commercially available nonprescription tablets containing a combination of multivitamins and ferrous iron, ferrous iron only, or multivitamins only. (The vitamin-iron combination tablets most commonly used in pregnancy in Sweden all contain vitamins A, B, C, and D and some also contain vitamins E and B_{12} and folic acid.) None of the supplements contained calcium. Laboratory results did not vary between subgroups.

Laboratory results. Some test data were lost for one patient. Laboratory tests performed on the remaining Linköping patients are summarized in Table III ($n = 33$). All tests (including calcium changes) were statistically unchanged after treatment, with the exception of total 24-hour urinary magnesium excretion, which increased significantly in the magnesium group ($p < 0.002$) compared with placebo. Total serum magnesium remained at or below the lower reference limit for both groups (Table III).

Comment

Magnesium treatment has been found to be valuable in a wide range of pathologic disorders, but it can be difficult to determine whether a particular disorder represents a primary magnesium deficiency or whether an observed magnesium deficiency is a result of underlying disease.[1-3]

Riss et al.[10] found a possible positive effect of oral magnesium on leg cramps in pregnancy, but an open study design without placebo control renders the results inconclusive.

Our results indicate that pregnant women with leg cramps have a low level of serum magnesium compared with the nonpregnant state, present both before and after treatment. Unfortunately, we had no simultaneous measurements from a matched asymptomatic control group, but a recent longitudinal study of 23 healthy pregnant Swedish women showed a drop in maternal serum magnesium starting as early as the eighteenth week, the lowest value being a mean of 0.71 mmol/L in the thirtieth week.[17]

Magnesium deficiency in general can be difficult to diagnose and correlate with clinical symptoms, because about 50% of the total body magnesium (25 to 28 gm) is stored in the bones, and only 1% of the remaining part is to be found in the extracellular compartment. Intracellular assays have remained difficult and unreliable, and there is no strict correlation between the accurate plasma assay and intracellular magnesium concentrations. Although serum total magnesium was measured in this study, ionized magnesium might be more informative in further studies on leg cramps. Analysis of ionized magnesium is, however, not yet reliable enough for routine clinical use. In spite of these uncertainties serum total magnesium constitutes an important element in the diagnosis of magnesium deficiency, where hypomagnesemia is defined to be ≤ 0.7 mmol/L.[2] The assay must, however, not be considered separately but should be correlated to symptoms.[2]

Most of the women in our study had symptom debut

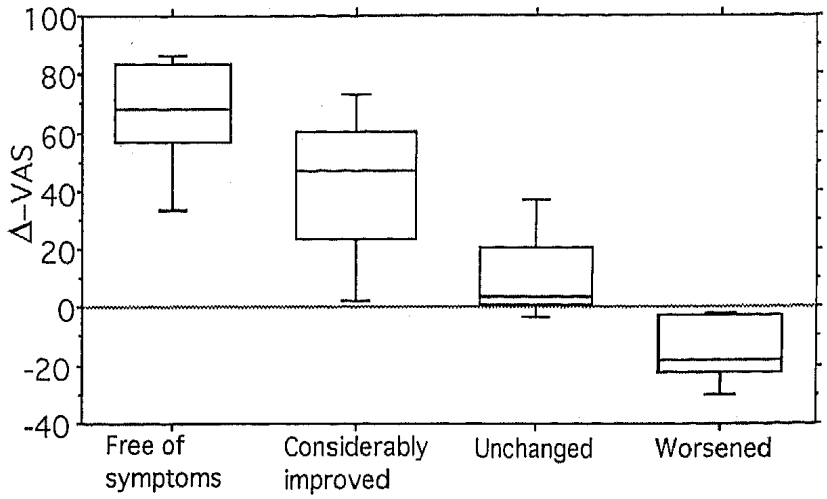

Fig. 2. Symptom development as measured by visual analog scale after treatment with magnesium or placebo (Fig. 1) correlated well with patient evaluation of treatment effect (Table III), validating visual analog scale as a relevant method in this study (n = 69). Symptoms by visual analog scale: 0 to 100 mm (0, insignificant, 100, extremely painful). Visual analog scale improvement is represented as Δ-VAS = $VAS_{1st\ visit} - VAS_{2nd\ visit}$. Patient grading of treatment effect at second visit was as follows: 1, entirely free of symptoms; 2, considerably improved; 3, unchanged; 4, worsened; 5, considerably worsened. *Box plot center line,* Δvisual analog scale median; *box boundaries,* 25% to 75% interval; *hooks,* 10% to 90% interval.

in the second trimester, but symptoms could also begin in first or third trimesters. The number of patients reporting symptoms and distress tended to be greatest in the warm summer months. Degree of distress before treatment could not be related directly to pregnancy length, serum magnesium levels, or urinary magnesium excretion at initial evaluation. Our patients proved to be well randomized, and follow-up of clinical treatment response showed a good placebo effect but a significantly better effect of magnesium substitution.

The possibility of positive vitamin synergism with magnesium is an interesting question that unfortunately cannot be answered by this study, because our study design did not address this question in sufficient detail. We do know, however, that magnesium is necessary for many enzyme systems that also are dependent on several vitamins and trace minerals.[18] The prime example is that of magnesium and pyridoxine (vitamin B_1), with numerous enzymes dependent on both and with many clinical disorders caused by deficiency of one, at least in part responsive to administration of the other but in fact best treated by a combination of both.[18] Pyridoxine deficiency intensifies that of magnesium, because it requires increased amounts of magnesium as a cofactor of the enzymes and pregnancy is a condition associated with biochemical evidence of pyridoxine deficiency.[18] Thiamine (vitamin B_6) is another vitamin that is known to have important interactions with magnesium, where most of the clinically relevant data pertains to central nervous system effects, and more complex interrelationships are known to exist between vitamin D and magnesium.[18] There are also possible interrelations between magnesium and vitamins E and C, as between magnesium and trace mineral antioxidants such as selenium and zinc.[18]

The fact that serum magnesium levels remained unchanged after the treatment period for both groups is not surprising with knowledge that only 0.5% of the body magnesium is to be found in the extracellular compartment and that correlation with clinical symptoms is poor. The difference in treatment effects might, however, better correspond to possible changes in the level of serum ionized magnesium or intracellular magnesium, which might not be reflected in the serum total magnesium concentration. It is, for example, known that serum total calcium correlates poorly with ionized calcium in up to 40% of all measurements.[19] This could also be the case for total magnesium, because serum ionized magnesium constitutes 60% of the serum total magnesium.[20] The only laboratory result that changed significantly during treatment was urinary magnesium excretion, which increased significantly in the magnesium group after treatment, possibly indicating indirectly that a relative surplus of magnesium had been attained in this group compared with the untreated group (Table III).

In conclusion, our results with oral magnesium supplementation in patients with pregnancy-induced nightly leg cramps have yielded good clinical treatment results with insignificant side effects, leading us to recommend oral magnesium supplementation as a treatment option for this patient group. Simultaneous oral intake of multivitamins or ferrous iron had no adverse effect on treatment results, and the possibility of positive synergism between other mineral or vitamin intake and magnesium should be considered more

carefully in future studies. The exact milligram equivalent of the dosage given in the study would be 122 mg of magnesium morning and twice that in the evening.

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