Magnesium Oxide Monohydrate for Nocturnal Leg Cramps (MgNLC); a Prospective, Randomized, Double Blind, Placebo Controlled Clinical Trial

Protocol No.: 1

Version: 3

Date of Protocol Version: 20/12/2013

Sponsor: Dr Uzi Milman

Principal Investigator: Dr Noga Maor Roguin
Magnesium Oxide Monohydrate for Nocturnal Leg Cramps (MgNLC); a Prospective, Randomized, Double Blind, Placebo Controlled Clinical Trial

Approvals

Sponsor Signature: _____________ Date: _______________

Principal Investigator Agreement:
I have carefully read and understood the provisions of this protocol and I am prepared to follow them in every detail in the conduct of this study.

Principal Investigator Signature: _________ Date: ________________

Protocol Modifications History:

<table>
<thead>
<tr>
<th>Date</th>
<th>Protocol No (Ver)</th>
<th>Protocol Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Sept. 2012</td>
<td>MgNLC_001(2)</td>
<td>Minor technical modifications as requested by the IRB</td>
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<tr>
<td>4 Nov. 2012</td>
<td>NIH Registration</td>
<td>ClinicalTrials.gov Identifier: NCT01709968</td>
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The Nocturnal Cramps Sleep Diary (NCSD)

SYNOPSIS:

STUDY TITLE: Magnesium Oxide Monohydrate for Nocturnal Leg Cramps (MgNLC); a Prospective, Randomized, Double Blind, Placebo Controlled Clinical Trial.

SPONSOR: Dr Uzi Milman (will also act as the study monitor)

INVESTIGATIONAL PRODUCT AND FORMULATION: MAGNOX 520® (un-organic granular magnesium complex, composed of Magnesium Oxide & Magnesium Oxide Monohydrate 865mg, Provides 520 mg of free elemental Mg++, NavehPharma Ltd., Israel.

STUDY PHASE: 4
INDICATION: Nocturnal Leg Cramps (NLC).

OBJECTIVES: To assess the effect of treatment with Magnox 520®, as compared with placebo, on frequency and severity of NLC, quality of sleep and quality of life.

TRIAL DESIGN: A single center, prospective, randomized, double blind, placebo controlled clinical trial

SAMPLE SIZE AND TREATMENT GROUPS: A total of 220 subjects (200 subjects adjusted for about 10% withdrawal rate) will randomly be assigned to two study arms employing a 1:1 randomization scheme. Each randomized individual will be given once daily either MAGNOX 520® or a similarly looking placebo for a treatment period of 4 weeks.

CLINICAL TRIAL DURATION: Two weeks of eligibility screening followed by 4-week double-blind treatment.

INCLUSION CRITERIA:
- Signed informed consent before any procedure or assessment is done.
- Age over 21 years old.
- Over 4 episodes of documented NLC during 2 weeks of eligibility screening (for the treatment phase).
- Insured by Clalit Health Services (CHS).
- Hebrew speaking

EXCLUSION CRITERIA:
- Pregnancy
- Currently taking Quinidine or Magnesium additive
- Renal failure – serum creatinine more than 2 mg/DL. If the result is near these creatinine limits (i.e. serum 1.5-2) a second analysis will be done near the study enrollment.
- Major neurological disease- ALS, MS, Paraplegia or Quadriplegia.

DOSAGE OF INVESTIGATIONAL PRODUCT: MAGNOX 520® (un-organic granular magnesium complex, composed of Magnesium Oxide & Magnesium Oxide Monohydrate 865mg, Provides 520 mg of free elemental Mg ++) ,NavehPharma Ltd., Israel.

CONTROL PRODUCTS: Similarly looking placebo.

MODALITIES OF DRUG ADMINISTRATION: Oral administration once daily for 4 weeks.

MAIN STUDY PARAMETERS:
- Efficacy
Number of episodes of NLC;  
Severity of NLC;  
Duration of NLC;  
Quality of life;  
Quality of sleep;  

The primary assessment will compare outcomes between MAGNOX 520® and placebo treated individuals during a treatment period of 4 weeks.

**CLINICAL TRIAL PROCEDURES:**
The number, severity and duration of NLC will be measured daily as documented in a designated, structured sleep dairy - The Nocturnal Cramps Sleep Diary (NCSD). Quality of life and quality of sleep will be assessed by SF-36 and PSQI questionnaires, respectively, to be completed twice - at enrolment and within one week of the end of the treatment period.

**STATISTICAL METHODS:**
The study was designed as a proof-of-concept study, single-center, prospective, randomized, double blind, placebo-controlled, 2-arms parallel-groups, clinical trial, designed and powered to assess the efficacy of oral administration of MAGNOX 520® in subjects suffering from NLC.

**PRIMARY ENDPOINT:** the primary efficacy endpoint is the difference in the number of episodes of NLC documented in the NCSD, as compared between the MAGNOX 520® and the placebo treated individuals, during a treatment period of 4 weeks;

**KEY SECONDARY ENDPOINTS:**
The difference in the severity of episodes of NLC documented in the NCSD, as compared between the MAGNOX 520® and the placebo treated individuals, during a treatment period of 4 weeks;  
The difference in the duration of episodes of NLC documented in the NCSD, as compared between the MAGNOX 520® and the placebo treated individuals, during a treatment period of 4 weeks;  
The difference in the change in quality of life (measured by SF36 at enrolment and after the treatment period) between the MAGNOX 520® and the placebo treated individuals;  
The difference in the change in quality of sleep (measured by PSQI at enrolment and after the treatment period) between the MAGNOX 520® and the placebo treated individuals;

**SAMPLE SIZE RATIONALE:**
As this is a proof-of-concept study, the difference in the number of episodes of NLC documented in the NCSD, as compared between the MAGNOX 520® and the placebo treated individuals, during a treatment period of 4 weeks, will serve as the sole primary efficacy end point for this study.  
We calculated that a total of 200 patients will needed, for this two-treatment parallel-design study,
to achieve a probability is 90 percent that the study will detect a treatment difference at a two-sided 0.04 significance level, if the true difference between treatments is 3.801 (difference in means between treatment groups) NLC events. This is based on the assumption that the standard deviation of the mean number of NLC events is 8.

**STATISTICAL METHODS:** In order to examine the homogeneity between groups regarding outcome measures at enrollment and bio-demographic measures (study vs. control) a t-test will be conducted with group as independent variable, and study outcomes at enrollment and bio-demographic measures as dependents. Bio-demographic nominal scale variables will be tested using Chi square test. At the end of the study a composed subscales of the dependent variables will be computed, as follows: SF36 questionnaire, PSQI questionnaire, and number, severity and duration of NLC according to daily dairy. All the subscales will be computed according to instructions in the study tools manuals. 2-way (group X time) trend analysis will be conducted looking for possible trend of change in treatment effect across time. The effect of the study will be examined using repeated measures (RM) ANOVA. The repeated measures analysis will compare the difference scores of each of the dependent measures between study and control groups. In order to explore possible effects of bio-demographic variables a 2-way/ 3-way RM ANOVA with group X independent factors (for example: gender, age) will be conducted.
CRF: Magnesium Oxide for Nocturnal Leg Cramps (MgNLC) Study

Study Process Checklist
*(To be completed, in real time, in each visit)*

<table>
<thead>
<tr>
<th></th>
<th>Visit I</th>
<th>Two week Screening</th>
<th>Visit II</th>
<th>4 week Treatment Phase</th>
<th>Visit III</th>
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<tbody>
<tr>
<td>Enrolment</td>
<td>x</td>
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<td>Demography Questionnaire</td>
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<td>SF 36 completed</td>
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<td>PSQI completed</td>
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<td>NCSD x 2</td>
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<tr>
<td>Daily SMS and 2-3 weekly Reminder Calls</td>
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<tr>
<td>NCSD eligibility assessment</td>
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<td>Randomization</td>
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<td>Dispense Study Medication</td>
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<td>Retrieve of Study Medication Bottle</td>
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<td>SF 36 completed</td>
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<tr>
<td>PSQI completed</td>
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<tr>
<td>NCSD and study medication Bottle retrieval; Remaining capsules count</td>
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List of Abbreviations:
ICF- Informed Consent Form; NCSD- Nocturnal Cramps Sleep Diary; SF36- The Short Form (36) Health Survey; PSQI- The Pittsburgh Sleep Quality Index.
Background:
Nocturnal leg cramps (NLC) are painful, involuntary contractions of muscles occurring at rest, mostly at night, and causing a palpable knot in the muscle, usually the gastrocnemius or soleus\(^1\). It is estimated that more than a third of people older than 60 years old suffer from nocturnal leg cramps\(^2\). The cause of night cramps is unclear. Night cramps can be associated with a variety of conditions such as hemodialysis, electrolyte imbalance and drugs such as diuretics, nifedipine, salbutamol and terbutaline\(^3\). Measures to prevent night cramps include calf stretching exercise\(^4\) but its effect has not been clearly confirmed\(^5\). Various drug regimens have been proposed without good evidence including verapamil, diazepam, diphenhydramine hydrochloride and vitamin E\(^6\). Quinine is more effective than placebo in reducing the number of night cramps\(^7\) but has potentially serious side effects. Consequently, the FDA has prohibited the over the counter sale of quinine because of safety concerns\(^8\). A Cochrane review on leg cramps in pregnancy showed some potential benefits in trials of magnesium\(^9\). Although a large randomized double blind study of 93 patients\(^10\) did not show any benefit, a smaller study\(^11\) from the UK showed that magnesium may be effective in older non pregnant individuals. A recent evidence based review\(^12\) recommends additional future research given the lack of evidence for the reviewed treatments.

Magnesium is an intracellular cation; only 1 percent is extracellular, 31 percent are intracellular and 67 percent in bone matrix. Consequently, magnesium blood level is only a rough index of total body magnesium stores and deficiency in magnesium can be present when serum levels are within normal range.

Magnesium is required for the activation of important enzyme system involving ATP and the metabolism of protein, carbohydrates, fat and nucleic acids, for normal cell membrane function and for neuromuscular transmission. Magnesium plays an important role in maintaining the sodium-potassium gradient across cell membranes and regulates the muscle cell function, cardiac rhythm, vasomotor tone, neuromuscular function and parathyroid hormone metabolism.

Magnesium is absorbed primarily in the jejunum and ileum. Food products rich in magnesium are green vegetables, seed grains, nuts, peas and beans. Magnesium consumption in the world is in decline, mostly because of over purification processes in the food industry\(^13,14,15\). Excess magnesium in the blood is freely filtered in the kidneys; therefore toxicity from dietary sources alone is rare. Minor reported side effects were abdominal discomfort and diarrhea occurring in magnesium and placebo-treated patients\(^10,11\). Overdose with magnesium supplements is possible,
particularly in people with poor renal function. The recommended daily consumption of magnesium is 420 mg, and in special situations such as pregnancy or prolonged sickness the consumption can be increased up to 720 mg.

Two oral magnesium preparations are available in Israel: Magnesium Diasporal (magnesium citrate, elemental magnesium 98.6 mg, PROTINA GMBH, ISMANING, Germany) and MAGNOX 520® (un-organic granular magnesium complex, composed of Magnesium Oxide & Magnesium Oxide Monohydrate 865mg, Provides 520 mg of free elemental Mg ++, NavehPharma Ltd., Israel).

In a recent study researchers investigated the impact of supplemental oral magnesium citrate versus Magnesium Oxide Monohydrate on intracellular magnesium levels. They found that oral Magnesium Oxide Monohydrate, rather than magnesium citrate, significantly increased intracellular magnesium levels in healthy subjects.

**Hypothesis**

Magnox 520® may reduce the number and severity of NLC; an improvement in the quality of life and quality of sleep may ensue.

**Objective:**

To assess the effect of treatment with Magnox 520®, as compared with placebo, on frequency and severity of NLC, quality of sleep and quality of life.

**Methods**

**Study design:**

A prospective, randomized, double blind, placebo controlled clinical trial.

**Participants:**

Two hundred individuals afflicted by NLC will be recruited for the study.

**Inclusion criteria:**

1. Age > 21 years old.
2. Over 4 episodes of documented NLC during 2 weeks of eligibility screening.
3. Insured by Clalit Health Services (CHS).
4. Hebrew speakers

**Exclusion criteria:**

1. Pregnancy
2. Currently taking Quinidine or magnesium additive
3. Renal failure – serum creatinine more than 2 mg/Dl. If the result is near these limits (i.e. serum 1.5-2) a second analysis will be done before the study treatment phase.
4. Major neurological disease- ALS, MS, Paraplegia or Quadriplegia.

Setting:
Community clinics of Clalit Health Services.

Intervention:
Each randomized individual will be given once daily either MAGNOX 520® (un-organic granular magnesium complex, composed of Magnesium Oxide & Magnesium Oxide Monohydrate 865mg, Provides 520 mg of free elemental Mg++) or a similarly looking placebo, in number coded bottles containing 30 capsules each, for a treatment period of 4 weeks.

Outcomes:*  
The primary outcome is the number of reported episodes of NLC during the 4 weeks of treatment period.
The secondary outcomes are: Severity of NLC; Duration of NLC; Quality of life; Quality of sleep.

Outcomes measurement in each participant
The number, severity and duration of NLC will be measured daily as documented in a designated, structured sleep dairy; The Nocturnal Cramps Sleep Diary (NCSD).

Quality of life and quality of sleep will be assessed by SF-36 and PSQI questionnaires, respectively, to be completed twice - at enrolment and within one week of the end of the treatment period.  
(*A detailed, referenced, description of the study measurement tools is provided in the appendix)

Outcome and compliance ascertainment
During the treatment phase of the study (4 weeks) a daily structured sleep dairy will be filled by the participating individuals; we will initiate a daily Short Message Service (SMS) reminder and 1-2 weekly telephone calls in order to ensure compliance and proper monitoring and documentation of sleep and NLC events. The degree of pain will be recorded in the dairy on a scale of 0 to 10 (0=no pain, 10= intolerable pain). Capsules count will be conducted upon the medication bottles retrieval at the end of the treatment phase of the study in each participating individual.

Interim analysis and stopping guidelines
A blinded interim analysis of efficacy will be performed when outcome results for 50% of the anticipated number of participants will be available. It will be presented to an independent data reviewing and monitoring committee appointed to monitor the safety and scientific integrity of the study, and to make recommendations regarding the early termination of the trial for efficacy, for
harms or for futility. The committee members are Miri Sarid PhD, Statistician, and Professor Giora Pilar, MD, PhD, expert in sleep medicine.

**Ethical Issues**

The study medication is a freely available, over the counter (OTC), supplement. Participating individuals will sign an informed consent form approved by the Independent Review Board (IRB) of Meir Medical Center (see *Enrolment and Eligibility Screening* section below), prior to any study procedure. Informed consent will be obtained by GCP certified physicians.

Additional Ethical Comments:

Those subjects who respond to the advertisements have implicitly given their permission to be contacted by doing so. Consequently, as an optional pre-screening procedure, when a potential participant calls the research center, it is ethically acceptable to receive an oral approval to extract the patient's latest Creatinine measurement from the medical records, in order to prevent unnecessary invitation and disappointment. We specifically ask the CHS Community IRB for an approval for this pre-screening procedure.

Individuals, that report at enrollment that they are currently taking Magnesium supplements, cannot be included in the study according to the exclusion criteria. However, since the study starts with a two weeks screening phase (without treatment), if this individuals express their willingness to stop taking the Magnesium supplement and by that wish to be able participate in the study, this exclusion criteria is no longer valid in this particular subjects. Consequently, they may be enrolled in the study if they freely wish to do so. We believe that this is ethically acceptable since Magnesium supplement is a freely available OTC and there is no evidence that Magnesium supplement is beneficial.

**Recruitment and Follow Up:**

*Outreach*

Patients suffering from NLC will be recruited, by self selection through advertisements in CHS clinics, local media and pharmacies. Patients calling the research center will be asked, as a optional pre-screening procedure, to provide an oral approval to extract their latest Creatinine measurement from the medical records, in order to prevent unnecessary invitation and disappointment. This oral consent is given freely and is not a condition to proceed in the study. Patient taking currently Magnesium OTC supplement will have to agree to stop taking this OTC in order to be included in the study.

*Enrolment and Eligibility Screening*
Eligible individuals will be invited for enrollment. A comprehensive description of the study rational and process will be provided and, after questioning and elaboration as requested by the candidate, a signed informed consent will be obtained. Each candidate will then undergo 2 weeks of primary eligibility screening during which he will be asked to report all episodes of NLC by filling the NCSD. Individuals with more than 4 NLC episodes during 2 week will be eligible to start the treatment phase of the study and receive the study medication.

**Randomization**

Eligible participants will be randomly assigned, following simple randomization procedure (computerized random numbers), to one of the two treatment groups. Participants will be assigned a sequential order number and received the capsules in the corresponding numbered pre-packed bottles.

**Treatment Phase**

Each randomized individual will be given once daily either MAGNOX 520® (un-organic granular magnesium complex, composed of Magnesium Oxide & Magnesium Oxide Monohydrate 865mg, Provides 520 mg of free elemental Mg++) or a similarly looking placebo, in number coded bottles containing 30 capsules each, for a treatment period of 4 weeks.

**Masking**

Identical capsules, containing Mg or placebo according to the randomization schedule, are pre-packed in identical bottles and consecutively numbered for each enrolled individual. Both patients and investigators are blinded to treatment allocation for each individual. All participants will be instructed to avoid consumption of any vitamin or mineral supplements during the treatment phase of the study.

**Expected side effects:**

Minor reported side effects were abdominal discomfort and diarrhea occurring in magnesium and placebo- treated patients.\(^\text{10,11}\)

**Adverse Events reporting:**

Participants will be asked about any adverse event (AE) during the treatment phase of the study by 1-2 weekly telephone. Any adverse event will be reported to the PI immediately by filling an AE form. Any serious adverse event (SAE) will be reported immediately by telephone to the PI.

**Statistical methods:**
We estimated that 110 participants would be needed in each group to achieve 80% power to detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is one (difference in means change between treatment groups) NLC per week. This was based on the assumption, and the results reported by Roffe et al, that the standard deviation of the mean number of NLC per week is three.

In order to examine the homogeneity between groups regarding outcome measures at enrollment and bio-demographic measures (study vs. control) a t-test will be conducted with group as independent variable, and study outcomes at enrollment and bio-demographic measures as dependents. Bio-demographic nominal scale variables will be tested using Chi square test. At the end of the study a composed subscales of the dependent variables will be computed, as follows: SF36 questionnaire, PSQI questionnaire, and number, severity and duration of NLC according to daily dairy. All the subscales will be computed according to instructions in the study tools manuals. 2-way (group X time) trend analysis will be conducted looking for possible trend of change in treatment effect across time. The effect of the study will be examined using repeated measures (RM) ANOVA. The repeated measures analysis will compare the difference scores of each of the dependent measures between study and control groups. In order to explore possible effects of bio-demographic variables a 2-way/3-way RM ANOVA with group X independent factors (for example: gender, age) will be conducted.

**Role of Sponsor, Investigators and Manufacturer**

Sponsor and study monitor: Uzi milman MD (UM), director, research unit, Clalit Health Services, Haifa and Western Galilee District and the Department of Family Medicine, Faculty of Medicine, Technion- Israel Institute of Technology, HAIFA, ISRAEL.

Principal Investigator: Noga Maor Roguin MD (NMR), researcher, research unit, Clalit Health Services, Haifa and Western Galilee District.

Co-investigators: Yelena Shtorman MD (YS), Mordechai Alperin MD (MA), Hassan Khir Al din MD (HK), Khaled Karkaby (KK), Moran Freidman (MF); all researchers from the research unit, Clalit Health Services, Haifa and Western Galilee District and the Department of Family Medicine, Faculty of Medicine, Technion- Israel Institute of Technology, HAIFA, ISRAEL.

The study was conceived by NMR and UM. The protocol was drafted by UM, NMR and MA; the final version was approved by all investigators, without any involvement of the manufacturer,
Nevepharma LTD, in the preparation of the study protocol, the design, conduct, data analysis and report of the study.

Individuals will be recruited by the researchers that will obtain an informed consent; study procedures, conduct, follow up and analysis will be contracted directly by the manufacturer with Sarid institute INC. Process and analysis results will be reported directly to the researchers.

**Funding:**

Study capsules (MAGNOX 520™ or placebo) will be supplied by the manufacturer, Nevepharma LTD. All the needed research resources, as described in the study protocol MgNLC ver 003, (including statistical analysis and consultation, a research assistant and the study forms and coordination) will be provided to the study researchers by Sarid Institute INC contracted directly with Nevepharma LTD. These resources and the study medication will be available for the researchers free of any charge and without any involvement of Nevepharma LTD in the preparation of the study protocol, the design, conduct, data analysis and reporting of the study. The sponsor and investigators will not receive any personal or any other funding from the manufacturer, Nevepharma LTD. Participating individuals will be offered travel expenses reimbursement of 50$ (200 NIS).
REFERENCES

Nocturnal Cramps Sleep Diary

<table>
<thead>
<tr>
<th>Participant code</th>
<th>Week No.</th>
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### Evening questionnaire – Should be filled before going to sleep

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<tbody>
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<td>Date</td>
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<table>
<thead>
<tr>
<th>Did you sleep during the day?</th>
<th>Yes/ No</th>
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<tbody>
<tr>
<td>Did you do any physical activity?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>How long?</td>
<td></td>
</tr>
<tr>
<td>Did you take a sleeping medication?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>Did you drink alcohol?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>Did you drink coffee after 15:00?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>Did you smoke before sleeping?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>Was it a normal /typical day?</td>
<td>Yes/ No</td>
</tr>
</tbody>
</table>

### Morning questionnaire - should be filled in the morning

<table>
<thead>
<tr>
<th>At what time did you get into bed?</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>How long did it take until you fell asleep (minutes)?</td>
<td></td>
</tr>
<tr>
<td>How many hours did you sleep at night?</td>
<td></td>
</tr>
<tr>
<td>How many times did you wake up because of cramps?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What was the severity of pain of each cramp (on a 0-10 scale: 0= almost no pain, 10- unbearable pain)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First cramp</td>
<td></td>
</tr>
<tr>
<td>Second cramp</td>
<td></td>
</tr>
<tr>
<td>Third cramp</td>
<td></td>
</tr>
<tr>
<td>Fourth cramp</td>
<td></td>
</tr>
<tr>
<td>How long on average did every cramp last (minutes)?</td>
<td></td>
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<tr>
<td>How long did it take until you fell back to sleep (minutes)?</td>
<td></td>
</tr>
<tr>
<td>How long did you actually sleep this night (hours)?</td>
<td></td>
</tr>
<tr>
<td>Did you have a sore calf in the morning?</td>
<td></td>
</tr>
<tr>
<td>What was the quality of your night sleep? (0=extremely bad, 1=bad, 2-moderate, 3- good 4- very good)</td>
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</tr>
</tbody>
</table>

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*a the answer to this question defines the primary outcome of the study of frequency of NLC; we counted the number of NLC events, during each week of the entire study, for each participant; for the statistical analysis the weekly means were calculated for each treatment group during the two weeks screening and the four weeks treatment phases.*

*b the answer to this question defines the secondary outcomes of the study; to assess severity of NLC we calculated the weekly average of severity of pain of the reported events (sum of pain severity in all NLC divided by their number); for the statistical analysis the weekly means were calculated for each treatment group during the two weeks screening and the four weeks treatment phases.*

*c similar assessment, as was done for severity of pain, was used for the duration of NLC.*