Research Article

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The Effect of a Topical Homeopathic Solution on Nocturnal Leg Cramps and Associated Symptoms

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Abstract

Background: Approximately 33% of individuals age 50 years and older report Nocturnal Leg Cramps (NLC). NLC are associated with poor sleep quality, declining quality of life and depression. The purpose of this study was to determine the effect of a topical homeopathic solution dispensed as a foam on the frequency and severity of night-time cramps and associated symptoms including, sleep quality, quality of life, and depression.
Materials: A topical homeopathic solution dispensed as a foam containing magnesium sulfate.
Methods: 50 subjects who reported NLC volunteered to participate in a 4-week double blind clinical trial. Subjects self-reported their sleep quality, quality of life and depression upon entering into the study following two weeks of no treatment and again following 2 weeks of either topically applying a homeopathic solution dispensed as a foam or a placebo foam. Subjects also completed a daily diary indicating the frequency and severity of their night-time cramps. During the two week treatment period subjects were instructed to apply their assigned topical foam to their legs bilaterally before retiring to bed.
Results: The subjects who received the homeopathic solution exhibited declines ($p<.05$) in the frequency of cramps and the severity by frequency of cramps between weeks 1 and 4. Subjects receiving the homeopathic solution reported improvements ($p<.05$) in their sleep quality, quality of life and depression. Subjects receiving the placebo did not change on any outcome measures between weeks 1 and 4.
Conclusion: The homeopathic solution may provide a complimentary therapy to treating NLCs and associated symptoms.

Keywords: Nocturnal leg cramps; Sleep quality; Topical homeopathic

Introduction

Nocturnal Leg Cramps (NLC) are involuntary and painful contractions of muscles usually involving the thigh, calf, or foot muscles most commonly occurring at rest in the evening [1,2]. Although widely prevalent there are few effective or standard therapies to treat this condition [3,4]. A definition of NLC has been proposed by American Academy of Sleep Medicine International Classification of Sleep Disorders [5,6] to include the following criteria:

- A painful sensation in the leg or foot associated with sudden, involuntary muscle hardness or tightness, indicating a strong muscle contraction.
- The painful muscle contractions occur during the time in bed, although they may arise from either wakefulness or sleep.
- The pain is relieved by forceful stretching of the

affected muscles, thus releasing the contraction.

While NLC can occur over the entire life span, this condition is more common and severe in later life with approximately 40% of a clinical sample of older adults reporting NLC more than three times per week and 21% describing their symptoms as very distressing [7]. In another study of 350 older adults, 50% of the sample reported NLC, twenty percent of the sample experienced symptoms for over 10 years with a majority of these individuals not reporting the symptoms to their physician [8]. NLC reported by older adults can have a significant negative impact on sleep quality and quality of life [2,7].

Magnesium has been implicated in playing a role in leg cramps [9]. Magnesium is a critical element in numerous metabolic reactions and in muscle functioning [10]. Magnesium deficiency can lead to neural excitability and muscle cramping [11]. The administration of oral magnesium salts has been shown to be effective in the treatment of pregnancy-associated leg cramps [12]. In contrast, previous investigators [13,14] have reported that daily oral administration of magnesium oxide was not superior to a placebo condition in reducing the severity and duration of NLC, improving sleep quality or improving quality of life among older adults. These results are consistent with the results of a systematic review, whose authors reported no clear efficacy of orally administered magnesium salts for leg cramps [15]. A limitation of the previously mentioned studies is that the magnesium treatment was administered orally to subjects with no known magnesium deficiency. Since magnesium is an intracellular cation, elevations in serum concentrations as a result of oral administration may have been filtered by the kidneys prior to increasing intracellular magnesium concentrations in the targeted tissue of the leg muscles. The current study attempts to address this limitation by administering the magnesium treatment topically in order to facilitate tissue absorption at the site where muscle cramping is occurring.

Materials

THERAWORX RELIEF™ (https://theraworx.com/) is a topical homeopathic solution dispensed as foam and available over the counter. Preliminary studies of this topical solution conducted by the manufacturer indicate the formula can reduce the duration of muscle cramps experienced during a sporting event (Avadim Technologies Inc. http://avadimtechnologies.com/). The formula for this topical homeopathic solution was initially developed as a skin cleanser and all of its ingredients being biocompatible. The formula for this topical homeopathic solution is proprietary (Patent #6,358,516, #6,780,825 Avadim Technologies, Inc., Ashville, NC.) with the active ingredients including magnesium sulfate 6x. The manufacture of this topical homeopathic solution, Avadim, also hypothesizes that this product is absorbed through the skin and has an effect on the underlying tissues adjacent to where it is applied. A recent double blinded, placebo controlled trial demonstrated that this topical homeopathic solution dispensed as a foam inhibited the accumulation of serum lactate compared to placebo during exhaustive exercise [16]. Additionally, a double blinded placebo controlled pilot demonstrated that when this topical homeopathic solution dispensed as a foam was topically applied it resulted in a significant increase in deep tissue blood flow during exercise, rest and with occlusion as detected by near infrared spectroscopy [17]. The proposed mechanism of action of this topical foam is an increased oxygenation, increased blood flow and increased intracellular magnesium concentrations to the underlying tissues adjacent to the topical application. These mechanisms are therefore theorized to decrease muscle cramping.

The purpose of this study was to determine the effect of a topical homeopathic solution dispensed as a foam on the frequency and severity of night-time cramps and associated symptoms including, sleep quality, quality of life, and depression.

The following hypotheses will be tested in this study:

•H1: Individuals who experience night-time cramps greater than three times per week will report fewer night-time cramps and a decreased severity of cramps as a result of a 14-day application of a topical homeopathic solution.

•H2: Individuals who experience night-time cramps greater than three times per week will report improved sleep quality as a result of a 14-day application of a topical homeopathic solution.

•H3: Individuals who experience night-time cramps symptoms greater than three times per week will report improved quality of life as a result of a 14-day application of a topical homeopathic solution.

•H4: Individuals who experience night-time cramps greater than three times per week will report lower depression as a result of a 14-day application of a topical homeopathic solution.

Table 1: Demographic Variables at Baseline by Treatment Group.

Variable	Treatment Group	Mean Std. Deviation		t-value	P-value
Age	Foam A (Placebo)	50.52 ± 11.87		0.32	.75
	Foam B (Treatment)	49.40 ± 13.21			
Caffeine (cups/day)	Foam A (Placebo)	1.42 ± 1.11		1.04	.31
	Foam B (Treatment)	1.76 ± 1.20			
Exercise (days/wk)	Foam A (Placebo)	2.64 ± 1.93		1.19	.24
	Foam B (Treatment)	3.64 ± 2.14			
How Long Have You Experienced Cramps (yrs)	Foam A (Placebo)	6.84 ± 6.76		0.88	.38
	Foam B (Treatment)	5.32 ± 5.36			
Days with Cramps per week	Foam A (Placebo)	4.16 ± 1.28		1.07	.29
	Foam B (Treatment)	4.60 ± 1.61			
Duration of Cramp (mins)	Foam A (Placebo)	14.25 ± 17.22		1.34	.19
	Foam B (Treatment)	8.28 ± 13.68			
		Male	Female	Chi-Square	P-value
Gender	Foam A (Placebo)	14 (56%)	11 (44%)	8.68	.00
	Foam B (Treatment)	4 (16%)	21 (84%)		

Methods

Subjects were recruited through various targeted methods including newspaper ads, fliers in pharmacies and physician offices, social media, sleep disorder support groups, and word of mouth. Individuals were excluded from the study if they were pregnant, have been previously diagnosed with Restless Leg Syndrome (RLS), schizophrenia, and/or any other neurological disorder. Individuals were included in the study if they reported experiencing night-time leg cramps on average at least three times per week. Eligible individuals were scheduled to attend an initial assessment (Baseline) at a community-based physical therapy clinic. During this visit, the study was described and the individual was asked to provide written consent to participate in the protocol (IRB#:2016.3). Following providing informed consent, the subjects were asked to complete a series of questionnaires about their demographic characteristics, symptoms associated with NLC including sleep quality, quality of life and depression. Once these questionnaires were completed all subjects engaged in a 14-day no

Table 2: Treatment Compliance and Reported Benefit by Treatment Group.

Variable	Treatment Group	Mean± Std. Deviation		t-value	P-value
Additional Pumps of Foam per week	Foam A (Placebo)	6.64 ± 8.11		0.24	.82
	Foam B (Treatment)	7.20 ± 8.73			
Compliance with Treatment	Foam A (Placebo)	96.03 ± 19.84		1.00	.32
	Foam B (Treatment)	100.00 ± .00			
		Yes	No	Chi-Square	P-value
Reported Benefit of Treatment on NLCs	Foam A (Placebo)	11 (44%)	14 (56%)	1.28	.26
	Foam B (Treatment)	15 (60%)	10 (40%)		

Table 3: Weekly Frequency, Severity and Frequency by Severity of NLC by Treatment Group.

Treatment Group	Week	Frequency of Cramp Events Mean ± SE	Severity of Cramp Events Mean ± SE	Frequency by Severity of Cramp Mean ± SE
Foam A (Placebo)	1	4.72 ±.34	4.09±.35	21.06±2.85
	2	4.80 ±.42	4.67±.42*	24.72±3.89
	3	3.22 ±.45*	3.37±.43	14.63±3.25*
	4	3.92 ±.59	3.43±.45	17.29±3.55
Foam B (Treatment)	1	5.12 ±.34	4.85±.36	25.09±2.86
	2	4.72 ±.42	5.30±.42	26.19±3.90
	3	4.44 ±.40	4.09±.43*	20.75±3.26
	4	3.92* ±.59*	4.40±.45	20.73±3.55*

SE: Standard Error of the Mean

* Indicates a significant change within treatment group from week 1

treatment period in which they were told not to change their usual activities and treatments. Each morning during the 14 day no treatment period subjects were asked to complete a Symptom Log on which they documented the frequency and severity of night-time cramps they experienced the previous night.

Subjects returned to clinic following this 14-day no treatment period (Post Control) and completed the same questionnaires excluding the demographic questions, as these demographic characteristics were not expected to change during the trial. Variables that were collected at the Post Control data collection point included the same measures of sleep quality, quality of life and depression that were collected at Baseline. Subjects were asked to refer their responses on these instruments to the previous two weeks following completion of the Baseline assessment. Once the subjects completed these instruments they were randomly assigned to one of two study groups by selecting 1 of 50 shuffled envelopes. Within 25 of these envelopes a card indicated "Foam A" and the remaining 25 envelopes contained a card indicating "Foam B." Subjects received two 3-ounce foam dispensers corresponding to their group assignment (Foam A or Foam B) and a 2-week

Table 4: Patient Functional Scale and Depression by Time and Treatment Group.

Treatment Group	Data Collection	Patient-Specific Functional Scale Mean ± SE	Beck Depression Scale Mean ± SE
Foam A (Placebo)	Baseline	5.76±.58	8.84 ± 1.75
	Post Control	6.59±.55*	6.92 ±1.60
	Post Treatment	7.40±.59	5.60 ±1.30
Foam B (Treatment)	Baseline	4.53±.58	12.40 ±1.75
	Post Control	4.99±.55	9.56 ±1.60*
	Post Treatment	6.47±.59*#	6.88 ±1.30*#

SE: Standard Error of the Mean
*Indicates a significant change from Baseline within the group
# indicates a significant change from Post Control to Post Treatment within the group

Table 5: Restless Legs Syndrome (RLS) Quality of Life Instrument (RLS-QLI) subscales by Time and Treatment Group.

Treatment Group	Data Collection	Social Functioning Mean ± SE	Daily Functioning Mean ± SE	Sleep Quality Mean ± SE	Emotional Wellbeing Mean ± SE	Quality of Life Mean ± SE
Foam A (Placebo)	Baseline	80.75±4.36	73.17±5.11	37.11±4.23	67.00±6.18	64.51±4.42
	Post Control	83.16±3.97	77.49±4.47	42.04±3.96*	72.33±5.59	68.29±3.94*
	Post Treatment	87.03±3.35	85.50±3.73	53.88±4.48	82.37±4.61	76.29±3.63
Foam B (Treatment)	Baseline	78.92±4.36	65.33±4.91	29.56±4.07	58.00±5.93	58.02±4.24
	Post Control	77.75±3.98	69.50±4.30	35.33±3.80*	64.33±5.37	61.30±3.78
	Post Treatment	87.00±3.47 *#	81.50 ±3.58*#	47.55±4.31*#	77.00±4.43*#	72.82±3.49*#

SE: Standard Error of the Mean
*Indicates a significant change from Baseline
# indicates a significant change from Post Control to Post Treatment

Compliance and Symptom Log. The contents of these two foams remained blind to the subjects and the data collectors throughout the duration of the study until data analysis was completed. One of the foams contained the topical homeopathic solution (treatment) and the other contained a physiologically inert substance (placebo). Subjects were instructed to apply the foam they had been assigned to their entire upper and lower legs and feet using eight pumps from the product dispenser per leg (upper thigh to foot) before retiring each evening for the next 14 days. If a subject experienced leg cramps after applying their assigned foam, they were instructed to reapply two pumps of the foam to the affected area in response to each event. Each morning during the 14 days in which subjects applied the foam they were asked to complete the Compliance and Symptom Log that documented the frequency and severity of night-time cramps and their use of the assigned foam they used to treat their night-time cramps the previous evening. Following 14 consecutive evenings of applying their

assigned foam, subjects returned to the community clinic (Post Treatment), and return their completed Compliance and Symptom Log. During this final visit subjects again completed the same measures of sleep quality, quality of life, and depression that they completed during their Baseline and Post Control visits, referring their responses to the previous two weeks when they were applying the assigned foam to their legs. Subjects were compensated $25 for completing the Baseline and Post Control data collection visits and $100 for completing the Post Treatment data collection visit.

The outcome variables of sleep quality, quality of life, and depression were collected by subjects completing a series of questionnaires at Baseline, Post Control and Post Treatment. The outcome variables of frequency and severity of night-time cramps were collected by the subject keeping a daily Symptom Log on which they recorded the frequency and severity of their night-time leg cramps over the entire 4-week protocol. Each morning during the 4-week study subjects recorded on the Symptom Log if they experienced any leg cramping the previous night (frequency), and if so the severity of the cramp on a scale from 1 (very minor) to 10 (worst possible). The frequency and severity of the leg cramps recorded by subjects on the Symptom Log were averaged over each week over the 4-week study protocol. During weeks three & four of the protocol subjects were asked to record their compliance (Yes/No) with applying the assigned foam to their legs. Finally, at the Post Treatment data collection point, subjects were asked if they recognized a benefit from applying the foam on their NLC by responding Yes or No.

The Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) was used to measure sleep quality and quality of life among the sample. This 17-item questionnaire asked the subject to respond regarding the impact of night-time cramps and spasms on various aspects of their life during the previous two weeks. Responses were recorded on a five-point scale indicating greater degrees of impact. These items were combined into four subscales including Daily Function, Social Function, Sleep Quality, and Emotional Well-Being with higher scores indicating lower sleep quality or quality of life. Each of these subscales scale had acceptable psychometric properties [18].

Quality of life was also measured by having subjects complete the Modified Patient Specific Functional Scale (MPSFS). This instrument asks the subject to identify three important activities that they are unable to do or are having difficulty with as a result of their NLC and to rate the severity of their reduced functioning [19]. Subjects rated their difficulty in performing each task on an 11-point numerical scale with "0" indicating being unable to perform the activity and "10" indicating being able to perform the activity at the same level before experiencing NLC. An average functional limitation score was calculated by the sum of the reduced functioning scores divided by the total number of activities cited. At subsequent reassessments subjects were informed of the activities and corresponding difficulty scores identified at the previous assessment and asked to provide a current difficulty score. Higher scores indicted reduced functional limitations attributable to NLCs. The concurrent validity, sensitivity to change over time and reliability of the MPSFS was deemed adequate for using the tool in clinical practice [19].

The Beck Depression Index (BDI) was developed by Beck and co-workers [20,21] and consists of 21-question multiple-choice self-report items quantifying depressive symptoms. Higher scores on the BDI indicates a greater number of depressive symptoms. A meta-analysis of the BDI's internal consistency estimates yielded a mean coefficient alpha of 0.86 for psychiatric patients and 0.81 for non-psychiatric subjects. The concurrent validity of the BDI with respect to clinical ratings and the Hamilton Psychiatric Rating Scale for Depression (HRSD) were also high.

The recruitment and randomization efforts resulted in 50 subjects randomly assigned to the Foam A (n=25) or Foam B (n=25) study groups following two weeks of no treatment. The analysis was conducted in two phases. During phase one descriptive statistics were calculated to describe the demographic characteristics of the sample in order to assess the external validity of the results and the application of the findings to the larger population of patients suffering with NLC. The second phase of the analysis involved addressing the study hypotheses. Repeated measures analysis of variance (R-ANOVA) were calculated to determine if any of the outcome variables differed ($p<.05$) between or within the two study groups over the duration of the study. Main or interaction effects detected by the R-ANOVA were explored further through calculating Tukey's post hoc comparisons. Finally, univariate comparisons (e.g. t-tests) determined if compliance rates or reported benefits differed between the study groups.

Results

Table 1 indicates that the two study groups reported similar ages (ranging from 36 to 63 years), caffeine intake, days of exercise per week, years of experiencing NLC, and days per week affected by NLC. This table did indicate that a greater proportion of the group receiving Foam A were male (56%) versus the group receiving Foam B (16%) ($\chi 2$= 8.68, p<.00).

Table 2 presents comparisons that indicate no statistical difference in the treatment group's compliance with their respective treatment (Foam A = 96.03% vs Foam B = 100%) or the use of additional treatment (pumps of foam per week) in response to NLC (Foam A = 6.64 vs Foam B = 7.20). Finally, this table indicates no differences in the proportion of subjects who reported a benefit of using their respective foam on reducing their NLC (Foam A = 44% vs Foam B = 60%).

Table 3 reports the group receiving the Foam B (treatment) which contained the topical homeopathic solution recorded a significant decline in the frequency of weekly NLCs between week one and week four. The group who received Foam A (placebo) recorded a decline in weekly frequency of NLC between weeks one and three but did not sustain this significant decline between weeks one and four. The group receiving the placebo did not report a significant change in the severity of their NLC from week one during weeks three and four when they were applying their respective therapy. The treatment group reported a significant decline from their week one measures of cramp severity during week three that was not sustained during week four of the study. Finally, the group receiving the placebo reported a significant decline in frequency by severity of NLC between weeks one and three that was not sustained between weeks one and four. In contrast, the group who received the treatment experienced a significant decline in frequency by severity on NLC between weeks one and four.

Table 4 presents the Patient-Specific Functional Scale and Beck Depression values of the two study groups at Baseline, Post Control and Post Treatment data collection points. For each of these measures the Treatment group reported a significant improvement in their functional scale and a decrease in depression between Baseline and Post Treatment and between Post Control to Post Treatment. The group who received the Placebo did not change on these outcome measures at Post Treatment compared with Baseline or Post Control. These results are similar to the findings of the analysis of the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) presented in table 5. As evidenced in this table the group who received the foam containing the topical homeopathic solution recorded significant improvements in social functioning, daily functioning, sleep quality, emotional wellbeing and quality of life between Baseline and Post Treatment and between Post Control to Post Treatment. The group who received the foam containing the placebo did not change on these measures at post treatment compared to their measurements at the Baseline and Post Control data collection points.

Discussion

The statistical results support the study hypotheses. In support of hypotheses 1 only the group who received the foam containing the topical homeopathic solution reported a sustained decrease in the frequency and frequency by severity of their NLC between weeks one and four. The group receiving the Placebo reported a decline at week three in NLC frequency and frequency by severity compared to week one, although these initial benefits of the Placebo were not sustained into week four as the placebo group experienced an increase in incidence and severity between weeks three and four of the study. These findings may indicate the important effect of a placebo on reducing NLC symptoms during the first week of application, although these favorable placebo effects were not sustained longer than one week. This is in contrast to the beneficial effects of the foam containing the topical homeopathic solution on reducing NLC frequency and frequency by severity being sustained between weeks one and four of the study.

Hypotheses 2, 3, and 4 were also supported by the results. During the 14-day period when the foam containing the topical homeopathic solution was applied the subjects receiving this intervention reported significant improvements in their sleep quality while the subjects who received the placebo did not report a change in their sleep quality. A similar pattern in the data emerged with the measures of quality of life and depression. The group who received the topical homeopathic solution consistently improved on all of these symptoms associated with NLC between Baseline and Post Treatment and Post Control and Post Treatment. The group receiving the Placebo did not change on these symptoms associated with NLC.

Although encouraging, these findings warrant further consideration and more study. The sample did appear to represent the larger population of individuals who

suffer from NLC. The 50 subjects exhibited demographic characteristics similar to the population of NLC patients. A majority of the sample was female (67%) [2,10], older (mean age=50 years), who have suffered from NLC for an average of six years [8] with NLC associated symptoms including reduced sleep quality, quality of life, and depression [7,22]. The two study groups reported similar levels on all five of the RLS-QLI subscales at Baseline with sleep quality being particularly low and consistent with individuals with diagnosed sleep disorders [18]. The results of the Beck Depression Scale indicated the sample was on the threshold of mild mood disturbance (BDS = 11-16) which is common among individuals with a sleep disorder [23]. Although representative of the larger population of NLC patients, the sample size and duration of the study may have been inadequate to detect significant differences between groups resulting from the treatment. This is based on the observation that the placebo had a beneficial effect on reducing cramp frequency and severity during the initial week of applying the Placebo (third week of the study). Although this placebo effect could not be maintained into the second week of treatment once any potential novelty effect had subsided. A continued deterioration of the placebo effect and the continued beneficial effect of the topical homeopathic solution may have resulted in significantly different outcomes measures between the groups if the study had continued for a longer duration. The treatment containing the topical homeopathic solution dispensed as foam in this study that included magnesium resulted in reduced NLC and associated symptoms, appears divergent to the prevailing studies who reported that orally administered magnesium did not affect NLC [13-15].

The favorable effect of the topical homeopathic solution intervention may be because it was applied topically and the magnesium passed through the affected tissues responsible for NLC before being absorbed into the body's serum and excreted through the kidneys. In addition to the potential benefits of topical magnesium reducing NLC, the topical homeopathic solution has also been demonstrated to increase tissue blood flow, and inhibit serum lactate, possibly contributing to stabilization of tissue pH [17]. These changes in tissue pH and blood flow resulting from the topical application of the topical homeopathic solution appear related to reductions in the frequency and severity of night-time cramps and associated symptoms, including sleep quality, quality of life, and depression.

The findings of this study may have important clinical implications due to the emerging policies for use of pharmaceutical interventions to treat NLC particularly among older adults. Considering up to 29 million Americans have NLC and spasms on a nightly basis and another 116 million report the symptoms in some capacity, the condition causes individuals significant disruption of sleep and quality of life. The need for a safe, low-risk, and high-benefit solution therefore has broad application.

Quinine has been a long-standing common treatment for NLC and has been found to result in significant relief of NLC symptoms [24]. As this is an off-label use for the medication, in 2006, because of efficacy and safety issues, the US Food and Drug Administration cautioned its use, citing "665 reports of adverse events with serious outcomes…including 93 deaths" [25]. Authors completing a meta-analysis reported that patients who were prescribed Quinine increased their risk of death three fold compared to a placebo or no treatment [26]. In a more recent study, the rate of death in individuals with heart failure who initiated Quinine for leg cramps was significantly higher compared with those who did not initiate the medication [27]. Thus, practitioners treating patients with NLC are advised to not use Quinine and are left searching for an effective therapy for this condition that is accompanied by few side effects.

Conclusion

The current study presents evidence that the topical homeopathic solution may provide relief from NLC and associated symptoms. Considering risks associated with current medication such as the previously mentioned Quinine, the topical homeopathic solution may be a viable alternative to treating NLC. Furthermore, since the topical homeopathic solution is an over the counter homeopathic treatment with a no know side effects [28], practitioners may easily prescribe this therapy in treating NLC. This topical homeopathic solution appears to offer Physicians, Pharmacists, Nurse Practitioners, Physician Assistants, and patients a truly obtainable and beneficial option to treat NLC.

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