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Neuromuscular Electrical Stimulation Reduces Leg Cramps in Patients With Lumbar Degenerative Disorders: A Randomized Placebo-Controlled Trial

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ABSTRACT

Objectives: Lumbar spinal stenosis (LSS) and lumbar disc herniation (LDH) are often accompanied by frequently occurring leg cramps severely affecting patients' life and sleep quality. Recent evidence suggests that neuromuscular electric stimulation (NMES) of cramp-prone muscles may prevent cramps in lumbar disorders.

Materials and Methods: Thirty-two men and women (63 ± 9 years) with LSS and/or LDH suffering from cramps were randomly allocated to four different groups. Unilateral stimulation of the gastrocnemius was applied twice a week over four weeks (3 × 6 × 5 sec stimulation trains at 30 Hz above the individual cramp threshold frequency [CTF]). Three groups received either 85%, 55%, or 25% of their maximum tolerated stimulation intensity, whereas one group only received pseudo-stimulation.

Results: The number of reported leg cramps decreased in the 25% (25 ± 14 to 7 ± 4; $p = 0.002$), 55% (24 ± 10 to 10 ± 11; $p = 0.014$) and 85%NMES (23 ± 17 to 1 ± 1; $p < 0.001$) group, whereas it remained unchanged after pseudo-stimulation (20 ± 32 to 19 ± 33; $p > 0.999$). In the 25% and 85%NMES group, this improvement was accompanied by an increased CTF ($p < 0.001$).

Conclusion: Regularly applied NMES of the calf muscles reduces leg cramps in patients with LSS/LDH even at low stimulation intensity.

Keywords: Disc herniation, electromyostimulation, gastrocnemius, hyperexcitability, lumbar spinal canal stenosis, NMES

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INTRODUCTION

The incidence of leg cramps in healthy populations has been extensively studied with nationwide age-independent surveys revealing that one in every three people reported at least one muscle cramp during the prior year (1,2). In people aged 65 years and older, even one in two people reported to experience regular leg cramps at rest (3). In contrast, the psychological and physical strain, as well as the social relevance of leg cramps in patients with lumbar degenerative disorders such as lumbar spinal stenosis (LSS) and lumbar disc herniation (LDH) (4–7), is underestimated.

LSS implies several consequential pain syndromes that can be treated in a conservative or surgical manner and hence can be alleviated in most cases. In contrast, frequently occurring and painful leg cramps pose an underrated side effect often remaining or even worsening after surgery (5–7). These leg cramps usually occur at rest and force patients to wake up at night. Spinal cord compression, which often occurs simultaneously with LDH and LSS and has been shown to cause spastic weakness, is one of the pathologic mechanisms that may largely contribute to the higher susceptibility to cramps in these disorders (8). Matsumoto and colleagues (5) recruited 120 men and women with LSS who reported to suffer significantly more often

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from nocturnal calf cramps than healthy controls. As part of the study, the LSS patients underwent decompression surgery. Forty-six percent reported the occurrence of leg cramps to be unchanged and 26% reported worsening of cramp symptoms after surgery. In patients with LDH the frequent incidence of muscle cramps appears to be characteristic to the extent that a cramp induction test has become a diagnostic tool for LDH (4). In this context, the patient is asked to flex the knee against manual resistance to provoke cramping of the hamstring muscles. Demircan and colleagues (4) showed that a negative cramp induction test strongly correlates with patient satisfaction after surgery. Therefore, the development of effective treatment alternatives beyond surgery needs to be addressed.

Recently, we showed that neuromuscular electrical stimulation (NMES) of the gastrocnemius muscle performed twice a week for six weeks reduced the frequency of leg cramps by up to 78% (9). This trial included 19 cramp-prone males of which nine started suffering from regularly occurring leg cramps after LDH. Especially these LDH participants reported improved life quality after NMES as they experienced significantly less (nocturnal) cramps. However, a major drawback of the currently used NMES protocol was the marked discomfort associated with the applied calf stimulations performed at high current settings, which can trigger cramping themselves. Moreover, our previous study design failed to control for a placebo effect, and we used a very heterogeneous sample in terms of age and cramp background.

This study, therefore, set out to assess the efficacy and tolerability of NMES at various stimulation intensities in reducing the frequency of leg cramps in patients with LDH and LSS when compared to pseudo-stimulation. We hypothesized that all NMES treatments would reduce the frequency of leg cramps when compared to pseudo-stimulation.

MATERIAL AND METHODS

Ethics Statement

The study has been performed according to the Declaration of Helsinki, and the local institutional review board has approved the procedures. Written informed consent of all participants has been obtained before enrollment in the study. The present study was preregistered in a clinical trial registry (German Clinical Trials Register; Registration number: DRKS00011294).

Participants

Women and men between the age of 20 and 80 years with a medical history of LDH and/or LSS associated with regular leg cramps (defined as at least one cramp per week in any of the muscles of the lower extremities) were included in the present study (Table 1). Nocturnal-, rest-, and exercise-associated muscle cramps were included. The participants were recruited based on self-reported information about their disease, but before being included in the study they presented their diagnoses in the form of doctor's letters and/or MRI images. The level of lumbar disease was recorded and a broad range from L2 to S1 was represented (S1, L5, and L4 were most common). With the help of local general physicians and orthopedics as well as using several articles in local newspapers, numerous patients who met the inclusion criteria contacted our laboratory to participate. In a first phone call, interested patients were informed about the study design and interviewed about their medical history, particularly their lumbar pathology, diagnosis, and occurrence of leg cramps. Any alternative treatment to reduce leg cramps within three weeks before enrollment in the study was defined as an exclusion criterion, and participants were asked to abstain from any other medical- and non-medical cramp treatment during the entire eight-week observation period. In the case of additional cardiovascular disease, patients could only participate when they provided written consent from their general practitioner. Despite not fixed as exclusion criteria, none of the included participants had ever undergone decompression surgery. Similarly, no participant suffered from peripheral neuropathy or had been diagnosed with diabetes mellitus. The patient flow is illustrated as a CONSORT diagram (Fig. 1).

A bio-impedance analysis was conducted to assess the participants' percentage of body fat, using the segmental body composition analyzer BC-418 (Tanita, IL, USA). Before the start of the intervention, all subjects completed a cramp specific questionnaire referring to cramp characteristics, potential causes, treatment strategies, individual lifestyle, intake of medication, and pre-existing conditions. Participants were instructed to keep physical activity consistent with their routine before enrollment in the study.

Sample Size Calculation

Due to different primary outcome measures and more heterogenous samples, the effects found in our previous studies (9–13) cannot be transferred one-to-one to the current investigation. However, based on the large effects seen in our previous studies, we assumed that we could achieve at least a medium effect (Partial eta^2 = 0.09; corresponding to an f-value of 0.31) on the total number of reported leg cramps. For a repeated measures ANOVA design with a within-between interaction, this resulted (calculated with the software G-Power) in a necessary sample size of 32 subjects for a power of 1-β = 0.8.

Trial Design and Allocation

The study was designed as a prospective, randomized, controlled and single-blind (patient only) trial. In order to form four groups of subjects of equal size, the following randomization procedure was carried out: envelopes containing one of the letters A to D (corresponding to the four groups, each letter had to occur eight times) was generated in advance by an uninvolved person. Participants were then assigned to their stimulation group according to the letter written in the drawn envelope in chronological order of the date of their first session. Three groups received regular NMES treatment at different stimulation intensities (85%, 55%, or 25%), whereas the fourth group received a pseudo-stimulation.

Personal Cramp Log

In our previous study (9), participants had to record each muscle cramp that occurred in their everyday life with remarks on its severity and anatomical localization by using a standardized cramp log. In that study, the time period of keeping the cramp log included two baseline weeks, six weeks of NMES intervention, and two weeks post, adding up to ten weeks in total. We observed that participants tended to become less diligent in reporting every cramp due to the long-lasting time commitment of the log. Therefore, in the present study, only cramps occurring in the two weeks before the first NMES session (pre) and the two weeks after the last session (post) had to be reported (Fig. 2) to reduce this potential interfering factor. Participants were also asked to report whether cramping occurred during exercise, at

Table 1. Descriptive Baseline Characteristics of Participants Divided by Groups.

	25%	55%	85%	Placebo	*p*-value
Age (years)	62 ± 9	66 ± 11	63 ± 10	63 ± 6	0.5155
Gender (female/male)	4/4	3/5	1/7	3/5	0.4519
Body weight (kg)	86.1 ± 19.9	78.4 ± 15.1	84.9 ± 13.3	88.2 ± 23.4	0.7018
Body height (cm)	169.6 ± 9.8	177.8 ± 11.2	178 ± 6.1	175.4 ± 11.9	0.4075
BMI (kg/m^2)	30.3 ± 8.8	24.7 ± 3.2	26.7 ± 3.1	28.4 ± 5.9	0.2661
Body fat (%)	33.9 ± 8.6	28.8 ± 6.4	26.4 ± 5.1	29.2 ± 11.8	0.3565
Reported fluid intake (L/days)	2.3 ± 0.5	1.5 ± 0.5	2.1 ± 0.9	2.1 ± 0.8	0.1007
LDH (*n*)	7	7	6	5	
LSS (*n*)	7	3	7	7	
LDH and LSS (*n*)	6	2	5	4	

Three groups received regular NMES treatment at different stimulation intensities (25%, 55%, or 85% of the maximally tolerated stimulation intensity), whereas the fourth group received a pseudo-stimulation (Placebo). BMI, body mass index; LDH, lumbar disc herniation; LSS, lumbar spinal stenosis.

rest or at night during sleep. For the cramp log, any sudden involuntary and painful muscle contraction was defined as a cramp. Each cramp had to be immediately recorded after its occurrence to avoid recall bias. The severity was rated using a visual analog scale (VAS), including a range from no pain (0 mm) to unbearable pain (100 mm). In line with Boonstra et al. (14), VAS scores of 10–38, 39–57, and 58–100 mm were defined as mild, moderate, and severe pain, respectively. After the first two weeks of keeping the cramp log, participants came to the laboratory for pretests, including the collection of anthropometric data and the determination of the motor point from the medial gastrocnemius of the more cramp-prone leg. On this occasion, the cramp threshold frequency (CTF, see below) was also measured and right afterward the first NMES session was performed.

Motor Point

The motor point (MP) represents the skin area above the muscle belly at which a minimal current is able to evoke a visible muscle contraction (8). To detect the MP, the skin area of the medial gastrocnemius was scanned with a small pen electrode (motor point pen, Cefar Compex, Compex Medical SA, Ecublens VD). This scan was started at a low stimulation intensity (2 mA) and frequency (3 Hz). If no MP could be identified using these settings, the current was gradually increased by 1 mA and the scan of the skin was rerun until a visible muscle contraction emerged. The location of the MP was marked with permanent ink and participants were asked to refresh this mark regularly to stop it from fading. For electrical stimulation of the muscle, two self-adhesive gel electrodes (Performance self-adhesive electrodes, Cefar Compex, Compex Medical SA, Ecublens VD, 5 cm × 5 cm) were placed over the MP and the most proximal region of the medial gastrocnemius, right below the popliteal cavity (9). The identification of the motor point was essential for the placement of the distal muscle stimulation electrode to maximize muscle tension (15) and minimize discomfort (16).

Cramp Threshold Frequency

To determine the cramp threshold frequency (CTF), we used the same approach as described in our previous studies (9–13). Accordingly, a stimulation train of 5 sec was applied to the muscle belly every 55 sec, while participants were instructed to lay prone on an examination bench with their ankle joints flexed at ∼120°. The stimulation frequency of these trains began at 4 Hz and progressively increased by 2 Hz until the onset of a cramp. The waveform of the stimulation pulse was biphasic rectangular, and the impulse width and current intensity remained constant at 400 μsec and 40 mA, respectively. All stimuli were applied via a handheld battery-powered myostimulator (Cefar Compex, Compex 3 Professional, Compex Medical SA, Ecublens VD). The test was discontinued if no cramp was observed up to a frequency of 40 Hz. The participants were asked to relax in the lying position to minimize electromyography (EMG) artifacts from interfering voluntary contractions. A muscle cramp was defined by the following three criteria: 1) the subjective cramp sensation of the participant; 2) a sustained plantar flexion of the foot due to an involuntary contraction of the calf muscles after a stimulation train observed by the investigator; and 3) as the most objective criterium, an average EMG root mean square amplitude (aRMSA) within the 4-sec interval following the stimulation trains that exceeded a value of 2x the standard deviation above the 2-sec baseline aRMSA (preceding the first stimulation train). Except the longer EMG analysis periods used in the present and our previous studies (9,10), the used criteria have been applied in other trials to define the occurrence of an electrically induced muscle cramp (17,18).

In this regard, surface EMG signals of the medial gastrocnemius were displayed live on a computer screen after 12-bit analog-to-digital conversion (NI-DAQ 6024E; National Instruments Corporation, Austin, TX, USA). The respective data were recorded via the software package MyoResearch XP 1.08 Master Edition (Noraxon USA Inc., Scottsdale, AZ, USA). The sampling frequency was 3000 Hz. Data were exported to Matlab (R2105a; Version 8.5, MathWorks, Natick, MA, USA) for further analyses. All data were filtered with a recursive Butterworth filter of the fourth order; frequencies of applied high- and low-pass filters were 10 and 500 Hz. The aRMSA was calculated for the 4-sec interval following each stimulation train and compared to a fixed 2-sec resting interval at baseline.

CTF tests were performed before (Pre), halfway through the intervention before the fifth NMES session (Mid), one day (Post 1), one week (Post 2), and two weeks (Post 3) after the last NMES session (Fig. 2). As soon as the CTF was reached, participants were asked to evaluate the pain associated with the evoked cramp on the same VAS as used in the cramp log (see above). As our previous studies demonstrated that no significant changes in the CTF of the nonstimulated control leg occur (9,10), we only assessed the CTF of the leg that also received NMES to avoid painful stimulation wherever possible.

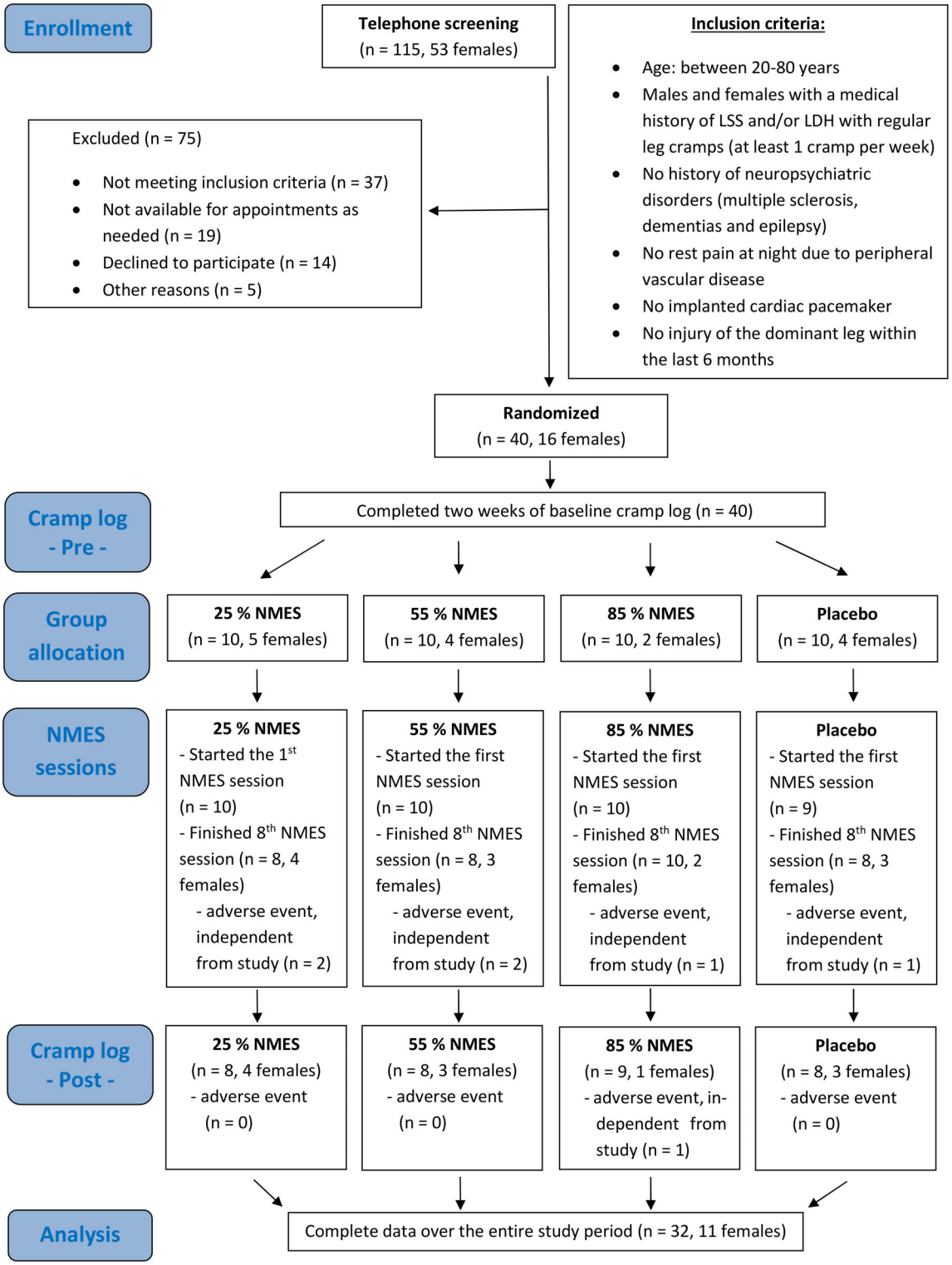

Figure 1. CONSORT diagram of patient flow.

Neuromuscular Stimulation

Except for the applied current the stimulation parameters of the applied protocol were the same as published previously because these parameter settings induced a significant CTF increase in healthy subjects (10,12) and in a cramp-prone population (9). In short, the stimulation sessions included three sets of biphasic rectangular-wave pulsed currents at 30 Hz above the individual CTF (see above); each set included 6 × 5 sec stimulation trains with 10-sec rest between stimulations. Only the medial gastrocnemius of the leg that was predominantly affected by muscle cramps, according to the cramp log, was stimulated. If the CTF increased halfway through the intervention (Mid), the

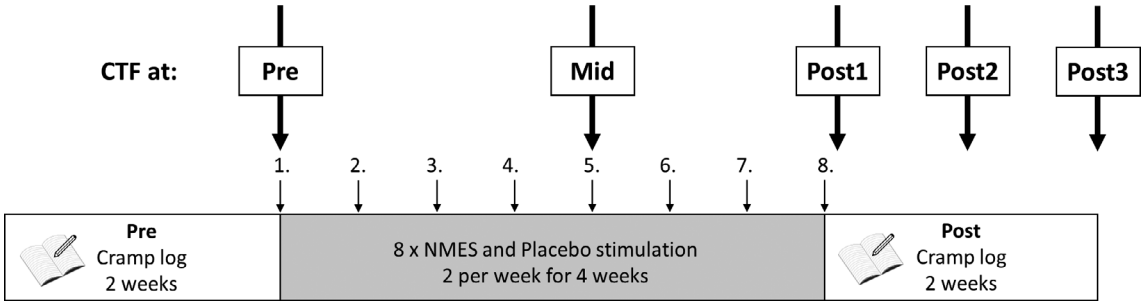

Figure 2. Study design. CTF, cramp threshold frequency; NMES, neuromuscular electrical stimulation.

stimulation frequency was adjusted thereafter to maintain 30 Hz above CTF. The range of applied stimulation frequencies was 36–70 Hz. During stimulation, participants sat on an elevated bench to enable their calf muscles to passively shorten as their lower legs were freely hanging down. Each stimulation session was followed by a rest period of at least 24 hours. Depending on the group assignment of the individuals, the stimulation amplitude was set to 85%, 55%, or 25% of the maximum tolerated stimulation intensity (mTSI), which was tested at the beginning of each session. For this purpose, the intensity was adjusted upwards on a scale of 0–1000 intensity levels of the Compex device (the value of 1000 corresponds to 120 mA at an impulse width of 400 µsec) until the volunteers stated that they would not tolerate a further increase. The stimulation was immediately stopped at that moment and the achieved intensity value was noted for the calculation of the group-specific stimulation intensities. For all three sets, the respective stimulation intensity was held constant or slightly reduced if it was too painful. The perceived discomfort of each set was evaluated on the same 100 mm VAS as used in the cramp log (see above). In total, eight NMES sessions were performed over four weeks with two sessions scheduled per week (Fig. 2).

Placebo Stimulation

The eight participants of the Placebo group also attended our laboratory for eight sessions, where they were treated in the same manner as the three intervention groups. However, instead of upregulating the stimulation intensity at the beginning of each session in order to determine the mTSI, only a minimal current of a few mA lasting a few seconds was applied to evoke a short sensation of the current. For the subsequent three sets of stimulation, the stimulator was switched off and placed out of the participant's field of vision. The times of rest between pretended sets were the same as in the intervention groups. Over the course of the whole study, participants of the placebo group had to adhere to the same instructions as the other groups and completed all post measurements.

STATISTICS

A two-way repeated-measures ANOVA (4 × 2) with groups and testing times as factors was used to compare the effects of different stimulation intensities and placebo treatment on the occurrence of muscle cramps reported in the cramp log. A two-way ANOVA (3 × 8) with groups and NMES sessions as factors was used to compare the effects of different stimulation intensities and placebo treatment on the mTSI and VAS. For the latter analysis, the placebo group was excluded. When significant main effects and interactions were observed, a series of post hoc comparisons corrected for alpha inflation (Bonferroni correction) were performed to identify in which groups and at what testing occasions the differences occurred. For comparisons of the baseline characteristics between groups, the Kruskal–Wallis test was used. A one-way ANOVA was used to detect significant differences in aRMSA values after different stimulation frequencies to confirm the CTF value. The Pearson product moment correlation was used to establish the relationship between the changes (%) of CTF, total cramps, and mTSI from pre to post and also between all baseline characteristics (n = 32). The level of significance was set to <0.05 for all analyses; means with respective standard deviations are used to present data in tables and the running text. Vertical bars in figures represent the standard deviations of the mean. All statistical analyses were performed using the GraphPad Prism 8 software package (GraphPad Software, San Diego, CA, USA).

RESULTS

Baseline Group Characteristics

The random allocation of participants to the four groups did not lead to any significant differences in anthropometric and cramp characteristics between groups at baseline. Descriptive baseline and cramp characteristics of participants divided by groups are shown in Tables 1 and 2, respectively.

Cramp Log

The total number of leg cramps documented in the two weeks before the intervention started was not significantly different between the four groups (p = 0.248) (Table 2). A significant interaction (p = 0.014) between group × time could be found for the total number of leg cramps. The total number of leg cramps decreased in the 25%NMES group from 25 ± 14 to 7 ± 4 (p = 0.002), in the 55%NMES group from 24 ± 10 to 10 ± 11 (p = 0.014) and in the 85%NMES group from 23 ± 17 to 1 ± 1 (p < 0.001). The Placebo group did not show any change (from 20 ± 32 to 19 ± 33, p > 0.999). No significant interaction (p = 0.228) between group × time could be found for the total number of nocturnal leg cramps. Only the 25%NMES group showed a significant reduction in nocturnal leg cramps (from 11 ± 14 to 1 ± 2, p = 0.014), whereas the 55%NMES (from 9 ± 9 to 5 ± 8, p = 0.976), 85%NMES (from 7 ± 9 to 1 ± 1, p = 0.273) and Placebo group (from 7 ± 9 to 6 ± 6, p > 0.999) remained

Table 2. Cramp Characteristics Divided by Groups.

	25%	55%	85%	Placebo	*p*-value
Cramps in two weeks pre (*n*)	25 ± 14	24 ± 10	23 ± 17	20 ± 32	0.2479
Nocturnal cramps in two weeks pre (*n*)	11 ± 14	9 ± 9	7 ± 10	7 ± 9	0.936
Pain on VAS for cramps pre (mm)	63 ± 14	59 ± 14	67 ± 12	60 ± 23	0.5199
Suffering from cramps since (years)	9 ± 10	8 ± 8	12 ± 17	14 ± 17	0.097
CTF at pre (Hz)	14 ± 3	15 ± 8	12 ± 5	18 ± 8	0.132
mTSI at pre (au)	69 ± 29	64 ± 26	51 ± 17	n.a.	0.405
mTSI at pre (mA)	31 ± 7	30 ± 7	27 ± 4	n.a.	0.405
Cramp treatment approaches					
Acute					
Stretching (*n*)	5	6	6	6	
Massage (*n*)	1	4	2	2	
Stand up and walk (*n*)	2	3	0	3	
Prevention					
Increase fluid intake (*n*)	3	4	5	3	
Acupuncture (*n*)	1	1	1	0	
Osteopathy (*n*)	1	0	1	0	
Local heat and cold therapy (*n*)	0	0	2	0	
Drug intake					
Magnesium (*n*)	3	3	2	5	
Quinine (*n*)	0	4	0	1	

VAS, visual analogue scale; mTSI, maximally tolerated stimulation intensity; au, arbitrary unit for the intensity levels from 0 to 1000, where 1000 corresponds to a current of 120 mA at 400 µsec pulse width.

unchanged. Individual data of each group are illustrated in Figure 3.

Cramp Threshold Frequency

At Pre, the CTF was not significantly different between the four groups ($p = 0.132$) (Table 2). A significant interaction ($p = 0.008$) between group × time could be found for CTF measurements (Fig. 4a). Post hoc Bonferroni tests revealed that the CTF increased over time in the 25% and 85%NMES group for all post-measurements compared to pre ($p < 0.001$), but not in the 55% NMES group. Only the 25%NMES group already showed an increase at Mid ($p = 0.002$). The perceived discomfort during the CTF measurements significantly decreased from Pre to Post 1 (55 ± 31 to 32 ± 24 mm, 53 ± 25 mm to 27 ± 31 mm; $p < 0.05$) in the 25%, 55%, and 85%NMES group, and from Pre to Post 2 (39 ± 31 mm, 12 ± 14; $p < 0.01$) in the 55%NMES and 85% NMES group. The CTF measurement was aborted when no cramp was induced up to the frequency of 40 Hz. This was the case for three participants (two in 25%NMES and one in 85%NMES) at post-measurements.

The EMG activity (i.e., aRMSA) within the 4-sec interval after each stimulation train increased with each 2 Hz increase in frequency. The CTF was characterized by a substantial increase in EMG activity, which was significantly higher compared to baseline and the two preceding trains at CTF-4 Hz and CTF-2 Hz ($p < 0.001$) illustrated in Figure 4b. CTF-4 Hz and CTF-2 Hz were also significantly higher than baseline ($p < 0.01$).

Applied Stimulation Intensity and VAS

In the first NMES session, the maximally tolerated stimulation intensity (mTSI) was not significantly different between the three stimulation groups ($p = 0.405$) (Table 2); the Placebo group did not receive the stimulation needed to assess the mTSI. Based on the mTSI, the applied stimulation intensity was adjusted to the respective percentage value of the three stimulation groups leading to an applied current of 15.7 ± 3.4 mA in the 25%NMES group, 21.8 ± 5.2 mA in the 55%NMES group, and 24.8 ± 4.1 mA in the 85%NMES group during the first NMES session. A significant interaction ($p = 0.026$) between group × time could be found for the applied stimulation intensity (Fig. 5a). Post hoc Bonferroni tests revealed that the applied current was significantly increased compared to the first session in the fourth, sixth up to the eighth NMES session for the 55%NMES group ($p < 0.05$), and after the third session for the 85%NMES group ($p < 0.01$). Compared to the

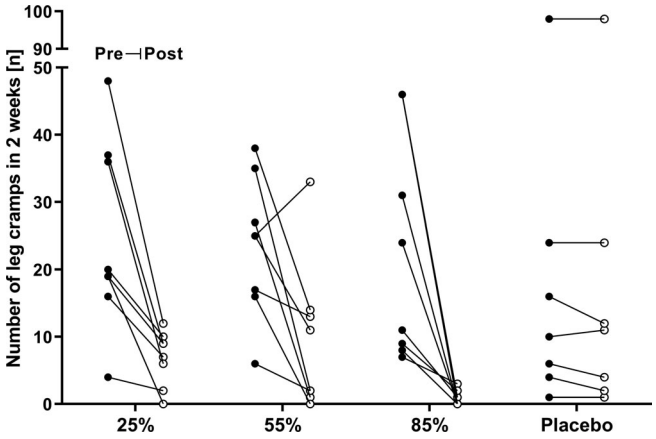

Figure 3. Pre (filled circles) vs. post (open circles) individual data of total number of leg cramps documented for two weeks in the cramp log. All groups showed a significant decrease ($p < 0.05$) except for the Placebo group. Note that for the 85% and the Placebo group, it seems that data are only plotted for seven individuals. However, in the 85% group, two individuals went from 46 cramps at pre to 0 and 1 cramp at post, respectively. In the Placebo group, two individuals reported only 1 cramp at pre and post.

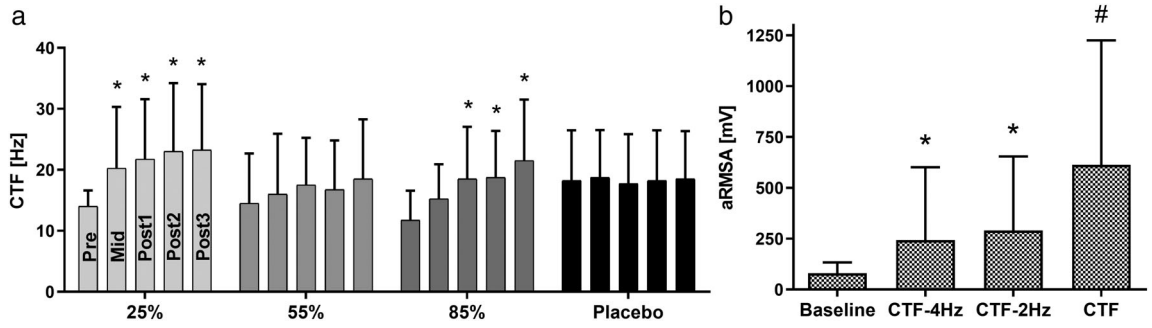

Figure 4. a. The CTF was assessed at pre, before the fifth NMES session (Mid), one day after the last NMES session (Post 1), one week (Post 2) and two weeks after the last NMES session (Post 3). b. Average root mean square amplitude (aRMSA) of the m. gastrocnemius medialis measured 2 sec prior to the first stimulation train (baseline), 4 sec after the CTF, and 4 sec after the two stimulation trains preceding the CTF (CTF-2 Hz, CTF-4 Hz)- averaged over all measurement time points. *$p < 0.01$ from pre or baseline, respectively. #$p < 0.001$ from CTF-4 Hz and CTF-2 Hz. Bars and error bars represent means and standard deviations, respectively.

55% and 85%NMES group, the applied stimulation intensity was significantly lower in all eight sessions of the 25%NMES group ($p < 0.05$). The applied stimulation intensity of the 85%NMES group was significantly higher than the 55%NMES group only in the third and seventh session ($p < 0.05$).

A significant group effect ($p < 0.001$) could be found for the pain sensation on the VAS over the eight sessions, but no significant time effect was apparent ($p = 0.094$) (Fig. 5b). The VAS of the 25%NMES group and the Placebo group was significantly lower than the 85%NMES group in every session ($p < 0.05$). For the 55% NMES group, only in the fourth session, the VAS was lower than the 85%NMES group.

Correlation Analysis

Between baseline characteristics ($n = 32$), there were significant correlations between total body fat and number of cramps during daytime ($r = -0.50$), CTF and mTSI ($r = 0.41$), and BMI and daily fluid intake ($r = 0.45$; for all $p < 0.05$).

Pre to post changes in % correlated significantly for the total number of cramps and CTF at all postmeasurements ($p < 0.01$), the highest correlation was at Post 1 ($r = -0.534$, $p = 0.002$). The change in mTSI from the first to eighth session did not show any significant correlations to the other factors.

DISCUSSION

The primary aim of this study was to assess the efficacy of NMES to treat leg cramps in patients with lumbar degenerative disorders and to investigate the effect of different stimulation intensities. The number of leg cramps in the 25%, 55%, and 85% NMES group decreased significantly after four weeks of NMES treatment, with the highest reductions in the 85%NMES group. The occurrence of leg cramps after the pseudo-stimulation protocol remained unchanged, indicating that the reduction of leg cramps in the three stimulation groups was indeed due to actions of NMES.

This study provides first evidence that the applied stimulation intensity of the NMES protocol might play a crucial role to reduce the occurrence of leg cramps. First, the pseudo-stimulation still contained very low intensity stimulation at the beginning of each session and high-intensity stimulation to determine the CTF at Pre and Mid but was not sufficient to induce any reductions in leg cramps. Surprisingly, only the 25%NMES protocol resulted in significant reductions of nocturnal leg cramps. However, it is important to mention that the 25%NMES group consisted of individuals with very high incidence of muscle cramps, resulting in the large variance at Pre (11 ± 14 cramps). This high starting value of some individuals could explain the increased

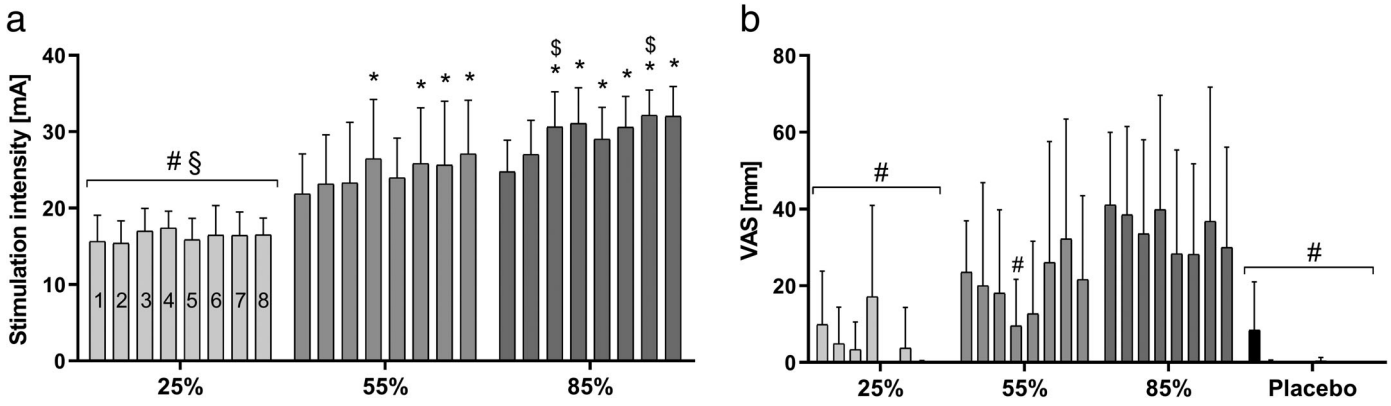

Figure 5. a. The applied stimulation intensity and b. pain sensation on the VAS over the eight sessions between groups. Note that some participants of the Placebo group reported some pain in a few sessions although no current was applied during the sets. *$p < 0.05$ from the respective first session within that group, \$$p < 0.05$ from 55%NMES within the same session, #$p < 0.05$ from 85%NMES within the same session, §$p < 0.05$ from 55%NMES within the same session. Bars and error bars represent means and standard deviations, respectively.

effectiveness in this group. Taking into account that the total number of leg cramps was similarly reduced in all three stimulation groups upon different levels of pain perception, it seems reasonable to recommend that even the application of low current NMES (25% of the maximally tolerated stimulation intensity [mTSI]), is sufficient to reduce the occurrence of leg cramps associated with LDH and LSS. The 25%NMES should therefore be preferably used to minimize pain associated with the stimulation. In our previous study (9), we reported that the 85%NMES protocol was associated with moderate pain sensation (VAS: 55 $\pm$ 20 mm). In contrast, our present study showed that older patients with lumbar degenerative disorders had only mild pain sensation (VAS: 31 $\pm$ 5 mm) during the 85%NMES protocol. Whether these differences were due to the homogenously higher age or due to the lumbar degenerative disorders decreasing their pain sensitivity compared to the previous heterogeneous sample remains to be investigated.

Besides the data recorded in the cramp log, regular measurements of the CTF served as an important parameter to evaluate the effects of NMES since earlier studies demonstrated an association of an individual's cramp susceptibility with the CTF. Whenever the susceptibility to cramp could be reduced by means of NMES, there was always a corresponding CTF increase (9–13). In line with findings from other authors (19), the negative correlation between cramp susceptibility and the CTF is well established. The present study provides additional evidence for this correlation: first, patients with lumbar degenerative disorders demonstrated a generally lower CTF (mean of all groups at Pre: 15.3 $\pm$ 7.1 Hz) when compared to less cramp-prone healthy individuals in other studies (range of mean values: 18–25 Hz) (10–13). Second, the reduction of leg cramps in the 25% and 85%NMES group was accompanied by an increase of the CTF lasting for at least two weeks after the last NMES session. Within the 55%NMES group, there was a similar increasing trend but without reaching statistical significance due to one individual for which the CTF decreased and two individuals for which it remained unchanged. Over the whole sample (n = 32), we also found significant negative correlations between the %change in the number of leg cramps and the %change of the CTF at all post measurements. However, it needs to be highlighted that six participants within the three stimulation groups did not show a response in CTF ($\pm$2 Hz change) despite reporting strong reductions of leg cramps. Therefore, we conclude that the CTF does not reflect an individual's cramp susceptibility at all times in an absolute manner.

Although the strong association between LDH/LSS and an increased occurrence of leg cramps has been known for many years, scarcely any attempts have been made to describe the causal mechanisms. LDH/LSS can lead to constriction of the lumbar neuroforamina by emerging nerve roots, causing numbness and reduced sensitivity of the legs innervated by the affected nerves (7). Hence, we hypothesize that the lumbar nerve damage concurrently disturbs the balance between inhibitory and excitatory inputs to the alpha motor neuron by either blunting inhibitory factors or promoting excitation, respectively. In this context, Khan and Burne (20) showed that the inhibitory input to the alpha motor neuron coming from golgi tendon organ (GTO) Ib afferents was reduced in individuals that were able to induce calf cramping by maximal voluntary plantarflexion compared to individuals that failed to cramp with the same task. Moreover, the passively maximally shortened position of the calf muscles was found to generally decrease the inhibition generated by the GTOs. Taking nocturnal calf cramps experienced by our participants as an example, the feet are plantar-flexed burdened either by bedclothes when lying supine or by the mattress when lying prone. Thereby placing the calf and ventral foot muscles in the most shortened position (21). Whereas most people can easily bear these sleeping positions without developing any nocturnal cramps, patients with lumbar degenerative disorders seem to be vulnerable to cramp when fallen asleep, suggesting that they lack some kind of autoregulatory inhibitory feedback. It seems possible that spinal nerves branching off at the site of lumbar degeneration are irritated and thereby affect the regulatory interplay between inhibitory and excitatory inputs to the alpha motor neuron.

Further supporting evidence for this hypothesis can be derived from animal studies. It has been shown that chronic compression of the dorsal root ganglion in mice causes a decreased rheobase, the minimal strength of an electric stimulus required to cause excitation, in sensory neurons. Within the dorsal root ganglion neurons, increased Na+ current and decreased K+ current were observed likely contributing to a state of hyperexcitability (22). Similarly, compromised functionality of the axonal Na+/K+ ATPase has been shown to contribute to the occurrence of muscle cramps in endstage kidney disease (23), Machado–Joseph disease (24), Charcot–Marie–Tooth disease (25) and diabetic polyneuropathy (26). Moreover, the increased occurrence of leg cramps in LSS patients after decompression surgery could also be due to instable axonal sprouts linked to reinnervation of the affected muscles causing enhanced hyperexcitability of respective motor units (5, 27).

As our four-week NMES intervention led to strong reductions of leg cramps, we hypothesize that NMES was able to abolish this state of hyperexcitability by potentially increasing GTO Ib (20), recurrent Renshaw cell inhibition (28) and/or decreasing excitatory pathways. In our previous study (9), we observed that NMES did not only reduce the number of leg cramps in the ipsilateral leg but also in the contralateral (nonstimulated) leg. Thus, it is very unlikely that NMES reduces leg cramps by changing peripheral factors within the respective stimulated muscles. Chen and colleagues (29) applied NMES for one month on the muscle–tendon junction of spastic gastrocnemius in stroke patients and found signs of suppressed spasticity like, for example, prolonged H-reflex latencies known to be decreased in spastic limbs (30). If future studies could determine the precise excitatory and inhibitory pathways that respond to NMES, the potential neurophysiologic mechanism underlying muscle cramps might be revealed.

Recently, Bekhet and colleagues (31) conducted a systematic review on the effects of NMES and functional electrical stimulation in managing spasticity after spinal cord injury. They identified specific stimulation parameters (frequency of 20–30 Hz, pulse duration of 300–350 μsec, and current amplitude >100 mA) that induced reductions in spasticity by 45–60%, reflected by decreases in EMG activity. Considering regular leg cramps as a form of spasticity, the finding of reductions in leg cramps induced through our NMES protocol mostly confirms these stimulation settings, albeit applying a lower current amplitude. All subjects in the three stimulation groups were stimulated with their individual maximally tolerated stimulation intensity (mTSI) at the beginning of each session for two times (lowest individual mTSI over all eight sessions: 19 mA). The regular application of the mTSI could, therefore, be the common denominator of the three stimulation groups leading to similar reductions of leg cramps. As the mTSI was naturally associated with strong pain sensation, one could

also assume that NMES reduces leg cramps through nociceptive pathways. However, the pseudo-stimulation group did not show a reduction in leg cramps despite still receiving true multiple stimulations at 40 mA for the determination of the CTF (at Pre and Mid) associated with strong pain sensation. Therefore, to achieve reductions in leg cramps through NMES, either the regularity of the stimulus (two sessions per week each with three sets of six true stimulations) or the application of a stimulation frequency above CTF (individual minimum of all groups: 36 Hz) combined with an applied current above 6.5 mA seems necessary.

Lastly, it should be noted that by far not all patients with LDH/LSS automatically suffer from regularly occurring leg cramps, and that our sample was specifically selected to meet this criterium. For LDH/LSS patients not suffering from cramps, it needs to be highlighted that we cannot draw any conclusions on whether NMES also reduces lower back pain symptoms and/or associated radiating leg pain, since no methodology to detect such outcomes was included in the present study. In addition, it should be acknowledged that by including both LDH and LSS patients, we reduced the complexity of both pathologies to their shared feature of spinal cord compression, potentially contributing to the increased occurrence of leg cramps. However, it needs to be stressed that LDH and LSS can clearly differ in their pathology and different underlying mechanisms for the higher cramp susceptibility cannot be ruled out. Our findings should further be interpreted with caution considering the small sample size per group (n = 8) and the short follow-up period of only two weeks. The sample size was sufficient to show that the number of leg cramps was reduced in all three stimulation groups compared to placebo but was not sufficient to assess the efficacy within the three stimulation groups. Larger trials are needed to investigate whether there are any differences in efficacy between the different stimulation intensities.

Whereas NMES and functional electrical stimulation are increasingly integrated into the treatment of spinal cord injury, the value of these approaches to prevent and treat leg cramps in patients with lumbar degenerative disorders should also be acknowledged. Considering that recurring leg cramps represent a true burden to these patients and that other treatment options without noticeable side-effects are currently lacking, this study lays the groundwork for future research to develop a nondrug treatment approach to improve life quality in these patients. Taking into account that there was no drop-out in the present and previous study (9) and the positive feedback of participants about the bearable pain associated with 25%NMES renders the here described NMES protocol feasible in the real-world scenario. Further research could usefully explore if even lower intensities prove to be effective and if only one session per week might be sufficient to elicit similar benefits as it has been shown after a single bout for increasing the CTF (22).

CONCLUSION

LSS and LDH are often accompanied by frequently occurring leg cramps that can severely affect patients' life and sleep quality. The present study provides first evidence that regularly applied NMES of the calf muscles can reduce leg cramps in patients with LSS/LDH. Even low currents (25%NMES) associated with only mild pain sensation reduced leg cramps, whereas the occurrence of leg cramps remained unchanged after a pseudo-stimulation protocol. As one of the first nondrug treatment approaches, NMES could be used cost-effectively in the future in order to prevent the unmanageable occurrence of leg cramps often associated with LSS/LDH.

Authorship Statements

Jan-Frieder Harmsen, Anna Sistig, Alessandro Fasse, Michael Hackl, Kilian Wegmann, and Michael Behringer contributed to the concept and design of the study. Jan-Frieder Harmsen and Anna Sistig collected the data; Anna Sistig conducted the experiments; Jan-Frieder Harmsen, Alessandro Fasse, and Anna Sistig analyzed and interpreted the data. Jan-Frieder Harmsen and Anna Sistig created the figures. Jan-Frieder Harmsen, Anna Sistig, and Michael Behringer wrote the initial draft of the manuscript; and all authors reviewed the manuscript, commented critically and approved the final version of the manuscript for submission.

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COMMENT

Muscle cramps are commonly known as involuntary, painful, and momentary muscle contractions. However, an event that can be temporary and slightly noticeable for a healthy individual, is a disabling condition for people with lumbar degenerative disorders. In particular, patients with lumbar spinal stenosis (LSS) and/or disc herniation (LDH) are frequently affected by muscle cramps at rest, and the current solutions are invasive and not resolutive. The mechanism underlying skeletal muscle cramps is still debated (1,2); however, it has been previously found that a period of treatment with neuromuscular electrical stimulation (NMES) increases the cramp threshold frequency (CTF), decreasing susceptibility in healthy individuals (3). This technique's application to patients with lumbar degenerative disorders by the same research group, was the natural consequence of their knowledge and skills on the topic. This interesting research has measured the efficacy and tolerability of different intensities of NMES in reducing leg cramps' frequency in LSS and LDH. Harmsen and colleagues concluded that unilateral NMES of the gastrocnemius (3×6×5s stimulation trains at 30 Hz above the individual CTF), applied twice a week over four weeks, reduces leg cramps in patients with LSS and/or LDH. The interesting point was that the output of the different intensities was overall the same, so that 25% of the max tolerable stimulation intensity showed solid advantages. In fact, it is commonly known that NMES can be really painful even at low intensities, thus the suggestion of an indicative "sweet spot" intensity is helpful for future studies. Moreover, it would be interesting to understand how NMES can affect the CTF's inhibitory pathways to understand the neurophysiological mechanism underlying muscle cramps, but this should be a topic of future research.

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