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Whole body and local cryotherapy in restless legs syndrome: A randomized, single-blind, controlled parallel group pilot study

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ABSTRACT

Objective: Treatment of restless legs syndrome (RLS) is primarily based on drugs. Since many patients report improvement of symptoms due to cooling their legs, we examined the efficacy of cryotherapy in RLS.
Patients and methods: 35 patients (28 women, 60.9 ± 12.5 years) with idiopathic RLS and symptoms starting not later than 6 pm were randomized into three groups: cold air chamber at −60 °C (n = 12); cold air chamber at −10 °C (n = 12); local cryotherapy at −17 °C (n = 11). After a two week baseline, the different therapies were applied three minutes daily at 6 pm over two weeks, followed by a four week observation period. The patients completed several questionnaires regarding RLS symptoms, sleep, and quality of life on a weekly basis (IRLS, ESS), VAS and sleep/morning protocol were completed daily, MOSS/RLS-QLI were completed once in each period. Additionally, the PLM index was measured by a mobile device at the end of baseline, intervention, and follow-up. The IRLS score was chosen as primary efficacy parameter.
Results: At the end of follow-up, significant improvement of RLS symptoms and quality of life could be observed only in the −60 °C group as compared to baseline (IRLS: $p = 0.009$; RLS-QLI: $p = 0.006$; ESS: $p = 0.020$). Local cryotherapy led to improvement in quality of life (VAS4: $p = 0.028$; RLS-QLI: $p = 0.014$) and sleep quality (MOSS: $p = 0.020$; MOSS2: $p = 0.022$) but not in IRLS and ESS. In the −10 °C group, the only significant effect was shortening of number of wake phases per night. Serious side-effects were not reported.
Conclusions: Whole body cryotherapy at −60 °C and, to a less extent, local cryotherapy seem to be a treatment option for RLS in addition to conventional pharmacological treatment. However, the exact mode of cryotherapy needs to be established.

1. Introduction

Restless legs syndrome (RLS) is a neurological sensorimotor disorder which leads to unpleasant sensations of the legs resulting in an almost irresistible urge to move the legs [1]. Onset occurs at all ages, from early childhood to late adult life [2] but is more common in older individuals [3] and more common in women than men [4]. The most accepted hypothesis about the pathophysiology of RLS is a dopaminergic dysfunction but the definite cause is still unknown [5,6]. Although there are several pharmacological agents approved for symptomatic treatment, there is no real cure for RLS. All drugs have potential side-effects such as dependence, confusion, blurred vision and coordination problems, which can lead to serious problems, especially in the elderly population [7,8].

Aside from pharmacological treatment, several alternative, non-pharmacological interventions have been investigated. Improvement of symptom severity has been reported for pneumatic compressions [9], exercises such as aerobic [10], transcutaneous spinal direct current stimulation [11], endovascular laser ablation in patients with additional superficial venous insufficiency [12], massage therapy [13], gentle yoga program [14], and infrared therapy [15]. In an observational study, injection of botulinum toxin type A demonstrated symptom improvement, reduced medication use, and a reduction in daytime sleepiness [16], but this was not confirmed in a double-blind, placebo-controlled, pilot trial of botulinum toxin in humans [17]. Acupuncture was not shown to be sufficiently effective according to a metaanalysis [18].

Single reports of patients with idiopathic RLS entering a cold chamber or applying cold to the legs showed a reduction of symptoms which gave rise to the assumption that cold decreases RLS symptoms.

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However, randomized data on the effect of cold in RLS do not exist to date. Application of cold, especially very low temperatures in a cold air chamber, is widely used in rheumatology due to its analgesic and antiphlogistic effects [19–21]. It has been shown that the number of leucocytes is increased after cryotherapy, and changes in the concentration of interleukin [22] as well as a decreasing histamine level [23] result primarily in an immunomodulatory effect. Application of cold along an extended period of time showed a positive effect on antioxidative status in patients suffering from multiple sclerosis [24]. Furthermore, studies showed a positive effect on cardiovascular conditions [25] which is aided by increased activity of creatin-kinase and lactate-hydrogenase [26] resulting in better regeneration of impaired cardiomuscular and skeletal muscular tissue. Another study found elevated plasma norepinephrine suggesting peripheral cooling results in a release of neurotransmitters from the central nervous system (CNS) [27]. Besides the effect on the CNS, it is also mentioned that joint cooling has both peripheral and central effects. The positive effect of cryotherapy seems not to be limited to physical conditions but also improves psychic conditions such as depressive disorders or anxiety [28]. All these modifications due to cryotherapy might also be effective in treating RLS.

We therefore performed a randomized, prospective, single-blind, controlled parallel-group, single centre pilot study on the efficacy of whole body and local cryotherapy in patients with idiopathic RLS.

2. Patients and methods

2.1. Patient selection

Altogether, 262 patients with idiopathic RLS were screened for participation in this randomized, single-blind, prospective, controlled parallel group pilot study. Participants were recruited via the database of the Institute of Clinical Neurophysiology (Klinikum Bremen-Ost) and advertisements in the hospital as well as in the local newspaper (see Fig. 1 for recruitment). Criteria were checked first via telephone interview, and possibly suitable participants were invited to a medical screening. Clinical and demographic data were gathered and a physical examination, particularly for the exclusion of polyneuropathy, was performed. Minimal diagnostic criteria according to the International RLS Study Group (IRLSSG) had to be fulfilled [1]. Patients had to be between 18 and 75 years of age, without pharmacological treatment or under stable treatment of RLS for at least three months and during the entire study without any signs of augmentation. RLS severity score (IRLS) [29] had to be ≥15, and RLS symptoms had to start not later than 6 pm or earlier in the day in order to ensure a more homogenous sample.

Exclusion criteria were intake of analgesics or hypnotics, irregular appearance to therapeutic sessions, drug or alcohol abuse, pregnancy or breastfeeding, participation in another study during the last three months and use of other alternative therapies for RLS. Additionally, contraindications of cryotherapy like planned surgery, severe cardiovascular disorder, myocardial failure (≥NYHA III), severe cardiac dysrhythmia, severe coronary artery disease or angina pectoris, uncontrolled hypertension, peripheral arterial disease ≥ stage III, Raynaud phenomenon, severe infection of the upper airways, cold induced bronchial asthma, and severe claustrophobia had to be excluded. Before participating in the study, all patients gave written informed consent. The local ethics committee of the Medical Board of Bremen, Germany, approved the protocol.

Altogether, 43 patients met all inclusion criteria and were included in the study. They were asked to complete various questionnaires (see below) and to return to the clinic after a baseline of two weeks. During baseline, the subjects had to complete the IRLS, ESS, and VAS 1 to 4 once a week, the sleep and morning protocol daily and RLS-QLI and MOSS only once at the beginning (for details see below).

Eight subjects cancelled their participation: five subjects withdrew consent; one subject was lost to follow up; two subjects developed augmentation under L-dopa during the study. In the end, 35 participants (60.9 ± 12.5 years, 28 female) completed the whole study and could be analyzed in the per-protocol analysis.

2.2. Treatment procedure

After baseline screening and confirmation of the inclusion criteria, the patients were allocated to one of three treatment groups by a computer generated randomisation list (Microsoft Excel 2003). One investigator (CT) received a sealed envelope with the randomisation number. The envelope contained the respective treatment group. The study was intended to be implemented as a randomized, single-blinded, prospective, controlled parallel group study. The duration of the study for each participant was limited to eight weeks, which were separated into three phases:

Phase I Baseline (first two weeks to capture the severity of each participant)

Phase II Intervention (daily treatment for the upcoming two weeks and documentation of treatment effects)

Phase III Follow-up (documentation of the treatment effects for the upcoming four weeks).

The patients were treated either with whole body cryotherapy (Cold air chamber, Crio-Med) at −60 °C (verum group) or −10 °C (sham group) or local cryotherapy (Cryo 5, Zimmer Elektromedizin) at

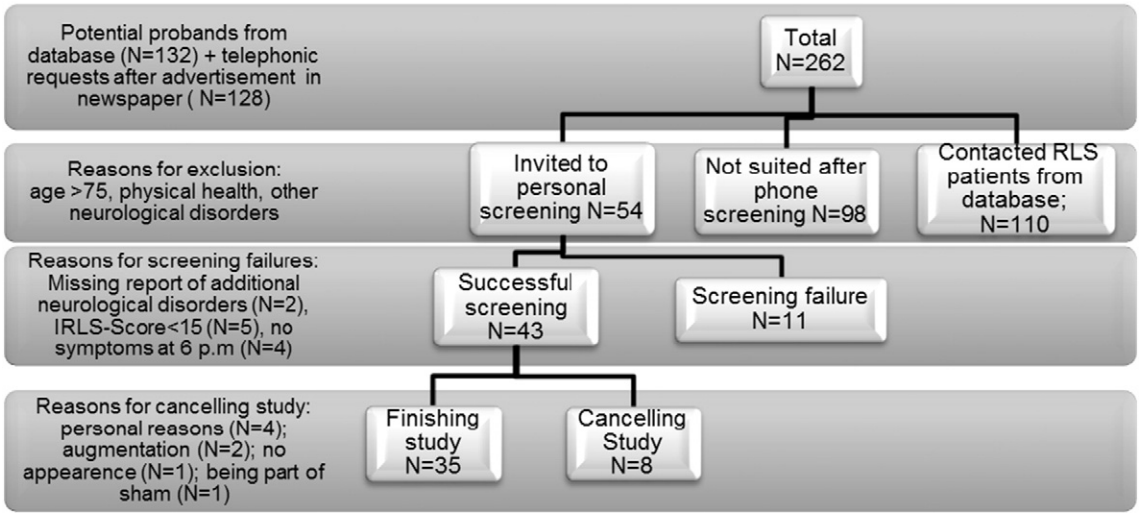

Fig. 1. Number of patients during the screening procedure.

−17 °C (local group). The reason for choosing −10 °C as sham temperature was that this temperature is experienced as cold but cannot easily be differentiated form lower temperature; in other studies on whole body cryotherapy, this temperature was without efficacy. Each participant of the two cold chamber groups spent three minutes inside the cold air chamber clothed only with swimsuit. Peripheral body parts (nose, ears, hands and feet) were protected by single pieces of clothing (headband, gloves, sturdy shoes, standard ear loop and face mask). Up to four participants entered the chamber at the same time and were encouraged to walk around and move their body during the whole time. For local therapy, cold air (about −17 °C) was applied directly with a flexible tube to the affected body areas on the lower legs up to the knee. Each lower leg was treated for three minutes (six minutes in total) with a mean distance towards the legs of 5 cm, whereas the flexible tube was constantly in motion up and down the lower leg. All interventions were started daily between 6 and 6.30 pm for two weeks except weekend days.

Periodic leg movements (PLM) were measured via a mobile device at home (Somnocheck 2 and Somnolab 2, Weinmann) at baseline, at the end of intervention and during the last two weeks of follow-up via surface electrodes over the anterior tibial muscle of each leg.

2.3. Questionnaires

The severity of symptoms was documented weekly by using the RLS Severity Scale [29,30] as well as daily completion of Visual Analogue Scales (VAS) for rating the feelings/perceptions according to (1) the urge to move the legs, (2) subjective perception of leg movements (such as PLM), (3) sleep quality as well as (4) quality of life [31].

Changes of sleep quality were investigated by daily completion of the sleep and morning protocol by the German Society of Sleep Research and Sleep Medicine, DGSM [32]. The Epworth-Sleepiness Scale (ESS, [33]) was completed weekly and the Medical outcomes study sleep scale (MOSS, [34]) once in each period. Quality of life was measured by the RLS quality of life index (RLS-QLI, [35]).

2.4. Statistics

The primary outcome measure was the IRLS score. We assessed a number of at least 10 patients per treatment group to obtain a statistical power strong enough to detect differences of >30% between placebo and verum for this primary outcome measure. Secondary parameters were the scores of the ESS, RLS-QLI, VAS1 to 4, MOSS 1 and 2, and sleep and morning protocol.

We used non-parametric tests with the $\times^2$-test for qualitative data (Fisher's exact test if applicable) and the Kruskal-Wallis test for quantitative data (Mann-Whitney-*U* test as post-hoc test). In the case of parametric data, the paired Student's *t*-test was applied. Friedman test was used for paired parameters (Wilcoxon test as post-hoc test). Correlation analysis was performed by calculation of Spearman's rank correlation coefficient test. $p < 0.05$ was set as significant. Data are presented as percentage or as arithmetic mean ± standard deviation (SD). The analysis was performed utilizing the SPSS (version 17.0) statistical analysis package (SPSS Chicago, IL).

3. Results

3.1. Characteristics of the study population

Altogether, 35 participants (mean age 60.9 years; 28 females) were included, 12 in the verum group, 11 in the sham group and 12 in the local group. Demographic data (gender, age, IRLS score, start of symptoms, duration of RLS symptoms and RLS medication) was not significantly different between the three groups (Table 1). At baseline, only the ESS was significantly lower in the local group as compared to the sham and verum group ($p = 0.014$).

Table 1
Demographic data of the three treatment groups (arithmetic mean ± standard deviation). Comparison by Kruskal-Wallis test, post-hoc test by Mann-Whitney-*U* test.

	Local n = 12	Verum n = 12	Sham n = 11	*p*-Value
Female sex	91.7%	75.0%	72.7%	0.386
Age (years)	64.3 ± 8.6	56.9 ± 16.1	61.6 ± 11.0	0.724
Age at symptom onset (years)	42.4 ± 13.6	35.7 ± 17.1	36.7 ± 17.1	0.476
Age at diagnosis (years)	53.8 ± 8.0	49.4 ± 14.1	51.5 ± 15.6	0.480
RLS medication	83.3%	91.7%	90.9%	0.386
IRLS score	23.8 ± 5.1	24.6 ± 5.0	25.7 ± 5.6	0.472
VAS1 (sleep quality)	45.4 ± 20.7	46.6 ± 13.4	43.6 ± 18.2	0.365
VAS2 (limb movement frequency)	46.9 ± 25.4	38.0 ± 16.7	51.7 ± 22.2	0.214
VAS3 (RLS severity)	56.6 ± 23.8	43.4 ± 16.8	58.7 ± 19.6	0.422
VAS4 (quality of life)	49.9 ± 20.8	52.8 ± 17.4	49.1 ± 18.8	0.775
RLS-QLI	58.1 ± 14.7	53.3 ± 13.5	48.2 ± 16.0	0.212
ESS	5.8 ± 2.9[#]	11.4 ± 5.1	9.7 ± 5.1	0.014
MOSS1	2.6 ± 1.2	2.5 ± 1.6	3.1 ± 1.6	0.516
MOSS2 (h)	5.7 ± 1.4	5.6 ± 0.9	5.5 ± 1.6	0.955
MOSS3 (score)	39.0 ± 6.7	35.0 ± 6.5	33.8 ± 6.3	0.156
PLM index	22.3 ± 18.0	21.3 ± 12.1	23.3 ± 10.4	0.127
Disruption of sleep (min)	38.0 ± 9.2	56.2 ± 9.0	43.9 ± 35.6	0.383
Disruption of sleep (number)	13.7 ± 1.9	18.9 ± 2.1	25.2 ± 8.3	0.386
Latency of falling asleep (min)	18.5 ± 2.3	30.7 ± 5.6	26.9 ± 14.2	0.906
TST (min)	361.8 ± 20.1	336.2 ± 18.7	380.8 ± 55.9	0.901

IRLS = restless legs syndrome severity scale.
RLS-QLI = restless legs syndrome quality of life.
ESS = Epworth sleepiness scale.
MOSS1 = medical outcomes study sleep scale question 1.
MOSS2 = medical outcomes study sleep scale question 2.
MOSS3 = medical outcomes study sleep scale question 3.
Disruption of sleep = averaged time of disruptions of sleep per night.
Disruption of sleep (number) = number of disruptions of sleep per week.
TST = total sleep time.
[#] $p < 0.05$ (local versus verum).

3.2. Intraindividual analysis

3.2.1. Verum group

At intervention and follow-up, IRLS score ($p = 0.009$) and PLM index ($p = 0.009$) decreased significantly, and RLS-QLI ($p = 0.006$) was significantly increased as compared to baseline. Four participants received 50% or more improvement of symptom severity (comparison between baseline and follow-up). The improvements in ESS ($p = 0.020$), disruption of sleep ($p = 0.005$) and TST ($p = 0.012$) were significant only at follow-up (see Table 2).

3.3. Local group

IRLS score did not change significantly, only two participants received 50% or more improvement of symptom severity (IRLS). At follow-up, quality of life (VAS4; $p = 0.028$), RLS-QLI ($p = 0.014$), subjective total sleep time (MOSS2; $p = 0.022$), subjective average duration of disruptions in sleep ($p = 0.016$) as well as the number of disruptions in sleep ($p = 0.017$) were improved significantly (see Table 3).

3.4. Sham group

IRLS score did not change significantly, no participant received 50% or more improvement of symptom severity (IRLS). Only the average duration of sleep disruptions showed a significant decline between baseline and intervention ($p = 0.004$) and a significant improvement of

Table 2
Data of questionnaires and periodic leg movements (PLM) of the verum group (arithmetic mean ± standard deviation) (n = 12). Statistical comparison by Student's *t*-test for parametric data or by Wilcoxon ranked test for non-parametric data.

	Baseline	Intervention	Follow-up	*p*-Value
IRLS score	24.6 ± 5.0	19.4 ± 6.5#	18.5 ± 8.6##	0.009
VAS1 (sleep quality)	46.6 ± 13.4	57.3 ± 13.8	59.4 ± 18.3	0.071
VAS2 (limb movement frequency)	38.0 ± 16.7	32.3 ± 19.3	34.5 ± 21.0	0.308
VAS3 (RLS severity)	43.4 ± 16.8	31.4 ± 22.6	32.7 ± 20.7	0.099
VAS4 (quality of life)	52.8 ± 17.4	57.3 ± 16.5	61.7 ± 19.2	0.099
RLS-QLI	53.0 ± 13.5	59.2 ± 15.1#	63.8 ± 16.8##	0.006
ESS	11.4 ± 5.1	10.1 ± 5.1	8.9 ± 5.3#	0.020
MOSS1	2.5 ± 1.6	2.1 ± 1.1	2.1 ± 0.9	0.437
MOSS2 (h)	5.6 ± 0.9	6.0 ± 0.9	6.2 ± 0.8	0.188
MOSS3 (score)	35.0 ± 6.5	37.4 ± 4.3	39.1 ± 4.2	0.154
PLM index	21.3 ± 12.1	17.0 ± 9.0#	16.7 ± 9.5##	0.009
Disruption of sleep (min)	56.2 ± 9.0	48.0 ± 6.6	43.4 ± 6.3##	0.005
Disruption of sleep (number)	18.9 ± 2.1	16.6 ± 2.0	17.0 ± 2.0	0.091
Latency of falling asleep (min)	30.7 ± 5.6	29.6 ± 5.0	29.1 ± 4.6	0.530
TST (min)	336.2 ± 18.7	346.9 ± 18.2	362.2 ± 15.7#	0.012

IRLS = restless legs syndrome severity scale.
ESS = Epworth sleepiness scale.
MOSS1 = medical outcomes study sleep scale question 1.
MOSS2 = medical outcomes study sleep scale question 2.
MOSS3 = medical outcomes study sleep scale question 3.
PLM = periodic leg movements during sleep and wakefulness.
Disruption of sleep = averaged time of disruptions of sleep per night.
Disruption of sleep (number) = number of disruptions of sleep per week.
TST = total sleep time.
# $p < 0.05$.
$p < 0.01$ as compared to baseline.

sleep latency (MOSS1) between baseline and intervention ($p = 0.024$) but no significant difference was found between baseline and follow-up. All data of the sham group is shown in Table 4.

Table 3
Data of questionnaires and periodic leg movements (PLM) of the local group (arithmetic mean ± standard deviation) (n = 12). Statistical comparison by Student's *t*-test for parametric data or by Wilcoxon ranked test for non-parametric data.

	Baseline	Intervention	Follow-up	*p*-Value
IRLS score	23.8 ± 5.1	19.8 ± 6.7	20.6 ± 9.2	0.140
VAS1 (sleep quality)	45.4 ± 20.7	54.5 ± 25.3	58.7 ± 26.8	0.388
VAS2 (limb movement frequency)	46.9 ± 25.4	46.4 ± 22.5	46.9 ± 14.9	0.937
VAS3 (RLS severity)	56.6 ± 23.8	49.2 ± 25.2	47.5 ± 27.3	0.388
VAS4 (quality of life)	49.9 ± 20.8	59.9 ± 24.8#	61.7 ± 26.6#	0.028
RLS-QLI	58.1 ± 14.7	60.5 ± 15.5	63.0 ± 15.5#	0.014
ESS	5.8 ± 2.9	5.4 ± 3.8	5.0 ± 3.8	0.212
MOSS1	2.6 ± 1.2	1.8 ± 0.9	1.6 ± 0.8###	0.020
MOSS2 (h)	5.7 ± 1.4	5.7 ± 1.4	6.5 ± 1.1#	0.022
MOSS3 (score)	39.0 ± 6.7	39.3 ± 6.0	38.2 ± 5.8	0.783
PLM-index	22.3 ± 18.0	22.0 ± 21.5	17.0 ± 11.8	0.369
Disruption of sleep (min)	38.0 ± 9.2	28.4 ± 6.8#	24.2 ± 5.5#	0.016
Disruption of sleep (number)	13.7 ± 1.9	11.2 ± 2.0	8.2 ± 1.6#	0.017
Latency of falling asleep (min)	18.5 ± 2.3	17.7 ± 3.0	17.1 ± 3.1	0.875
TST (min)	361.8 ± 20.1	375.9 ± 17.7	379.9 ± 21.0	0.117

IRLS = restless legs syndrome severity scale.
ESS = Epworth sleepiness scale.
MOSS1 = medical outcomes study sleep scale question 1.
MOSS2 = medical outcomes study sleep scale question 2.
MOSS3 = medical outcomes study sleep scale question 3.
PLM = periodic leg movements during sleep and wakefulness.
Disruption of sleep = averaged time of disruptions of sleep per night.
Disruption of sleep (number) = number of disruptions of sleep per week.
TST = total sleep time.
# $p < 0.05$.
$p < 0.001$ as compared to baseline.

3.5. Interindividual analysis

Analysis of the intervention phase revealed significant differences for VAS3 (individual perception of RLS symptoms) where the score (strength) was significantly lower in the verum group as compared to sham ($p = 0.015$). Additionally, the RLS-6 score was significantly higher in the sham group ($p = 0.013$), whereas the ESS score was significantly lower in the local group ($p = 0.031$). The data set of the follow-up phase displays significant differences as follows: VAS2 (individual perception of leg movements; $p = 0.016$) and VAS3 ($p = 0.010$) were significantly increased in the sham group as compared to the local and the verum group, whereas the number of disruptions during sleep was significantly decreased in the local group as compared to the verum and the sham group.

3.6. Side effects

Only few and mild side effects were observed in the verum group, such as coldness induced headache in two participants and slight flashes of the skin in three participants. A decline of present swellings was reported as a positive side effect in a single participant.

4. Discussion

In our randomized, single-blinded, controlled parallel group study of patients with idiopathic RLS treated either with whole body cryotherapy at −60 °C, local cryotherapy at −17 °C, or whole body cryotherapy at −10 °C, we found evidence that both local and particularly whole body cryotherapy at −60 °C succeeded in alleviating symptoms of RLS. The primary efficacy parameter (IRLS score) improved significantly only after whole body cryotherapy at −60 °C and not after the other interventions. This improvement started mainly during the intervention phase although single parameters improved after intervention, mainly within two weeks after intervention. Altogether, local cryotherapy seems to be less effective than whole body cryotherapy at −60 °C whereas whole body cryotherapy at −10 °C did not show any clinically relevant improvement of RLS symptoms. However, group comparisons for the degree of improvement indicated only few significantly

Table 4
Data of questionnaires and periodic leg movements (PLM) of the sham group (arithmetic mean ± standard deviation) (n = 11). Statistical comparison by Student's *t*-test for parametric data or by Wilcoxon ranked test for non-parametric data.

	Baseline	Intervention	Follow-up	*p*-Value
IRLS score	25.7 ± 5.6	23.5 ± 3.3	24.6 ± 3.8	0.183
VAS1 (sleep quality)	43.6 ± 18.2	56.7 ± 21.7	42.0 ± 16.4	0.148
VAS2 (limb movement frequency)	51.7 ± 22.2	44.2 ± 24.3	52.9 ± 24.0	0.148
VAS3 (RLS severity)	53.7 ± 19.6	59.0 ± 22.4	55.2 ± 21.9	0.643
VAS4 (quality of life)	49.1 ± 18.8	53.8 ± 15.7	53.8 ± 17.1	0.441
RLS-QLI	48.7 ± 16.0	53.5 ± 11.4	51.3 ± 15.0	0.529
ESS	9.7 ± 5.1	9.4 ± 5.0	9.1 ± 4.7	0.226
MOSS1	3.1 ± 1.6	2.4 ± 1.4[#]	2.5 ± 1.5	0.237
MOSS2 (h)	5.5 ± 1.6	5.8 ± 1.2	5.7 ± 1.2	0.644
MOSS3 (score)	33.8 ± 6.3	34.0 ± 4.7	34.7 ± 4.9	0.553
PLM-index	23.3 ± 10.4	15.6 ± 9.4	25.5 ± 16.4	0.403
Disruption of sleep (min)	44.5 ± 13.2	22.5 ± 7.3	30.6 ± 7.1	0.060
Disruption of sleep (number)	25.2 ± 4.1	15.9 ± 3.9[##]	16.2 ± 3.4[##]	0.004
Latency of falling asleep (min)	20.8 ± 3.1	23.6 ± 3.4	22.9 ± 4.1	0.486
TST (min)	365.7 ± 18.8	411.5 ± 8.7	403.6 ± 9.3	0.695

IRLS = restless legs syndrome severity scale.
ESS = Epworth sleepiness scale.
MOSS1 = medical outcomes study sleep scale question 1.
MOSS2 = medical outcomes study sleep scale question 2.
MOSS3 = medical outcomes study sleep scale question 3.
PLM = periodic leg movements during sleep and wakefulness.
Disruption of sleep = averaged time of disruptions of sleep per night.
Disruption of sleep [number] = number of disruptions of sleep per week.
TST = total sleep time.
[#] $p < 0.05$.
[##] $p < 0.001$ as compared to baseline.

improved parameters in the verum group as compared to the sham treatment.

Improvement by coldness at −60 °C might be due to a more distinct effect on the functionality of sensory receptors and causes a decreased neuronal activity with a larger analgesic response [36,37]. Cryotherapy is used as an alternative treatment in autoimmune disorders such as rheumatism. For this indication, patients spend about three minutes per application in a cold chamber (temperature can vary between −60 °C up to −110 °C depending on the cold chamber). The functional background of such a therapy is explained by the operating mode of sensory receptors [36]. Additionally, coldness mainly leads to a smaller amplitude and lower frequency of incoming impulses to the nerve endings resulting in lower perception of pain-feeling which leads to an analgesic response [19,20,21]. Another positive effect of coldness in rheumatism can be the increased number of leucocytes, the changes in concentration of interleukin, and a decreasing level of histamine [22] leading to an immunomodulatory effect as well as positive effect on psychological conditions [28].

Local cryotherapy on the other hand is applied directly towards single body parts (about −17 °C, not only for rheumatism but also for closed injuries and time-limited pain). The temperature of affected body surfaces can be reduced from 35 °C to about 10 °C by using local coldness resulting in decreased neuronal activity which leads to a local analgesia and edema reduction [19].

We hypothesize that all these effects utilized in treatment of rheumatism might, to a lesser degree, also be beneficial in RLS. Another possible explanation for the positive findings particularly in whole body cryotherapy at −60 °C might be a modulating effect on spinal cord excitability [27] since it is known that there is an enhanced spinal cord excitability in RLS [38].

In light of these arguments general cryotherapy might play a supporting role in RLS treatment in the future, as an addition to pharmacological treatment which might thus be reduced, but also as a first line treatment for some patients. Since no other study has attempted to estimate the efficacy of cryotherapy in RLS to date, a direct comparison with other studies is currently not feasible.

A strength of this study was that we were able to address three groups of different cold therapies, namely whole body cryotherapy at −60 °C and −10 °C as well as local cryotherapy at −17 °C. We could analyse different subjective aspects of RLS such as severity and sleep disturbances, daytime sleepiness and quality of life not only during the intervention phase but also at follow-up after four weeks. Additionally, the objective parameter PLM index was added to the other subjective parameters.

Nevertheless, there are limitations we are aware of. Since this study was a pilot study the number of participants was small in each group. Unfortunately, we were not able to fully exclude the effect of the medication as there were no de novo patients included. Medication, however, was stable during the whole study time and can therefore not explain the effects at intervention or follow-up phase. Further, the long time outcome of the patients after the four week follow-up period was not observed. It might be that patients with recurrent cryotherapy might benefit for a very long time. Another problem was that we selected patients with a very specific profile of RLS. This means that our findings cannot be transferred to patients e.g. with symptomatic RLS or with no medication. Finally, it cannot be ruled out that the weekend break during the treatment period had a negative impact on the study outcome.

Further studies should investigate cryotherapy in a larger sample and include polysomnography for each participant during each phase for better and more objective documentation e.g. total sleep time or disruptions during night which was not feasible in this study due to lack of facilities. A longer treatment period and a longer follow-up period would be helpful to determine whether the effects are of a longer-lasting nature.

5. Conclusion

This study investigated for the first time the effect of whole body and local cryotherapy in RLS patients. Results of the verum group (cold air chamber at −60 °C) showed an improvement of RLS symptoms, quality of life, and sleep quality. Some evidence for improving RLS symptoms was also found for the local cryotherapy (at −17 °C) though improvements were less distinct in symptom severity, sleep quality, and quality of life as compared to whole body cryotherapy at −60 °C. Improvements in whole body cryotherapy began directly during intervention and continued during follow-up. In the sham group (cold air chamber at −10 °C), which was used as a control group for the verum group and for investigating a possible placebo effect, we registered almost no changes of RLS symptoms, sleep, and quality of life. All these findings indicate that whole body cryotherapy at −60 °C improves RLS symptoms (local cryotherapy at −17 °C to a less degree).

Conflict of interest

While we believe that we have no conflict of interest that could inappropriately influence our work or writing of the manuscript with regard to the specific matter of the submitted paper, we report a full disclosure for the last three years for each of the authors below.

Christian Thiedemann states no conflict of interest.

Stefan Evers has received honoraria by Allergan, Mundipharma, Pfizer, Reckitt Benckiser, UCB Pharma.

Sabine Bunten has received honoraria by UCB Pharma and Boehringer Ingelheim.

Rudolf Siegert states no conflict of interest.

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