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RESEARCH REPORT

Restless legs syndrome and near-infrared light: An alternative treatment option

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ABSTRACT

There are few treatment options in managing restless legs syndrome (RLS); the most frequently used are dopaminergic drugs and movement. New treatment options are highly sought after. This study evaluated the effectiveness of monochromatic near-infrared light treatment in decreasing symptoms associated with RLS. The design used was 2×6 repeated-measures design with two groups (treatment and control) and six repeated measures (baseline, weeks 1–4, and posttreatment). Data collection took place in the university modalities laboratory. Thirty-four volunteers with symptoms of RLS were randomly assigned to a treatment or control group. Over a 4-week period subjects underwent twelve 30-min treatments to their lower legs with near-infrared light. The International RLS rating scale (IRLS) was used to assess and track patient symptoms. There was a steady decrease in symptoms associated with RLS over the 4 weeks in the treatment group. After 4 weeks of treatment the treatment group had a significantly greater improvement in restless legs syndrome symptoms than the control group ($p<0.001$); improvement was still significant after 4 weeks posttreatment compared to baseline ($p<0.001$). Treatment with near-infrared light does decrease symptoms associated with RLS as demonstrated in lower IRLS scores. This new noninvasive method of treating RLS might become a valuable new management option. More research is needed to determine the mechanism(s) behind infrared light treatment and RLS.

INTRODUCTION

Restless legs syndrome (RLS) has troubled many people over the centuries (Ekbom, 1960). It is characterized by a strong urge to move, accompanied or caused by uncomfortable, or even distressing paresthesia of the legs, described as a "creeping, tugging, pulling" feeling (Ekbom, 1960). The symptoms often become worse as the day progresses, leading to sleep disturbances or sleep deprivation that further results in impairment of alertness and daytime functions (Kushida, Allen, and Atkinson, 2004).

Ekbom (1960), who first described and defined this disease in modern days, reported that 24% of people with low serum iron levels (levels<60 μg/L) exhibit RLS symptoms and that these symptoms decreased when treated with iron injections. More recent research corroborated the association of low serum ferritin levels (<50 μg/L) with RLS (Lee, Zaffke, and Baratte-Beebe, 2001; Sun et al, 1998; Thorpy, 2005). Other pathologies, such as diabetes mellitus, end stage renal disease, vitamin B_{12} deficiency, folate deficiency (Lee, Zaffke, and Baratte-Beebe, 2001), or Parkinson's disease (Appiah-Kubi, Pal, and Chaudhuri, 2002), have been connected to RLS.

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1) they have an urge to move their legs, 2) symptoms begin or worsen during periods of inactivity, 3) the urge to move was at least partially relieved by movement, and 4) this urge to move was worse in the evening or night (Allen et al, 2003). Other investigations (Aukerman et al, 2006; Clavadetscher, Gugger, and Bassetti, 2004; McDonagh, King, and Guptan, 2007; Minai et al, 2007; Rajaram et al, 2005) used these criteria to identify subjects for their studies. The subjects had to score at least 11 points on the International RLS rating scale (IRLS) (The International Restless Legs Syndrome Study Group, 2003). This threshold was chosen because 11–20 points is considered to represent a "moderate" severity level of this pathology (The International Restless Legs Syndrome Study Group, 2003). The subjects had to have good skin integrity and no obvious signs of impaired circulation, as verified by visual inspection.

Exclusion criteria

The following subjects were excluded from the study: subjects who were not able to read the English informed consent form and RLS questionnaire; subjects who exhibited decreased sensation of the sole and dorsum of the feet, as tested by light manual touch; and subjects who were not able to come to the university campus the assigned number of times.

One subject from the control group decided not to continue the study after four treatments. He started having problems with focusing his eyes and his optometrist recommended discontinuance. This person was replaced. The demographic characteristics of subjects in the treatment and control groups are found in Table 1.

Instrumentation

The devices used in this study were Anodyne® Therapy System 480 (Anodyne Therapy, Tampa, FL). The device consists of a base power unit and 8 therapy pads, each containing 60 gallium aluminum arsenide diodes. The area of Anodyne LEDs per therapy pads is 22.5 cm^2, yielding a total treatment area of 180 cm^2. The Anodyne® therapy system delivers pulsed light at 292 Hz with a wavelength of 890 nm through the diodes (Anodyne Therapy, 2007). The active unit provided 62.4 Joules/cm^2 of energy density. For this study the treatment unit output was preset at 10 bars (maximum output) by the manufacturer. No adjustments could be made by the investigators. The manufacturer disabled the control unit so that no light or other energy was emitted, but the panel showed the same 10 illuminated bars as the treatment unit.

TABLE 1 Demographics of the two groups

	Treatment mean (SD)	Control mean (SD)
Age (yr)	54.4 (14.3)	55.5 (17.1)
How long symptoms (yr)	17.6 (19.3)	12.7 (13.3)
IRLS baseline score	24.5 (5.3)	23.6 (6.9)
	n (%)	*n* (%)
Female	12 (71)	8 (47)
Positive family history	9 (53)	12 (71)
Ferritin<50 ng/mL	9 (53)	9 (53)

The tool that allowed us to track improvement of the patients' symptoms was a validated RLS rating scale (IRLS) (The International Restless Legs Syndrome Study Group, 2003). This 10-question survey evaluated different facets of the disorder: 1) subjective assessment of the primary features (questions 1, 2, 3, 6); 2) intensity and frequency (questions 7, 8); 3) associated sleep problems (questions 4, 5); and 4) the impact of patient's symptoms on mood and daily functioning (questions 9, 10) (The International Restless Legs Syndrome Study Group, 2003). The 10-question scale has 5 response options with an associated score from 0 (no impact or symptoms) to 4 (severe), yielding a maximum score of 40. Hoegl and Gschliesser (2007) reviewed several assessment tools used for patients with restless legs syndrome. They strongly support the use of the IRLS rating scale as the gold standard for assessing the severity of the disorder. Other studies have used the IRLS exclusively to track changes associated with RLS symptoms (Aukerman et al, 2006; Clavadetscher, Gugger, and Bassetti, 2004; Minai et al, 2007).

Procedures

The study was approved by the university institutional review board. The patients read and signed an informed consent and were randomly assigned to the treatment or control group by drawing a number "1" or "2" out of a bag. The subjects indicated their RLS-relevant medication intake. For our secondary study purposes we conducted post hoc analyses. First, we classified the subjects into "familial" "and nonfamilial" RLS (Kimura and Winkelmann, 2007). This was done by interview. A person was classified as having "familial RLS" if at least one immediate family member had symptoms of RLS and "nonfamilial RLS" if no immediate family member had symptoms of RLS, or when it was unknown. Second, we grouped the subjects into "low ferritin" (<50 μg/L) and "normal ferritin" (≥50 μg/L) levels. Their blood was

In the 1940s and 1950s it was hypothesized that decreased blood flow led to the symptoms associated with RLS (Rajaram et al, 2005). Ekbom (1960) believed that vasodilators given to RLS sufferers would decrease the symptoms. The vascular hypothesis was later neglected until 2005, when increased vascular blood flow with enhanced external counter pulsation (EECP) was shown to significantly decrease RLS symptoms in six patients (Rajaram et al, 2005). Another study (McDonagh, King, and Guptan, 2007) showed a high prevalence (36%) of RLS in patients presenting with chronic venous disorder. This might be another piece of evidence that RLS is at least in part associated with vascular changes.

There are few options in managing RLS. Dopaminergic agents, such as levodopa and dopamine agonists are the best-studied drugs to date (Oertel et al, 2007) and are now considered the treatment of choice for RLS (Ferini-Strambi et al, 2008). Until May 2005 there were no FDA-approved drugs for the treatment of RLS on the market. Now ropinirole hydrochloride and pramipexole, both dopamine agonists, are available. Unfortunately, these drugs can have side effects, such as nausea, vomiting, dizziness, and somnolence (Ferini-Strambi et al, 2008). Recent research (Ondo, 2009) questions dopamine deficiency as being the reason for RLS.

Nonpharmacological treatment choices for RLS are welcomed options. Because the symptoms are usually lessened by movement (Ekbom, 1960), walking is considered as a management alternative (Oertel et al, 2007), but it loses its attraction when the patient wants to go to sleep. It was recently shown in a randomized controlled trial that a 3-day per week exercise program of aerobic and lower-body resistance training significantly decreased RLS symptom severity (Aukerman et al, 2006). No explanations of the mechanism behind the success of exercise were given, but it is conceivable that the increase in blood flow that results from activity played a role (Clifford and Hellsten, 2004). Other than regular exercise (Aukerman et al, 2006), nonpharmacological treatment choices for RLS include improving sleep quality by controlling sleep times and by reducing caffeine and alcohol consumption (Aukerman et al, 2006; Ferini-Strambi et al, 2008; Oertel et al, 2007; Thorpy, 2005). The success of the latter choices is not well documented. There is a need for other alternative treatments.

Based on anecdotal evidence of clinical success, this study examined another drug-free option; a device that delivers monochromatic near-infrared light (NIR). The Anodyne® therapy system is a noninvasive, drug-free device that delivers light with a wavelength of 890 nm through diodes (Anodyne Therapy, 2007). The proposed mechanism of infra-red light therapy is its ability to generate nitric oxide in the endothelium (Matsunaga and Furchgott, 1989). Nitric oxide is able to initiate and maintain vasodilation (Ignarro, Buga, Wood, and Byrns, 1987; Moncada, Palmer, and Higgs, 1991), and it has influence on neurotransmission (because it is a neurotransmitter itself) (Moncada, Palmer, and Higgs, 1991). Phototherapy, which includes NIR, elicits changes in cell membrane permeability, leading to enhanced synthesis of endorphins, increased nerve cell potential and hence pain relief (Hawkins and Abrahamse, 2007). The following three factors have been associated with RLS: 1) vasodilation (Rajaram et al, 2005); 2) neurotransmission (Trenkwalder and Paulus, 2004); and 3) pain relief (Winkelmann et al, 2000). Therefore, it is conceivable that NIR could positively impact this pathology. The primary purpose of this randomized single blind clinical trial was to investigate the effectiveness of monochromatic near-infrared light energy in decreasing symptoms associated with RLS compared to a sham treatment. Our secondary post hoc analyses examined the relationships between familial and nonfamilial RLS and their symptom resolution as well as serum ferritin levels and symptom changes.

METHODS

Experimental design

This is a 2×6 repeated-measures design with two groups (treatment and control) and six repeated measures (baseline, weeks 1–4, and posttreatment) over time. An analysis for necessary sample size, taking into account the variability associated with the RLS scale (Ferini-Strambi et al, 2008) and a self-determined clinical significant change in RLS score of 10 points (representing a 25% change), yielded a sample size of 34 subjects, 17 each in the treatment and control groups.

Subjects

From January 2009 through August 2009, 34 volunteers with symptoms of RLS were recruited for this study. The recruitment approaches were newspaper advertisements and flyers.

Inclusion criteria

Subjects had to meet the four minimal criteria established by the International Restless Legs Syndrome Study Group for the diagnosis of RLS (Allen et al, 2003) to be admitted to the study. Subjects did so by answering affirmatively to questions on whether

family member before her suffering from RLS. Her father had "circulation problems" in his legs, but details are unknown. However, both of her daughters, aged 43 and 39, reported symptoms of RLS. Neither of them was taking medication for RLS. Our patient's chief complaints were painful sensations in her legs and hips, triggering an urge to move the legs, as well as sleep disturbance. Her social life suffered due to her inability to sit still when going to the movies or the theater or when flying in a plane. She remembered having suffered from RLS before she knew her symptoms had a name–that was about 30 years ago. Since then the symptoms had become more pronounced. For many years she did not receive treatment for the symptoms, because doctors did not recognize her condition–until four years ago, when her family doctor diagnosed her with RLS. At that time she was given muscle relaxants (names not known), but they did not change her symptoms. Consequently, she was given a benzodiazepine (Clonazepam) combined with a sedative (zolpidem). Although her sleep improved, the symptoms associated with RLS remained. When ropinirole became available on the market as one of two FDA approved drugs for RLS, she tried the Starter Kit, where the pills with increasing strength were marked each day they needed to be taken. After less than two weeks she discontinued taking the drug because it made her feel "horrible". Our patient does not remember having had a positive response from the drug, just side effects. The side effects included nausea, balance problems, impaired thinking ability, and, worst of all, remaining RLS symptoms. Our patient was not aware of ever having periodic limb movements, in sleep or at rest.

She responded to the newspaper advertisement for this study because she hoped that some treatment would be available for her. She gave written informed consent to take part in this trial.

Vital signs: blood pressure is 120/78 with a pulse rate of 68. Sensation in lower extremities including feet was intact as measured with Semmes-Weinstein monofilament. The patient was non-diabetic.

Pathologies such as hypertension, arthritis, gastroesophageal reflux disease, depression, anxiety, and diabetes, as well as several lifestyle factors such as increased body mass index, lower income and being unemployed, smoking, lack of exercise, less than six hours of sleep, and low alcohol consumption are linked to this disorder [15]. With the exception of depression, our patient had none of the above.

Our patient exhibited normal range of motion in upper and lower extremities and trunk. Strength was graded 5/5 in all major muscle groups.

The history, systems review, and other examination findings seemed to corroborate her diagnosis of RLS; the differential diagnosis of neuropathy could be excluded.

Based on anecdotal evidence of NIR reducing symptoms associated with RLS, our patient received twelve 30-minute NIR treatment sessions. This is the same protocol that is used nationwide for neuropathy treatment.

The treatments were administered three times a week for four weeks. No other treatment was given, and our patient was asked not to change anything in her daily routine. She lay comfortably on a treatment bench in a quiet room at 21°C (+1°). For comfort, the knees were supported by a five-inch bolster. The lower leg skin area was covered with plastic wrap, which acted as a barrier between skin and diodes to ensure compliance with infection control procedures. Eight flexible monochromatic near-infrared photo energy diodes (60 on each pad) were placed on the lower legs. During each treatment the output was adjusted to the highest level of intensity. After a 30-minute supervised treatment period with NIR, the diodes and plastic wrap were removed. During the Anodyne treatment our patient received an 890 nm wavelength light, pulsed at 292 times/s, with a power output of 600 mW/cm^2. Our patient was asked to fill out a validated RLS self-rating scale[4] in the week before treatment, at the end of each treatment week, one week after and three weeks after cessation of treatment. It was determined that treatment with NIR therapy was deemed to be successful if the patient improved by 10 points on the scale after four weeks of treatment.

Our patient scored a "27" (out of "40") at her first visit, "14" after her first treatment week, "2" after her second week, and "1" after her third week. Weeks four and five were scored a "0" (no symptoms) (Figure 1). The symptoms associated with RLS decreased from "severe" (27/40 possible points on IRLS) to "no symptoms" (0/40 possible points on IRLS) after four weeks of treatment. Our patient stated that she felt marked improvement in every aspect of living. In her own words, –It has changed my "life". Our patient reported that the symptoms returned slowly during week seven and were at a "15" by the end of week eight (four weeks post treatment).

Discussion

The pathophysiology of RLS is not clear. In the 1940s and 1950s it was hypothesized that decreased blood flow was responsible for the symptoms associated with RLS [16]. Ekbom [2] believed that vasodilators given to RLS sufferers would decrease the symptoms. Today it is widely accepted that the central nervous system is involved in RLS, but the original hypothesis of a vascular association still exists. One study reports that increased vascular blood flow with enhanced external

drawn at a local hospital, at no cost to the subjects, before the first treatment and serum ferritin levels were obtained. The subjects' specific treatment days and times were established; the anticipated routine was Mondays, Wednesdays, and Fridays, preferably always at the same time. If the patient was not able to keep an appointment, it was made up on any of the other weekdays.

All subjects independently completed the IRLS on six occasions: 1 week prior to treatment (baseline); at the end of each week of treatment (weeks 1–4); and 1 week after cessation of treatment (post 1). In addition to these 6 weeks of data collection, the near-infrared treatment group was also asked to complete the IRLS at 4 weeks posttreatment (post 4). No data were collected 4 weeks after cessation of treatment from the control group. When subjects had questions concerning the IRLS, the primary investigator provided clarification.

The treatment group underwent 12 treatments with near-infrared light. The control group received 12 sham treatments, where no actual light was administered. The treatment frequency for both groups was three times a week for 4 weeks. No other treatment was given. The subjects were encouraged to maintain their level of medication and to make changes only after confirming with their doctor. At the end of each week the subjects were asked about any changes of medication in the preceding week.

Each subject sat comfortably in a quiet room at 21°C (±1°). The skin of the treatment area was covered with plastic wrap as a barrier between the skin and the diodes to ensure compliance with infection control procedures. Eight flexible monochromatic near-infrared photo energy diodes (60 on each pad) were placed on the lower legs and fastened with a strap. The energy setting was at 10 bars for every patient, as recommended by the Anodyne Therapy, LLC (Anodyne Therapy, 2005). After a 30-minute supervised treatment period with the Anodyne® system, the diodes and plastic wrap were removed.

Data analysis

To ascertain initial comparability in RLS severity, the baseline IRLS scores from the treatment and control groups were compared by using a two-sample t-test. The effect of 4 weeks of NIR treatment on severity of RLS symptoms was assessed by using ANCOVA. The outcome was the difference in baseline and week 4 IRLS scores; therefore, negative differences indicated a decline in severity and positive differences indicated an increase in severity. The analysis was controlled for gender. Finally, to explore at what point in time a discernible and significant difference in symptom amelioration between the treatment and control groups might occur, a series of two-sample t-tests were performed, with the outcomes being the differences in baseline and the 4 weeks of treatment. Because the intent of this latter analysis was simply exploratory, no Bonferroni correction was made to the significance level of these tests to maximize the power of the tests to detect potential differences.

RESULTS

Demographics for both treatment and control groups are presented in Table 1. RLS related drug intake was similar in both groups (Table 2). At baseline, the treatment and control groups were not significantly different in severity of RLS symptoms ($p=0.68$); however, after 4 weeks of near-infrared light treatment and after controlling for gender, the treatment group had significantly greater improvement in symptoms than the control group ($p<0.001$) (Table 3). There was no baseline by treatment interaction, indicating that the treatment effect was similar for all patients, regardless of the initial severity of their symptoms. After 1 week posttreatment, the treatment group continued to be significantly better than the control.

TABLE 2 RLS medication for the two treatment groups

	Treatment group	Control group
None	9	8
Ropinirole	5	4
Pramipexole	2	3
Gabapentin	1	1
Hydrocodone	0	1

TABLE 3 Decrease in mean IRLS score from baseline; comparison between groups

	Change from baseline (±SD)		
	Control $n=17$	Treatment $n=17$	p-value for t-test of change
Week 1	−2.0 (±3.5)	−4.2 (±3.8)	0.09
Week 2	−3.1 (±4.1)	−9.7 (±7.3)	0.003*
Week 3	−4.4 (±4.7)	−10.1 (±8.2)	0.02*
Week 4	−4.4 (±3.6)	−12.7 (±7.7)	0.001*
Week 1 posttreat	−4.5 (±5.0)	−13.4 (±8.1)	0.001*
Week 4 posttreat	n/t	−8.5 (±6.5)	n/a

*Significant difference between improvement in two groups at an alpha level of 0.05.

Both groups significantly improved over time. The mean decrease in the IRLS score within the treatment group after 4 weeks of treatment was 12.7 (±7.7) compared to a decline of 4.4 (±3.6) within the control group. In the treatment group the range of improvement was as small as 4 points and as large as 30. Two of the 17 subjects in the treatment group reported a complete resolution of RLS symptoms. On average, there was a steady decline in RLS symptoms over the 4 weeks of treatment for the subjects receiving the NIR treatment (Figure 1). All except one subject reported some improvement after the first week of near-infrared light treatment. However, in the control group there was a small initial improvement in symptoms after 1 week of treatment and very small changes after the second and third week of treatment. On the basis of the exploratory analysis, significant differences in symptom improvement between the treatment and control groups might appear as soon as 2 weeks of treatment (Table 3).

In the treatment group at 1 week posttreatment, 7 (41%) subjects reported an increase in symptoms compared to the week before, 5 (29%) reported no change in symptoms, and 5 (29%) reported a continued decrease in symptoms. However, of the 15 subjects who provided data at 4 weeks posttreatment, 10 (67%) reported an increase in symptoms compared to 1 week posttreatment, and 4 (27%) reported improvement. In the control group at 1 week posttreatment, 7 (41%) subjects reported an increase in symptoms from week 4 (conclusion of treatment), 6 (35%) reported no change in symptoms, and 4 (24%) reported a decrease in symptoms.

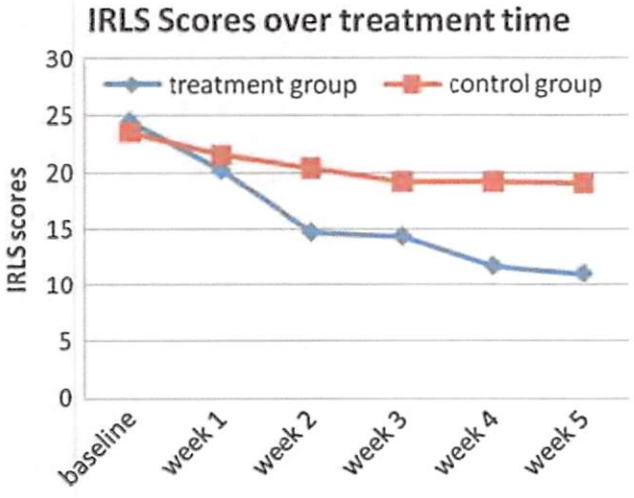

FIGURE 1 Improvement in IRLS scores over 4 weeks of treatment and 1 week posttreatment.

Post hoc analyses

Of the 34 patients who participated in our study, 18 had low ferritin levels; 9 in treatment group (average 19.2 μg/L, 3.4–42.6 μg/L; treatment group average 54 μg/L) and 9 in the control group (average 20.12 μg/L, from 5.8 to 38.7 μg/L; control group average 48 μg/L). The within-group comparisons between subjects with normal and low ferritin level revealed no difference in groups at baseline or after week 4 or 5 for either treatment (p=0.65, 0.13, and 0.43, respectively) or the control group (p=0.12, 0.14, 0.12, respectively).

Within-group comparisons between familial (F) and nonfamilial (NF) RLS were made to assess whether one reacted better to the treatment than the other. There was no difference in F-NF groups at baseline or after week 4 or week 5 for either the treatment (p=0.87, 0.38, and 0.89, respectively) or the control group (p=0.51, 0.21, 0.32, respectively).

DISCUSSION

RLS can be a life-impacting pathology for which only few treatment options exist. This study evaluated the efficacy of infrared treatment to the legs to reduce symptoms associated with RLS. After 12 treatments over 4 weeks the treatment group experienced a significantly greater reduction in RLS symptoms than the control. Two subjects had all of their symptoms associated with RLS abolished, which, in their own words "changed their lives." The symptoms in the treatment group were still significantly decreased from baseline 4 weeks after cessation of treatment, with an average decrease of 8.5 points from baseline (p<0.001).

An average reduction of almost 13 points in the IRLS score implies a significant clinical improvement for the patients suffering from restless legs syndrome. This is evident when it is considered that a 10-point difference on this questionnaire determines the pathology's severity level: "none" (0 points); "mild" (1–10 points); "moderate" (11–20 points); "severe" (21–30 points); or "very severe" (31–40 points). This drop in score is comparable to that of dopamine agonists (Oertel et al, 2007).

Although the average decrease in IRLS score in the control group was significant (4.4 points), this placebo effect, as indicated in the RLS literature (Fulda and Wetter, 2008), was expected. A meta-analysis of the placebo effect in RLS treatment studies using the IRLS showed a pooled weighted response rate of 40.09, indicating that about 40% of the treatment effect was due to a placebo response (Fulda and Wetter, 2008). The authors point out that the placebo

effect for the IRLS was larger than for other RLS scales and that this was possibly due to its multidimensional features.

RLS has been associated with low iron levels for 70 years (Ekbom, 1960), whereas "normal" serum ferritin levels are considered to be 12–300 μg/L (with an average of 33.6, 93.4, and 139.9 μg/L for premenopausal women, postmenopausal women, and men, respectively) (Jehn, Clark, and Guallar, 2004). In the RLS literature a low ferritin level is considered to be less than 45–50 μg/L (Thorpy, 2005; Sun et al, 1998). Of the 34 patients who participated in our study, 18 had low ferritin levels, equally distributed among the treatment and control groups. This ratio confirms the findings of others (Aul, Davis, and Rodnitzky, 1998; Ekbom, 1960; O'Keeffe, Gavin, and Lavan, 1994; O'Keeffe, Noel, and Lavan, 1993; Sun et al, 1998), who reported that low ferritin levels are related to RLS development or severity. On average, there was no difference, however, in treatment response for subjects with normal or low serum ferritin levels or with familial and nonfamilial RLS.

The purported mechanism behind the success of near-infrared light treatment for neuropathy is its ability to increase nitric oxide generation (Horwitz, Burke, and Carnegie, 1999). Supposedly, this is achieved two different ways: 1) by activating nitric oxide synthase (NOS-3), an enzyme that catalyzes the degradation of L-arginine to L-citrulline and NO (Buga, Gold, Fukuto, and Ingarro, 1991; Erzurum et al, 2007); or 2) by releasing free NO from hemoglobin. It was suggested that hemoglobin-bound NO might serve as a store of nitric oxide from which free NO can be released by intensive illumination (Vladimirov et al, 2000). Once NO is generated, a cascade of events is initiated, eventually leading to vasodilation (Burke, 2003; Erzurum et al, 2007). The unpleasant symptoms associated with RLS could be a sign of, or a direct effect from, decreased tissue perfusion. This lack of blood flow is usually countered and offset with walking or rubbing of the legs—activities that increase blood flow (Clifford and Hellsten, 2004; Thijssen et al, 2009) and decrease RLS symptoms. One of the diagnosing criteria is an affirmative answer to the question, does movement relieve the RLS discomfort? Hence, nitric oxide's chemical property of vasodilation could conceivably explain a temporary decrease in the symptoms associated with RLS. While light's primary effects on tissue (the direct absorption of photons in the tissue) and secondary anabolic effects (Dyson, 2006) can explain the immediate treatment result, its tertiary effect could account for the relatively long-term benefits incurred by our subjects (Dyson, 2006). The tertiary effect of phototherapy is systemic, which could continue to stimulate NO generation (Dyson, 2006).

Further research is warranted. No published paper has shown whether NO levels actually increase during treatment with near-infrared light. The reason for this probably lies in the difficulty of being able to accurately determine the amount of NO in blood because it is highly reactive with a very short half-life (4 seconds). It very quickly oxidizes to nitrite, which in turn further oxidizes to nitrate (Wennmalm, Benthin, and Petersson, 1992).

Limitations

The treatment and control groups did not have a balanced number of subjects with family history RLS (53% in the treatment group, compared to 71% in the control group); the time of symptoms present was different (17.6 years in the treatment group compared to 12.7 years in the control group); and the gender distribution was dissimilar (71% in the treatment group were female compared to 47% in the control group). The sample size was small but adequate as determined by a priori power analysis. It would be beneficial to expand the study to more subjects, maybe with possible blocking on either gender, familial, and nonfamilial RLS, medication intake, or other variables.

CONCLUSION

This randomized controlled study showed that NIR treatment to the lower legs significantly improved symptoms associated with RLS. The mechanisms for this response have yet to be determined. Nevertheless, NIR treatment could be a new drug-free treatment option, or adjunct treatment, for many RLS sufferers.

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This report adds to existing studies as it suggests a different, non-drug-related treatment option to patients who would otherwise have to take dopaminergic or other drugs. The mechanisms with which NIR can alleviate RLS symptoms are not clear. One supposition can be made: light has been shown to generate NO in the endothelium, which through a cascade of events leads to vasodilation. Vasodilation is also the result of exercise [18], one of the few non-drug related treatment options that decreases RLS symptoms. While no direct relationship between NO and RLS symptoms can be shown, it is plausible that this radical, generated in the lumen of blood vessels, might have similar benefits to the patients as exercise. Further research into this hypothesis is suggested.

It is of course too early to suggest that treatment with NIR is the best treatment option for patients suffering from RLS; a randomized clinical trial would shed more light on the usefulness of this treatment.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The author declares that they have no competing interests.

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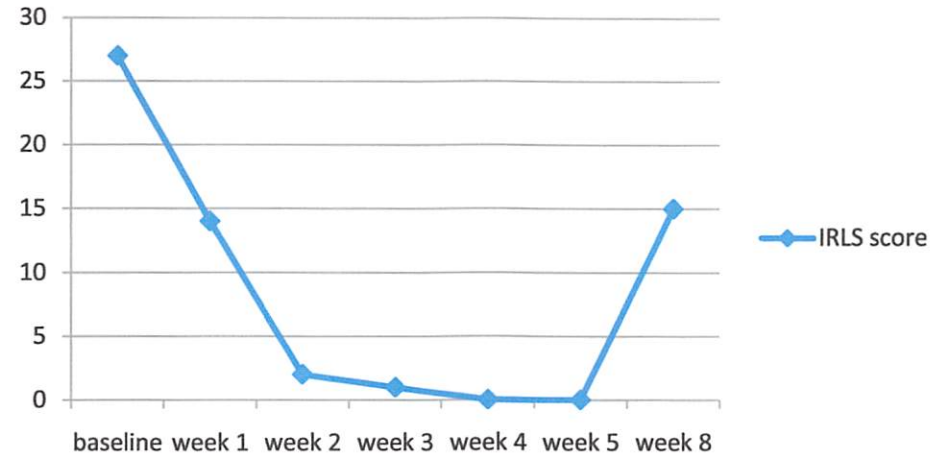

Figure 1 Patient's IRLS scores indicate resolution of RLS symptoms.

counter pulsation significantly decreased RLS symptoms in six patients [16]. Another study [17] showed a high prevalence (36%) of RLS in patients presenting with chronic venous disorder. The author of this case report theorizes that the symptoms associated with RLS could stem from a feedback mechanism where decreased tissue perfusion in the legs signals to the brain the need to move. Activity, such as movement or walking, increases blood flow to the muscle and tissue [18]. The proposed mechanism of NIR therapy is its ability to generate NO in the endothelium [19] and even in the lumen directly by dissociating NO from hemoglobin contained in erythrocytes [14,20]. Nitric oxide is able to initiate and sustain vasodilation [21,22] and, as a neurotransmitter itself, has influence on neurotransmission [22]. Phototherapy, which includes NIR, has been known to decrease pain by changing cell membrane permeability. This leads to enhanced synthesis of endorphins, increased nerve cell potential and hence to pain relief [23]. NIR consequently can affect three factors associated with RLS: vasodilation [16], neurotransmission [24] and pain relief [25]. It is thus conceivable that NIR could positively impact this pathology. Recent findings could validate this hypothesis as well as function as the missing link between theory and fact. A German study [26] discovered significant evidence for an association of RLS with sequence variations in the NOS1 gene, pointing to a possible involvement of the NO/arginine pathway in RLS disease susceptibility and in the etiology of RLS.

Other factors may have contributed to our patient's improvement. As in the study by Ferini-Strambi *et al.* [7], where IRLS scores decreased in medicated and non-medicated RLS patients after taking part in weekly group sessions, the social interaction between therapist and subject could have contributed to her improvement. However, the therapist/subject interaction in this case report was kept within the limits of a typical therapist/patient relationship and was not intended or designed to have a "support group" character.

A recent meta-analysis [27] assessing the placebo effect in RLS treatment studies found a substantial placebo response associated with RLS treatment. This response was greater for the IRLS compared to other scales, possibly related to its multidimensional assessment character. On average, more than one-third of RLS subjects experienced a major improvement of RLS symptoms while receiving placebo treatment. The author proposes that the reason for this might be related to the unique responsiveness of RLS to dopaminergic agents and opioids - both systems implicated in the placebo response. The question of whether our patient's improvement was likely due to a pure placebo effect can only be answered by conducting a randomized controlled trial.

Conclusions

This case report shows how NIR helped one patient suffering from RLS symptoms to eliminate her symptoms and suggests that this protocol might be a potential treatment option for other, similar patients. One patient received 30-minute NIR treatment sessions, three times a week for four weeks. This regimen was taken from a protocol used in home health to treat patients with neuropathy. If treatment with NIR could be used to alleviate RLS symptoms, the patients would be able to benefit greatly from this non-invasive option.