Original article

The effect of endovenous laser ablation on restless legs syndrome

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Abstract

***Objectives*:** Venous disease was proposed as a cause of restless legs syndrome (RLS) by Dr Karl A Ekbom in 1944, but has since remained largely unexplored. This study examines the effect of endovenous laser ablation (ELA) in patients with concurrent RLS and duplex-proven superficial venous insufficiency (SVI).

***Methods*:** Thirty-five patients with moderate to very severe RLS (as defined by the 2003 National Institute of Health (NIH) RLS criteria) and duplex-proven SVI completed an international RLS rating scale questionnaire (IRLS) and underwent standard duplex examination to objectively measure the baseline severity of their conditions. They were separated into non-operative and operative cohorts. The operative cohort underwent ELA of refluxing superficial axial veins using the CoolTouch CTEV 1320 nm laser and ultrasound-guided sclerotherapy of the associated varicose veins with foamed sodium tetradecyl sulphate (STS). All patients then completed a follow-up IRLS questionnaire. Baseline and follow-up IRLS scores were compared.

***Results*:** Operative correction of the SVI decreased the mean IRLS score by 21.4 points from 26.9 to 5.5, corresponding to an average of 80% improvement in symptoms. A total of 89% of patients enjoyed a decrease in their score of $\geq$15 points. Fifty-three percent of patients had a follow-up score of $\leq$5, indicating their symptoms had been largely alleviated and 31% had a follow-up score of zero, indicating a complete relief of RLS symptoms.

***Conclusions*:** ELA of refluxing axial veins with the CTEV 1320 nm laser and foamed STS sclerotherapy of associated varicosities alleviates RLS symptoms in patients with SVI and moderate to very severe RLS.

***Recommendations*:** SVI should be ruled-out in all patients with RLS before initiation or continuation of drug therapy.

Keywords: restless legs syndrome; endovenous laser treatment; oedema; varicose veins; venous insufficiency

Introduction

Restless legs syndrome (RLS) is a poorly understood disorder in which patients experience compelling urges to move the legs usually accompanied by intense, unpleasant sensations in their legs. RLS affects 5–15% of the American and European populations. Women are twice as likely to be affected. The earliest description of an RLS case was by English physician and anatomist Sir Thomas Willis in 1672. RLS lingered in anonymity until 1944, when Swedish neurologist Karl Ekbom first described the salient features.[1] In 1945 he coined the phrase 'restless legs'.[2] The addition of the word 'syndrome' designates this malady as a condition defined by clinical symptoms rather than by any specific pathological process.

Most patients find they cannot describe the nature of their sensations. Dr Ekbom felt that 'this is evidently due to the fact that the sensations do

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Have the patient rate his/her symptoms for the following ten questions.
The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.
The examiner should mark the patient's answers on the form.

In the past week...
(1) Overall, how would you rate the RLS discomfort in your legs or arms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(2) Overall, how would you rate the need to move around because of your RLS symptoms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?
_ (4) No relief
_ (3) Mild relief
_ (2) Moderate relief
_ (1) Either complete or almost complete relief
_ (0) No RLS symptoms to be relieved

In the past week...
(4) How severe was your sleep disturbance due to your RLS symptoms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(6) How severe was your RLS as a whole?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(7) How often did you get RLS symptoms?
_ (4) Very often (6–7 days in 1 week)
_ (3) Often (4–5 days in 1 week)
_ (2) Sometimes (2–3 days in 1 week)
_ (1) Occasionally (1 day in 1 week)
_ (0) Never

In the past week...
(8) When you had RLS symptoms, how severe were they on average?
_ (4) Very severe (8 h or more per 24 h)
_ (3) Severe (3–8 h per 24 h)
_ (2) Moderate (13 h per 24 h)
_ (1) Mild (less than 1 h per 24 h)
_ (0) None

In the past week...
(9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(10) How severe was your mood disturbance due to your RLS symptoms – for example angry, depressed, sad, anxious or irritable?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

Sum of scores =

Scoring criteria are: Mild (score 1–10); Moderate (score 11–20); Severe (score 21–30); Very severe (score 31–40)

1. Answers for this IRLS are scored from 4 for the first (top) answer (usually 'very severe') to 0 for the last answer (usually none). All items are scored. The sum of the item scores serves as the scale score.

Figure 1 International RLS Study Group rating scale questionnaire (IRLS)

not resemble any known phenomenon that can be used as a comparison'.[3] They are variably described as heebie-jeebies, antsy, Jimmy legs, and so on. The sensations are painful in about 30% of patients. There is a wide variation in severity with some patients experiencing only occasional mild symptoms, whereas others struggle with the disabling episodes on a nightly basis. Symptoms of RLS are worse in the evening and during periods of relaxation or decreased activity, especially while lying down or reclining. Patients are often completely asymptomatic in the morning. The reason for this is unknown. The desire to relieve the symptoms can lead to a compulsion involving excessive limb movements. The sensations and the compulsion to relieve them frequently become terribly distressing.[4] As RLS symptoms are stronger at bedtime, sleep-onset insomnia is common. RLS sufferers, often find they cannot sleep until the early morning hours. Patients with severe RLS

experience nightly attacks that lead to chronic sleep-deprivation with its accompanying psychological and cognitive deficits.[5]

Investigators have made great strides in the understanding and treatment of RLS over the last two decades, to the nightly relief of millions of victims. The aetiology of RLS remains elusive, however, and a final common pathway has yet to be described. According to Dr M J Thorpy, primary RLS 'may represent a heterogeneous group of disorders because no single pathophysiological mechanism explains all the clinical features exhibited'.[6]

There are no classic physical findings, no conclusive blood assays and no standard radiological or sleep studies to diagnose RLS. Because there is no known biomarker, the diagnosis of RLS can only be made based on the clinical history. In an attempt to more clearly define RLS, the IRLSSG developed RLS diagnostic criteria in 1995. An IRLSSG consensus panel at the NIH modified these criteria to their present form in 2003. These four criteria are necessary and sufficient for the diagnosis of RLS. They include: (1) urges to move the limbs with or without unpleasant sensations; (2) worsening of symptoms at rest; (3) improvement of symptoms with movement; and (4) worsening of symptoms at night.[4] The IRLS questionnaire (Figure 1) was developed by the IRLSSG and validated in 2003 as a consistent, reliable tool to objectively measure RLS severity.[7]

RLS is divided into primary (idiopathic) and secondary causes. Primary RLS is felt to be the most common form and is suspected to be a sensorimotor abnormality associated with central nervous system dysfunction involving abnormal brain iron metabolism and irregularity of central dopaminergic neurotransmitter pathways.[6] Secondary RLS occurs in such disparate conditions as back pain, iron deficiency, renal failure, pregnancy, neuropathy and venous disease. Various medications are known to precipitate RLS attacks. The fact that RLS is a 'mixed bag' diagnosis has complicated research, confounded investigators and frustrated clinicians; in that various medications work in only a percentage of affected patients. Current treatment therefore focuses on nightly management of symptoms rather than on cure.[8,9]

In 1995 Dr A H Kanter's groundbreaking study suggested that the sclerotherapy in patients with varicose veins and RLS is 98% effective in initial relief of RLS. This is the first article to describe operative treatment of RLS. Dr Kanter concluded that all RLS patients with varicose veins should be considered for phlebological evaluation and possible treatment before being consigned to chronic drug therapy.[10] We have received frequent reports of coincidental relief of RLS symptoms while treating patients with venous disease using new endovenous laser techniques. The aim of the study is to determine what effect ELA has in patients with RLS and SVI.

Methods

Patients and study design

We screened 89 patients with complaints of restlessness in their legs. The diagnosis of RLS was determined using the 2003 NIH criteria. All patients who met the criteria for RLS were interviewed to confirm the diagnosis of RLS and to exclude the conditions that mimic RLS (such as positional discomfort, neuropathy, night cramps and so on). They then completed an initial IRLS questionnaire to determine the baseline severity of their disease. Those patients with an IRLS score of 15 or greater (corresponding with moderate to very severe RLS) underwent a screening duplex ultrasound. Patients found to have greater than 500 ms of reflux in the great saphenous vein underwent a complete duplex evaluation of the deep, superficial and perforator systems. All reflux was mapped for appropriate treatment. Thirty-five patients met the criteria and were accepted into the study.

Sixteen patients were assigned to the non-operative cohort, 19 to the operative cohort. In the non-operative cohort 6.3% of patients were men and 93.7% were women. The mean age was 58.8, and the average weight was 180.2 pounds. In the operative cohort, 31.6% of patients were men and 68.4% were women. The mean age was 49.4, and the average weight was 202.5 pounds. One patient withdrew from each cohort for unrelated medical reasons.

Most RLS patients take medication nightly in order to get some sleep. We felt it important for this study to be applicable to the broader population. We therefore did not exclude patients who were taking RLS medications. In order to stabilize RLS medication as a variable, we did ask patients not to add or discontinue medications known to affect RLS symptoms during the study period.

Intervention

Patients were assigned to either the non-operative or operative cohort. Non-operative patients

completed a follow-up questionnaire six weeks after the initial questionnaire. This yielded objective measurements of the severity of the baseline and final RLS symptoms in the non-operative cohort.

The operative patients underwent ELA of all refluxing axial veins using the Cool-Touch 1320 nm laser at settings of 50 Hz and 7 W. The pull-back device was set on 0.5 mm/s for the first 10 cm, then 1.0 mm/s for the remainder of the vein. These laser settings applied 140 J/cm to the first 10 cm of vein, and 70 J/cm to the remainder of the vein (this rather high fluence was utilized to ensure 100% ablation of all treated veins). Varicose veins and refluxing perforator veins were treated with ultrasound-guided sclerotherapy using 1.0% STS foam. A 6-inch ACE wrap was applied immediately postoperatively and continued for 48 h, then replaced with 20–30 mmHg compression stockings for two weeks. Compression was then removed. Operative patients underwent a postoperative duplex examination for 2–3 days after the procedure, and again six weeks later. They completed a final IRLS questionnaire at the six-week follow-up appointment. The baseline and final IRLS scores of both groups were then compared.

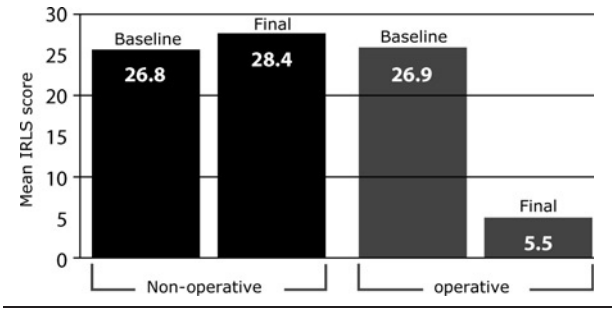
Study design and statistical analysis

Thirty-five patients, who met the inclusion criteria, were enrolled into this prospective, randomized, unblinded, parallel two-group, pre-post-test study. This study design involved outcome variables measured on binomial and continuous scales. For the continuous outcome variables (i.e. IRLS questionnaire), one-way analysis of variance with two distinct levels of the intervention was performed. Moreover, since unequal sample sizes were anticipated and observations were repeated over time, Bonferroni procedures were appropriate to control for experimentwise, multi-comparison error. Matched-pairs analysis was used to test the null hypothesis of zero change from IRLS baseline score.

When analysing binomial variables (i.e. RLS symptoms alleviated, yes or no), Chi-square and likelihood ratio statistics were computed to test the null hypothesis of no association between the intervention groups and the response variable(s). In addition, since single-group pre- and post-test comparisons were performed and the assumption of independent samples was not met, McNemar's test for matched pairs was appropriate. Exact tests were used and exact probabilities were computed where appropriate.

All statistical analysis activities were performed using SAS Statistical Software, Version 9.1.3, SAS Institute, Inc., NC, USA. The procedures used are PROC ANOVA, PROC GLM and PROC FREQ.

Table 1 Baseline and final mean IRLS scores – Non-operative vs. operative



Results

Duplex evaluation performed 6 weeks postoperatively and revealed that 100% of the treated veins were successfully ablated. Transient postoperative discomfort in the region of the treated veins was frequently reported. Most patients required only PRN Ibuprofen, foregoing the prescribed hydrocodone. All patients had mild bruising at the access sites. There were no major side-effects or complications.

When comparing with the mean baseline IRLS scores for the non-operative and operative cohorts, 26.8 vs. 26.9, respectively, the difference was not found to be statistically significant ($P = 0.971$). Consequently, one could assume homogeneity in RLS symptoms and severity across treatment groups prior to intervention. At the final evaluation, the mean IRLS score in the non-operative cohort was actually found to be slightly elevated (28.4) in contrast to their baseline mean score. The mean IRLS score in the operative cohort decreased by 21.4 points to 5.5 (Table 1). This represents a drop in symptom severity of 80%. The matched-pairs analysis was statistically significant ($P < 0.0001$) indicating that the change from baseline in IRLS score for the operative group was significantly greater than the change from baseline in IRLS score for the non-operative group.

Eighty-nine percent of operative patients enjoyed a decrease in their IRLS score of 15 points or more. Seventy-nine percent of patients improved to 'mild' disease (final score $\leq$10). Ninety-five percent of patients improved to 'mild' or 'moderate' disease (final score $\leq$20). Fifty-three percent of patients had a final score $\leq$5 indicating their RLS symptoms

had been largely alleviated. Thirty-one percent of patients had a final score of zero, indicating complete relief of RLS symptoms.

Discussion

In Dr K A Ekbom's original 1944 article, he presented eight patients with what he called asthenia crurum paraesthetica 'irritable legs'. He described the symptoms RLS and said that, in most patients, objective signs were lacking. One (12.5%) of these patients, however, was noted to have varicose veins. Dr Ekbom went on to say that all patients had palpable dorsalis pedis pulses, yet he concluded: 'It is possible that the condition is due to a functional vascular disorder'. He suspected venous congestion and an accumulation of metabolites to be a cause of RLS.[1,3] Our study suggests that in a percentage of RLS sufferers Dr Ekbom's suspicions were correct. Furthermore, treating the underlying venous disease can relieve the RLS symptoms.

The question naturally arises: how does venous disease cause RLS symptoms? This has yet to be explored. We hypothesize that the symptoms experienced by these patients are due to the nightly mobilization of oedema that coincides with the onset, duration and resolution of their RLS symptoms.

Venous insufficiency is an impedance of venous flow back to the heart. It is usually caused by venous reflux secondary to valvular failure and can occur in the deep, superficial or perforator veins. Venous insufficiency results in high venous pressures that are transmitted to tributary veins, venules, capillaries and interstitial tissues drained by the diseased vein. It affects 10–15% of men and 20–25% of women. SVI is much more common than deep venous insufficiency.[11–13]

According to the Starling concept, most of the fluid forced out of the capillary bed at the arterial end is normally returned into the lumen at the venous end. In tissues affected by venous hypertension, this delicate balance is disrupted. The high hydrostatic pressure in the venules and capillaries causes a net increase in the fluid remaining in the interstitial space. This increased interstitial fluid volume overwhelms the lymphatic capacity, resulting in oedema formation. As long as the leg is dependant, the interstitial fluid continues to accumulate, until the tissue pressure rises to a point at which the Starling equilibrium is restored. Considerable oedema can accumulate before this point of equilibrium is reached. Upon elevation of the leg (such as when the patient is lying down or reclining), the venous pressures diminish and the lymphatics can drain the engorged interstitium.[14]

The circadian ebb and flow of oedema fluid seen in venous insufficiency closely parallels the circadian timing of RLS symptoms. We believe this is more than mere coincidence. We know that the daily accumulation of soft tissue oedema creates unpleasant sensations in the legs, such as heaviness, fullness, achiness and so on. We propose that the nightly receding of that oedema fluid somehow causes the 'indescribable' sensations that typically plague RLS patients. This would explain why the typical RLS symptoms occur when the patient is reclining and at night (as the elevation mobilizes oedema from the legs), and why symptoms seem to wane in the early morning hours (the oedema has largely resolved by that time). We speculate that the restless leg movement may be subconscious activation of the musculovenous pump, stretching of afflicted muscles and tendons or a distractor to mask the tormenting sensations. This will require sorting-out by future research.

Our premise is supported by the fact that 26% of women are affected by RLS during their pregnancy. Pregnancy has been shown to exacerbate both RLS and oedema independently. Strong correlation is noted with the third trimester of pregnancy (when the pregnancy-associated oedema is at its peak) and tends to disappear with delivery (when the pregnancy-associated oedema has receded).[15]

Similar findings are seen in haemodialysis patients. RLS affects 20–80% of this population. Despite extensive research of various clinical and biochemical parameters, the cause of RLS in this population remains a mystery. It has been shown that the increasing dialysis from three days a week to five days a week (but not changing total number of hours per week) relieves the RLS symptoms. RLS symptoms disappear in haemodialysis patients who receive a kidney transplant. We feel that the frequent dialysis dampens and renal transplant eliminates the huge volume swings normally seen in haemodialysis patients, thus impacting their RLS symptoms.[16–18]

Primary RLS is generally felt to be a condition in which an abnormal nervous system is reacting inappropriately to relatively normal legs. In RLS patients with venous disease, it appears that RLS is due to a relatively normal nervous system reacting appropriately to abnormal legs.

Strengths and limitations of the study

We employed the NIH criteria to make the diagnosis of RLS and the IRLS questionnaire to grade the

severity of symptoms. These tools are widely utilized in current RLS research. They made possible accurate comparisons between operative and control groups. This allowed us to gather statistically significant results despite our small sample size.

Bias was introduced in this study by including only those RLS patients with duplex-proven SVI. All RLS patients with normal venous function were therefore excluded. Bias was also introduced in the manner in which the patients were assigned to operative vs. non-operative cohorts. Medicare and third party insurance carriers require a three to six-month trial of 'conservative non-operative measures'. Because of time constraints, patients who had not met these criteria before presenting to our vein centre were automatically placed in the non-operative cohort. Patients who had met these mandates were placed in the operative cohort. This is a weakness in our study. In addition, larger studies are needed to explore the connections between RLS, venous insufficiency and lower extremity oedema.

Conclusions

Our results suggest that ELA of refluxing axial veins and sclerotherapy of associated varicosities alleviates or relieves RLS symptoms in patients with moderate to very severe RLS and SVI. All RLS patients should be properly evaluated for venous insufficiency by a technician familiar with techniques to detect venous reflux before initiation or continuation of drug therapy. Any RLS patient with venous insufficiency should be referred for evaluation and treatment by a phlebologist. Only in this way can these patients escape the nightly torment of chronic RLS.

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