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ORIGINAL RESEARCH

Efficacy of neuromuscular electric stimulation versus aerobic exercise on uraemic restless legs syndrome

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Abstract

Background The prevalence of restless legs syndrome in haemodialysis patients is approximately ~30%, and it is significantly higher than in the general population. Restless legs syndrome is a sensory-motor disorder with negative effects on sleep and daytime activities that affect personal, family and occupational life. The overall impact of restless legs syndrome on quality of life is comparable to that of chronic and frustrating conditions such as depression and diabetes. The present study was conducted to compare the effect of neuromuscular electric stimulation with aerobic exercise on cases of uraemic restless legs syndrome.

Methods A total of 60 chronic renal failure patients with uraemic restless legs syndrome aged 20 to 65 years participated in this study. Participants were allocated to receive neuromuscular electric stimulation or aerobic exercises. All participants were evaluated before the first session of treatment and after 3 months, at the end of the treatment. Normal and fast walk gait speed tests and the Five Times Sit-to-Stand Test and 60 second Sit-to-Stand Test were used to assess participants' physical status. The Restless Legs Syndrome Rating Scale was used to determine the level of restless legs syndrome severity.

Results Neuromuscular electric stimulation resulted in significant improvements in all measures of physical performance and in Restless Legs Syndrome Rating Scale score when compared to baseline. Aerobic exercise produced significant improvements in all tests. At the end of the study, aerobic exercise had greater responses than neuromuscular electric stimulation in all parameters measured except the Five Times Sit-to-Stand Test.

Conclusions Neuromuscular electrical stimulation may be used as an alternative to aerobic exercise to improve physical performance in cases of less severe restless legs syndrome in those unable or unwilling to participate in physical training.

Key words: ■ Aerobic exercise ■ Neuromuscular electrical stimulation ■ Renal failure ■ Restless legs syndrome

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INTRODUCTION

Restless legs syndrome is a common neurological sensory-motor disorder characterised by intense restlessness and unpleasant creeping sensations deep inside the lower legs. Symptoms appear when the legs are at rest and are worst in the evening and at night. They force patients to keep moving their legs and often to get out of bed and

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wander about to relieve their symptoms (Ekbom et al, 2009). Restless legs syndrome is strongly associated with certain conditions including diabetes, chronic kidney disease (uraemic neuropathy), iron deficiency anaemia, obesity, vitamin deficiency states related with peripheral neuropathy and folate deficiency (Franco et al, 2013; Winter, 2013; Esteve et al, 2017).

Prevalence of restless legs syndrome in haemodialysis patients

The prevalence of restless legs syndrome in haemodialysis patients is much higher than in the general population, reaching approximately 30% (Stefanidis et al, 2013; Sakkas et al, 2017). Twice as many women are affected as men and the prevalence of the disorder has been shown to increase with age (Winter et al, 2013). Uraemic restless legs syndrome is frequently associated with increased morbidity and enhanced mortality in haemodialysis patients and has been linked to cardiovascular diseases (Franco et al, 2013; Sakkas, 2017).

Patients undergoing regular dialysis frequently complain of insomnia, restless legs syndrome, sleep-disordered breathing and excessive daytime sleepiness (Kim et al, 2008), and sleep disorders are common among patients undergoing dialysis for end-stage renal disease. Uraemic restless legs syndrome is one of the most important factors contributing to sleep disturbance in patients with chronic renal insufficiency (Kavanagh et al, 2004).

Physical rehabilitation

Haemodialysis is associated with decreased physical activity, muscle weakness, deterioration in quality of life and impaired activities of daily living. Urea metabolic disorder mainly affects type II muscle fibres and skeletal muscle nerve endings, causing myopathy and myelin sheath degeneration that, in the long term, will lead to severe muscular atrophy and various symptoms, such as fatigue, weakness, cramps, spasms or myoclonus (Simó et al, 2015).

One of the fundamental aspects of renal patient care should be physical rehabilitation to preserve functional capacity and autonomy. Exercise training consists of planned, structured and repetitive body movement to improve or maintain one or more components of physical fitness or other health benefits (Painter et al, 2005; Giannaki et al, 2013a).

Acute exercise appears to be very effective in reducing the acute motor symptoms often seen during a haemodialysis session (Giannaki et al, 2013b). Progressive exercise training has been prescribed for individuals with kidney disease in the hope of attenuating or ameliorating the muscle wasting and impaired physical function associated with the condition. Exercise training has also been shown to be a safe and effective low-cost approach to reducing the severity of restless legs syndrome symptoms in haemodialysis patients (Sakkas et al, 2008).

Neuromuscular electrical stimulation

Neuromuscular electrical stimulation causes the passive (non-volitional) contraction of skeletal muscles through the use of low-voltage electrical impulses delivered through the skin to underlying muscles via surface electrodes. The targeted muscles react by contracting as they would with normal muscular activity (Simó et al, 2015). Neuromuscular electrical stimulation can be commenced early, without the need for patient participation, and has been shown to prevent skeletal muscle atrophy and improve physical function and strength in chronic disease populations.

Aim

This study was conducted to compare the effects of neuromuscular electrical stimulation to acute exercise in the treatment of uraemic restless legs syndrome.

METHODS

Participants

Patients being treated for renal failure by the Department of Internal Medicine at Cairo University Hospitals between January and August 2017 and who had restless legs syndrome were eligible to enter this study.

Exclusion criteria

Participants were excluded from this study if they had an orthopaedic condition that limited ambulation or their ability to perform prescribed exercises, a coronary event in the preceding 6 months or uncontrolled hypertension.

Inclusion criteria

The inclusion criteria for the study were: dialysis for at least three months or more with adequate dialysis delivery and with stable clinical condition. In addition, all patients should have restless legs syndrome and none of them should have been treated with any medication for restless legs syndrome before the study.

Diagnosis of restless legs syndrome

Restless legs syndrome was diagnosed when one of the following criteria were met (Allen et al, 2003):

- An urge to move the legs (or sometimes other body parts) that is usually but not always accompanied or caused by uncomfortable and unpleasant sensations
- The urge to move or unpleasant sensations that begin or worsen during periods of rest or inactivity, such as lying or sitting down
- The urge to move or unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
- The urge to move or unpleasant sensations that are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Of the 215 patients receiving treatment, 75 patient met the inclusion criteria but 15 declined to participate. A total of 60 individuals with uraemic restless legs syndrome (46 female and 14 male) as a result of renal failure and who had been on haemodialysis for at least 3 years agreed to take part after referral from their doctors. These patients were undergoing 4 hours of haemodialysis on alternate days. Participants were randomly assigned to receive neuromuscular electrical stimulation (n=30) or aerobic exercise (n =30) (*Table 1*).

Table 1. Participants' demographic characteristics

Characteristic	Group	
	Neuromuscular electrical stimulation	Aerobic exercise
Age (years)	42.27 ± 12.56	47.03 ± 12.86
Gender		
Male	6	8
Female	24	22
Duration of kidney disease (years)	3.77 ± 1.36	2.67 ± 1.32
Duration of dialysis (years)	2.27 ± 0.74	1.70 ± 0.65
Time since restless legs syndrome onset (years)	1.70 ± 0.47	1.27 ± 0.45

Ethical considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All patients signed an informed consent form agreeing to be included in the study.

Assessing the impact of uraemic restless legs syndrome

The International Restless Legs Syndrome Study Group Rating Scale standardised clinical diagnostic criteria, introduced in 1995 by the International Restless Legs Syndrome Study Group (Walters et al, 1995), was used to determine the severity of participants' restless legs syndrome (Allen et al, 2003; Walters et al, 2003). This scale consists of 10 questions, each with five possible answers that are scored from 0–4, and the higher the score, the greater the severity of the patient's restless legs syndrome. When assessing restless legs syndrome, the patient should select the answer that most closely relates to their experience and the examiner should be present to clarify any misunderstandings that patients have about the questions.

Physical performance assessment

The patient's physical performance levels were assessed using a number of tests:

- Two sit-to-stand (STS) tests. STS-5, which is a measure of muscle power, is the time taken to complete five sit-to-stand-to-sit cycles, and STS-60, a measure of muscular endurance, which counts the number of sit-to-stand-to-sit cycles a person can perform in 60 seconds
- Two gait speed tests (normal and fast walk). Gait speed was determined by recording the time for each participant to walk the central 26 metres of a 30 metres course at usual, self-selected pace using a stopwatch. Gait speed was calculated as the distance (26 metres) divided by the time it took to complete the 26 metres walk in seconds. The first and last 2 metres were excluded from the calculation to eliminate the effects of acceleration and deceleration. The gait was reported in metres per seconds (m/s).This test was repeated twice for each participant and the average of two was used.

The neuromuscular electrical stimulation protocol

Neuromuscular electrical stimulation was administered using the three-channel BM-1006 Muscle Stimulator (HealthTronics, Austin, TX). Electrodes were placed on the motor points of the rectus femoris, vastus internus and vastus medialis of the quadriceps, on the calf muscles, on an area 2 cm below the knee joint and just over the proximal end of the Achilles tendon. Patients lay in a supine position with extended lower limbs. A soft cushion was placed under the popliteal fossa to flex both knees to 15°. The patient's thighs were bent 120° to the torso, as the muscles are able to produce their maximal force at this angle. A biphasic, low-frequency current (10–50 hertz) was administered through the surface electrodes and the amplitude of the stimulation gradually increased from 40–80 milliampere, or until the patient's pain threshold had been reached.

Patients were asked to make a voluntary contraction as soon as they felt the electrical impulse to achieve maximum contraction of the selected muscle. Maximum intensity was achieved by encouraging the patient to bear with the maximum painless level of stimulation, thus reaching a tolerable and effective muscle contraction (Simó et al, 2015; Maddocks et al, 2016). Low frequencies seem to work better in patients undergoing haemodialysis, since they stimulate the slow type I motor units, which are reduced in this group of individuals. Chronic low-frequency electrical stimulation produces an increase in oxidative capacity with reduced fatigability (Karavidas et al, 2010; Simó et al, 2015). Higher evoked-force levels can be reached when the quadriceps muscle has been stimulated with electrodes positioned longitudinally to the muscle fibres as compared to a transverse positioning (Brooks et al, 1990; Gregory et al, 2005). Each neuromuscular electrical stimulation session lasted for 30–45 minutes. The sessions occurred 3 days a week for 3 months.

Training programme

Participants in the aerobic exercise group were instructed to exercise for 30 minutes each session. The exercises were performed by each patient separately 3 days a week for 3 months in the department of internal medicine. The training programme included a 5-minute warm-up, stretching and strengthening exercises for the lower limbs in the form of range of motion exercises, hip flexion and extension, knee flexion and extension and ankle dorsi and planter flexion, followed by a 5-minute cool-down. Participants were asked to repeat each exercise 8–15 times.

Statistical analysis

Data were described in terms of mean ± standard deviation. The data collected were fed into a computer for statistical analysis. Microsoft Excel (Microsoft Corp, New York) 2010 and Minitab version 13.1 (Minitab LLC, Pennsylvania) were used to perform all statistical calculations. Statistical significance was set at a confidence level of 95% ($P<0.001$). Paired *t*-test used to compare pre- and post-treatment measurements for both groups.

RESULTS

Neuromuscular electrical stimulation was more significant in the STS5 test than aerobic exercise while aerobic exercise was more significant than neuromuscular electrical stimulation in the STS60 test (*Figure 1, Table 2*). Compared to neuromuscular electrical stimulation, aerobic exercise significantly increased muscular endurance, and normal and fast walking speeds while significantly reducing the severity of restless legs syndrome symptoms. Aerobic exercise was significant than the neuromuscular electrical stimulation in both normal and fast speed (*Figure 2*). Neuromuscular electrical stimulation resulted in small improvements in all measures compared to

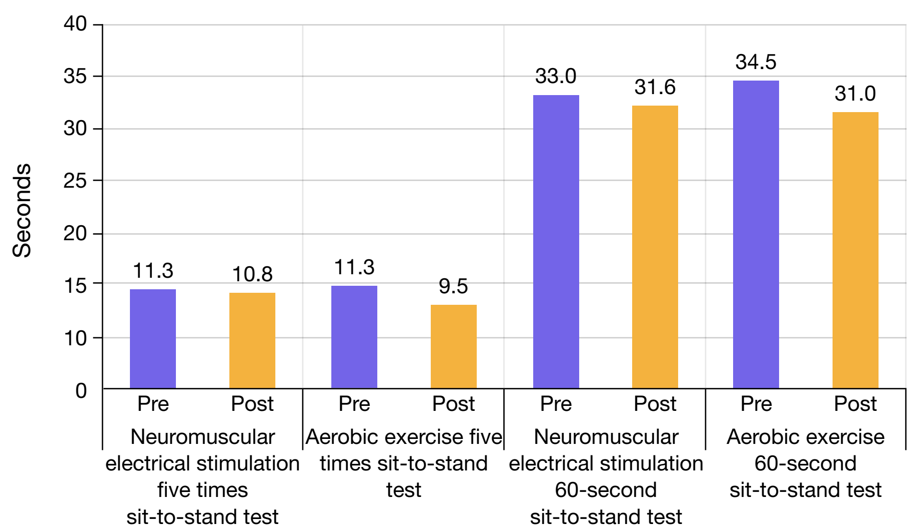

Figure 1. Pre- and post-treatment sit-to-stand measures in the neuromuscular electrical stimulation and aerobic exercise groups.

Table 2. Pre- and post-treatment physical performance in the neuromuscular electrical stimulation and aerobic exercise groups

	Neuromuscular electrical stimulation group				Aerobic exercise group			
Item	Before (mean ± standard deviation)	After (mean ± standard deviation)	*T*-test	*P*-value	Before (mean ± standard deviation)	After (mean ± standard deviation)	*T*-test	*P*-value
STS-5 (seconds)	11.3 ± 1.0	10.8 ± 0.7	1.82	0.089	11.5 ± 1.1	9.5 ± 0.5	6.12	0.000*
STS-60 (seconds)	33.0 ± 1.7	31.6 ± 1.9	2.40	0.031	34.5 ± 1.1	31.0 ± 1.1	7.97	0.000*
Normal speed (seconds)	7.7 ± 1.0	7.9 ± 0.8	–0.48	0.638	8.0 ± 0.8	6.8 ± 0.7	6.00	0.000*
Fast speed (seconds)	5.9 ± 0.7	5.8 ± 0.7	0.49	0.634	6.0 ± 0.8	5.3 ± 0.6	4.04	0.001*

**Significant difference; STS: sit-to-stand*

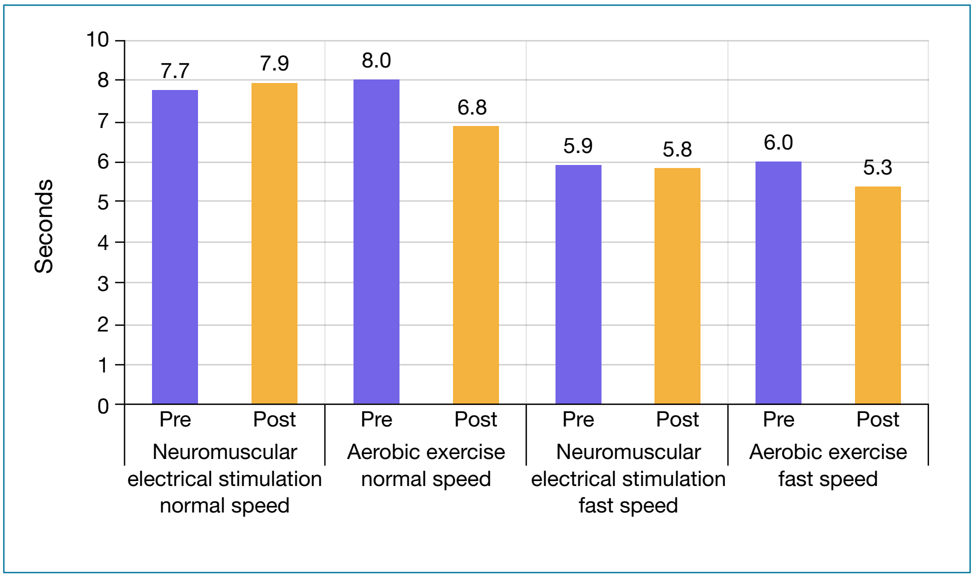

Figure 2. Normal and fast walk speeds pre and post treatment in the neuromuscular electrical stimulation and aerobic exercises groups.

baseline. However, the aerobic exercise group had significant improvements in all measures at the end of the study when compared to baseline. Aerobic exercise is significant than neuromuscular electrical stimulation in International Restless Legs Syndrome score (*Table 3, Figure 3*). There was a greater increase in muscle power, as measured by the STS-5 test, following treatment in the neuromuscular electrical stimulation group (4.6%) when compared to the aerobic exercises group (2.1%) (*Table 4*).

Table 3. Severity of restless legs before and after treatment

	Neuromuscular electrical stimulation group				Aerobic exercise group			
Item	Before (mean ± standard deviation)	After (mean ± standard deviation)	*T*-test	*P*-value	Before (mean ± standard deviation)	After (mean ± standard deviation)	*T*-test	*P*-value
Restless legs syndrome (score)	34.7 ± 1.2	34.0 ± 1.0	1.80	0.094	34.9 ± 2.4	29.4 ± 1.1	8.46	0.000*

**Significant difference*

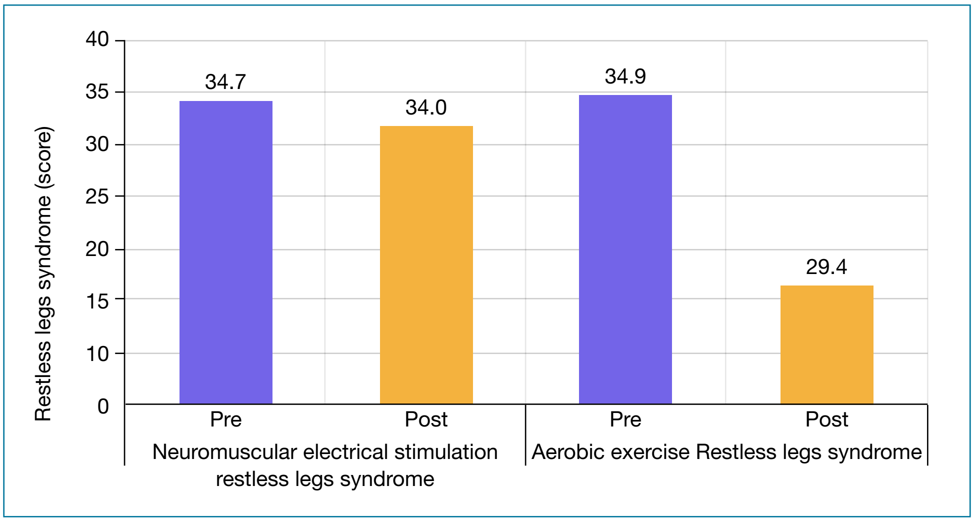

Figure 3. Restless legs syndrome scores before and after neuromuscular electrical stimulation or aerobic exercise.

Table 4. Improvement in test scores at the end of the treatment period (%)

Test	Neuromuscular electrical stimulation group	Aerobic exercise group
STS-5 (seconds)	4.6§	2.1
STS-60 (seconds)	4.6	11.3*§
Normal walking speed (seconds)	2.6	17.6*§
Fast walking speed (seconds)	1.7	13.2*§
International Restless Legs Syndrome score	2.0	18.7*§

**Significant difference from baseline; §significant between-group difference*

DISCUSSION

Recently, neuromuscular electrical stimulation has emerged as a new therapeutic alternative to improve patients' physical condition (Busch et al, 2011; Esteve et al, 2017). This study was conducted to compare the effect of neuromuscular electrical stimulation with aerobic exercise in cases of uraemic restless legs syndrome. It measured the STS-5 and STS-60 tests as well as normal speed and fast walking speeds as measures of physical performance and international restless legs syndrome rating scale scores as a measure of severity of restless legs syndrome.

The neuromuscular electrical stimulation group showed small improvements in all tests at the end of the study when compared to baseline, while aerobic exercise resulted in significant improvements in all parameters except STS-5 during the same period. With the exception of STS-5, however, there was a significantly greater improvement in all measures in the aerobic exercise group than in the neuromuscular electrical stimulation group.

These results suggest that both neuromuscular electrical stimulation and aerobic exercise benefit patients with uraemic restless legs syndrome, with the latter producing better outcomes. For those who are unable or unwilling to undertake physical training, neuromuscular electrical stimulation may therefore provide an alternative method of rehabilitation (Abetz et al, 2004; Allen et al, 2005; Innes et al, 2011; Cirillo et al, 2012; Yeh et al, 2012)

Uremic restless legs syndrome

Uraemic restless legs syndrome is one of the most predominant types of secondary restless legs syndrome and is frequently associated with increased morbidity and enhanced mortality (Giannaki et al, 2013a; Sakkas, 2017). Despite the fact that uraemic restless legs syndrome has been less well studied compared to idiopathic restless legs syndrome, research is now shedding light on many aspects of the syndrome, including its clinical characteristics, impact, epidemiology and treatment options. Several studies have found an association between restless legs syndrome and subjective impairment in physical functioning, even after adjusting for multiple potential confounders (Abetz et al, 2004; Allen et al, 2005; Innes et al, 2011; Cirillo et al, 2012; Yeh et al, 2012). Impaired function has been reported in previous studies, mainly in association with more vigorous activities such as running and climbing stairs, and but has also been demonstrated for some components of activities of daily living (Abetz et al, 2004; Allen et al, 2005; Innes et al, 2011; Cirillo et al, 2012; Yeh et al, 2012).

Muscle loss

Haemodialysis patients are characterised by significant muscle loss (McIntyre et al, 2006; Giannaki et al, 2013b). Simó et al (2015) measured the muscle status of uraemic restless legs syndrome patients, assessing the size and composition of thigh muscles via computed tomography scans. In uraemic restless legs syndrome patients, they observed a 15% reduction in thigh muscle size compared with their restless legs syndrome-free counterparts who did not have alterations in muscle composition. Sleep deprivation caused by restless legs syndrome was hypothesised to contribute to muscle atrophy in uraemic restless legs syndrome patients, as it can induce alterations in anabolic hormone secretion – including growth hormone and insulin-like growth factor 1 – and circulation levels.

Muscle atrophy and loss of total lean body mass are of concern as they are associated with high mortality in the haemodialysis population (Giannaki et al, 2013a). The mechanisms involved in structural muscle change in these patients are increased oxygen supply to the tissues, greater production of vascular endothelial growth factors, increased synthesis of certain proteins related to muscle metabolism (such as insulin-like growth factor 1), the inhibition of myostatin and a decrease in certain proinflammatory cytokines (such as interferon-γ or interleukin 6) caused by repeated and continuous electrical stimulation.

Neuromuscular electrical stimulation and muscle strength

Neuromuscular electrical stimulation activates large muscle mass, increases muscle strength and endurance, stimulates the leg muscle venous pump, facilitates venous return, increases cardiac preload and stroke volume through the Frank–Starling mechanism, and improves cardiac output. Neuromuscular electrical stimulation therefore promotes an increase in cardiovascular stress, which stimulates cardiovascular adaptation and consequently improves physical capacity.

Research using neuromuscular electrical stimulation in patients with chronic obstructive pulmonary disease and patients on haemodialysis has shown the level of improvement in exercise performance to be related to stimulation intensity and subsequent gains in quadriceps strength and reduced ventilatory demand during walking (Vivodtzev et al, 2012; Esteve et al, 2017). The increase in lower limb muscle strength was found to be associated with a significant increase in quadriceps muscle volume as well as in a significant decrease in fat (Vivodtzev et al, 2012; Esteve et al, 2017). The author found no previous papers referencing the use of neuromuscular electrical stimulation in cases of restless legs syndrome. The present study showed a 4.6% improvement in muscle strength and endurance as well as non-significant improvements in restless legs syndrome rating scale score, normal and fast walking speeds in the group receiving neuromuscular electrical stimulation. These improvements can be explained by an increase in lower limb muscle strength.

During neuromuscular electrical stimulation, fast-twitch muscle fibres can be activated at a low level of electrical stimulation. These fibres are usually recruited for high levels of muscle strength and power during voluntary actions. Neuromuscular electrical stimulation increases muscle strength by 30–50%, despite eliciting low contraction intensities (Bourjeily-Habr et al, 2002; Neder et al, 2002; Sillen et al, 2009). Higher evoked forces in the quadriceps muscle can also be achieved (Brooks et al, 1990; Gregory et al, 2005).

Therefore, there is evidence that electrical stimulation improves muscle strength at both high and low frequencies. Indeed, several studies have reported that neuromuscular electrical stimulation training has led to a significant improvement in oxidative capacity and a shift toward a slower muscle phenotype (Louie et al, 2010; Gondin et al, 2011). The findings of the present study are in agreement with previous research, as improvements in muscle strength and endurance were reflected in improvements in normal and fast walking speeds.

Aerobic exercise training

Aerobic and resistance training reverses ‘skeletal myopathy’. More specifically, exercise promotes the shift from a higher percentage of type IIB glycolytic muscle fibres to a higher percentage of types I and IIA oxidative fibres that, together with an increase in the cross-sectional area of both fibre types, leads to a significant improvement in muscle strength and endurance (Karavidas et al, 2010). Aerobic exercise training improved patients’ physical performance in the present study, confirming data from previous studies of haemodialysis patients with and without restless legs syndrome (Sakkas et al, 2003; Giannaki et al, 2013b; Bayoumi, 2015; Kopple et al, 2015). Aerobic exercise interventions have been shown to reduce pain, fatigue and depression and to improve health-related quality of life and physical fitness (Painter, 2005; Jones et al, 2006; Busch et al, 2011; Villareal et al, 2011). The fact that exercise training improved parameters of the SF36 quality of life questionnaire, lean body mass and muscle mass could explain the improved physical performance (Giannaki et al, 2010).

Exercise training has been used successfully in haemodialysis patients as a means of ameliorating restless legs syndrome symptoms and concomitantly improving aspects of quality of life. Improving physical performance in a frail population, such as haemodialysis patients, is clinically significant as inactivity and sedentary lifestyle are associated with poor quality of life, comorbidities and increased mortality (Johansen, 2005).

Sakkas et al (2008) found that exercise training did not have any acute effect on the International Restless Legs Syndrome rating score or augmentation during the first 3 weeks of the training programme. At the end of the study, however, the total score was 42% lower in the exercise group, denoting a reduction in severity, and quality of life had increased by 25% as a result of increases in both physical and mental health parameters. Functional capacity had improved by 28% and exercise capacity twofold. By comparison, there were no changes in the International Restless Legs Syndrome rating scale score, quality of life or functional capacity the control group. The findings of the present study are in agreement with those found by Sakkas et al (2008).

Walters et al (2009) reported reduced endorphin levels in the thalamus of patients with idiopathic restless legs syndrome. Endorphins are opioid neuropeptides that promote a sense of wellbeing and pain relief. It is known that the opioid system in the brain is involved in the pathophysiology of restless legs syndrome.

Pharmacological and non-pharmacological approaches

Evidence to date shows that both pharmacological and non-pharmacological approaches may be effective in terms of reducing uraemic restless legs syndrome symptom severity (Giannaki et al, 2013a). It is known that both dopamine antagonists and exercise training can ameliorate restless legs syndrome symptoms (Giannaki et al, 2013b); however, it has not yet been elucidated whether treatment with dopamine antagonists could improve parameters related to physical performance and muscle size in patients with uraemic restless legs syndrome.

A study that used a combination of aerobic and resistance exercise training with prescribed restless legs syndrome medication showed a 39% improvement in restless legs syndrome score in a non-dialysis population (Aukerman et al 2006). Restless legs syndrome in dialysis patients has been treated with dopamine precursors or dopamine antagonists, resulting in improvements of 33% and 73%, respectively (Pellecchia et al, 2004).

Promising results have been presented in a small study using gamma aminobutyric acid analogues, which resulted in significant improvements in quality of life and reductions in the severity of restless legs syndrome (Sakkas et al, 2008).

Limitations

This study was performed on a small number of patients with uraemic restless legs syndrome. The results cannot therefore be generalised to this population. Future research into the possible benefits of neuromuscular electrical stimulation in patients with uraemic restless legs syndrome should include a larger number of individuals. Further research is needed to compare between exercises, neuromuscular electric stimulation, and dopamine. In addition, research is needed to compare different types of exercises and their effects on restless legs syndrome.

CONCLUSIONS

Muscle strengthening is often used in rehabilitation of the musculoskeletal system. Increased muscle strength is usually obtained through adequately selected and conducted exercises. Both aerobic exercise and neuromuscular electrical stimulation reduced restless legs syndrome severity as well as improved physical performance and quality of life.

The results of this study suggest that neuromuscular electrical stimulation provides an alternative option for muscle strengthening in patients unwilling or unable to participate in physical training.

Further research with a larger group of patients is needed to verify the results of this study.

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