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Original Article

Comparison between dopaminergic agents and physical exercise as treatment for periodic limb movements in patients with spinal cord injury

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Study design: Randomized controlled trial of physical exercise and dopaminergic agonist in persons with spinal cord injury and periodic leg movement (PLM).
Objective: The objective of the present study was to compare the effectiveness of physical exercise and of a dopaminergic agonist in reducing the frequency of PLM.
Setting: Centro de Estudos em Psicobiologia e Exercício. Universidade Federal de São Paulo, Brazil.
Methods: A total of 13 volunteers (mean age: 31.6 ± 8.3 years) received L-DOPA (200 mg) and benserazide (50 mg) 1 h before sleeping time for 30 days and were then submitted to a physical exercise program on a manual bicycle ergometer for 45 days (3 times a week).
Results: Both L-DOPA administration (35.11–19.87 PLM/h, $P<0.03$) and physical exercise (35.11–18.53 PLM/h, $P<0.012$) significantly reduced PLM; however, no significant difference was observed between the two types of treatment.
Conclusions: The two types of treatment were found to be effective in the reduction of PLM; however, physical exercise is indicated as the first treatment approach, while dopaminergic agonists or other drugs should only be recommended for patients who do not respond to this type of treatment.
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Keywords: periodic limb movement (PLM); physical exercise; L-DOPA; aerobic training; spinal cord injury; sleep disorders

Introduction

Restless legs syndrome (RLS) and periodic limb movement (PLM) were originally described in 1945 and 1960.[1,2] PLM is an asleep phenomenon, characterized by periodic episodes of repetitive and highly stereotyped limb movements. These disturbances may result in decreased sleep efficiency and sleep quality.

A growing number of studies on the treatment of RLS and PLM using increasingly sophisticated methodologies and designs have been published. Clinical features, diagnostic standards, epidemiology, and some aspects of the pathophysiology of RLS and PLM have been studied and further clarified.[3,4]

Recently, a high incidence of PLM and RLS has been reported in subjects with spinal cord lesions.[5–8] These subjects spontaneously report sleep problems, and even mention the need to be tied to the bed so as to avoid falling on the floor due to the frequency of lower limb movements during sleep.[7]

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Polysomnography, especially all-night studies, supports the diagnosis of RLS by documenting the sleep disturbances and PLM by recording the K-complex. The K-complex is the characteristic wave stage II sleep and occurs with the leg jerk in PLM, roughly assuming the time course of cyclic, alternating patterns.[9–11] The relationship between RLS and the occurrences of K-complexes and α-activity has been described.[12] There is also an important positive correlation between PLM and K-complexes in spinal cord injured and nonparaplegic subjects.[8] All-night polysomnographic findings have shown that an increasing sleep latency, an increased number of arousals and decreasing sleep efficiency were all associated with the worsening of symptoms.[13,14]

The treatment for these disorders can be divided into several categories: (1) primary treatment to reduce subjective symptoms, (2) specific treatment directed at an underlying cause, (3) efficacy and usefulness of secondary treatment, and (4) ancillary treatments of a nonpharmacological nature that may assist therapy.[15]

Specific treatment includes medication selected from the three primary classes whose effectiveness in RLS/PLM has been well established: dopaminergic agents, opioids, and benzodiazepines. Several studies have reported a favorable treatment outcome of PLM with dopaminergic agonists.[16,17] Dopaminergic agents are useful for the treatment of both RLS and PLM, improving all cardinal features of RLS/PLM including subjective discomfort, dyskinesias while awake, and sleep quality. Dopamine precursors were first used and included either regular carbidopa/L-DOPA or sustained–release compounds. Typical doses were 25/100–100/400 (carbidopa/L-DOPA) taken in divided doses before bedtime or before bedtime and during the night.

Reduction of the incidence of PLM and RLS following acute physical activity in these patients may be helpful for the identification of the mechanisms underlying PLM and RLS.[7] Thus, it is possible that the reduction of limb movements may stem from endorphin secretion induced by the physical activity,[18] since the treatment with opiates often results in a reduction of PLM.[19]

The objective of the present study was to compare the effects of a dopamine agonist and physical exercise on the treatment of PLM in the spinal cord injury subjects.

Methodology

After all experimental procedures were approved by the Ethics Committee Federal University of São Paulo, 13 male volunteers (mean age: 31.6 ± 8.3 years) were selected following contact through associations for the disabled in the State of São Paulo, Brazil. The selected individuals were clinically stable, with no complications, had a spinal cord injury between T7 and T12 and impairment A = complete (following ASIA scales).[20] (Table 1) Total injury to the upper motoneurons as confirmed by radiologic, tomographic, neuroimaging analysis and that they presented index of PLM above 5 PLM/h, diagnosed by means of polysomnography accomplished previously.

Table 1 Identification of the patients containing neurological level, time injury (months), age, weight (kg) and stature (cm)

Patients	*Neurological level*	*Time injury (months)*	*Age (years)*	*Weight (kg)*	*Stature (cm)*
1	T9	49	27	44,00	168
2	T9	109	27	53,70	168
3	T11	132	22	68,00	162
4	T11	192	33	72,70	180
5	T12	161	28	67,40	170
6	T12	165	48	62,20	165
7	T11	231	41	42,80	175
8	T9	90	33	63,00	180
9	T10	152	35	72,40	169
10	T11	55	22	53,00	172
11	T10	94	35	65,60	167
12	T11	39	35	61,80	173
13	T7	10	24	57,00	165

A cross-sectional study was conducted in which all volunteers were submitted to the administration of L-DOPA and physical training. L-DOPA (200 mg) in combination with benserazide chloride (50 mg), or placebo was administered for 30 days, 1 h prior to sleeping time. This period of drug administration was followed by a 15-day washout period.

Training was prescribed after all the spinal cord injured individuals underwent a cardiopulmonary exercise test on a computerized metabolic gas exchange system (Vista Turbo Fit, Vacumed, Ventura, CA, USA) using a calibrated electromagnetically braked arm-crank ergometer (CYBEX MET-300, Cybex, USA). The protocol of the maximum effort test consisted of a 2-min warm-up with a load of 25 W in 5-W/min load increments until exhaustion, with 3 min of active recovery at a load of 25 W. Mean rotation speed was 70–80 rpm. The data were calculated automatically using the standard formulae and displayed in a descriptive numerical and graphic form (average of 20 s). The following data were obtained: oxygen uptake (ml/min STPD), carbon dioxide production (VCO_2, ml/min STPD), respiratory exchange ratio, minute ventilation (VE, l/min BTPS), respiratory frequency (breaths per min); ventilatory equivalent for O_2 and CO_2 (VE/VO_2 and VE/VCO_2); expired fraction of O_2 and CO_2 (FEO_2 and $FECO_2$, mmHg); heart rate (HR, bpm), and oxygen pulse (VO_2/HR, ml/bpm). VO_2 at the anaerobic threshold (VO_2AT) was estimated by the ventilatory method, when VE/VO_2 and FEO_2 increased while VE/VCO_2 and $FECO_2$ remained stable. In the present study, VO_2AT was identified in all the patients studied.

The anaerobic ventilatory threshold is a convenient mark used to delimit the upper intensity of aerobic exercise in training programs, corresponding to the work intensity at which the respiratory response to gradual exercise first deviates from linearity - LV1.

The training sessions were held on 45 consecutive days, three times a week, with a mean duration of 30 min, according to the results obtained during the maximum effort test. Total training time depended on the parameters evaluated (heart rate and W). During the sessions, heart rate was monitored and kept at the values established for LV1. Blood pressure measurements were made before and after each training session.

Polysomnography (PSG-Oxford/Medilog eight channels) was performed at the Sleep Institute of the Federal University of São Paulo (UNIFESP/EPM) and the variables observed were three electroencephalogram channels, two electro-oculogram channels, and three electromyogram channels, one of them submandibular and two on the legs (electromyographic recordings of the lower legs were obtained from the tibial muscle and femoris of the thigh). Polysomnographic data were obtained before and after intervention (physical exercise and L-DOPA). Data on leg movements (PLM) were analyzed by the Wilcoxon matched paired test, with the level of significance set at $P < 0.05$.

Table 2 Polysomnographic data (PSG) obtained before (baseline) and 30 days after the treatment of PLMs with a L-DOPA and 45 days after the treatment by physical exercise

Group	*Baseline PSG*	*PSG after treatment*	*NS*
L-DOPA (30 days)	35.11 (41.98)	19.87 (25.46)	<0.03
Physical exercise (45 days)	35.11 (41.98)	18.53 (29.50)	<0.02

Results

Physical exercise led to a significant reduction in the frequency of PLM, as seen when comparing basal polysomnographic data with those obtained after 45 days of training ($P<0.02$). A significant reduction in the frequency of PLM was also observed with the administration of L-DOPA ($P<0.03$) (Table 2).

Discussion

The two types of treatment were effective in reducing PLM. The reduction of PLM in paraplegic subjects upon physical exercise might be due to the release of β-endorphin and dopamine during exercise. Thus, physical exercise should be prescribed as a treatment approach to PLM and RLS, also in view of its beneficial effects on the quality of life and sleep.[21–23]

The initial hypothesis involving physical exercise is that the reduction of PLM might be influenced by an increase in the release of β-endorphin and dopamine during and after physical exercise, leading to an increase in the activity of the opiate and dopaminergic system,[24] thus decreasing PLM scores.

Bulbulian and Darados[25] reported an action of ß-endorphins on muscle relaxation in the brain and spinal cord, with correlations between exercise intensity and volume and β-endorphin release/action being demonstrable. Ferreira *et al*[26–28] observed pain mediation by opiate receptors at the peripheral level. Since opiate agonists have been shown to be effective in the treatment of PLM, ß-endorphin release during and after physical exercise might have been mediated by opiate receptors at both the central[24] and peripheral level[26–28] in the volunteers studied here.

With respect to dopaminergic agonists, one hypothesis accounting for this imbalance may involve the maintenance of a monosynaptic pathway capable of regulating the transmission of dopaminergic stimuli. Dopamine, by stimulating dopaminergic D2 receptors, might inhibit central cholinergic transmission yielding a neurochemical balance (excitatory/inhibitory), which would prevent the occurrence of such abnormal movements. In our group of paraplegic subjects with complete spinal cord injury, this monosynaptic pathway might have been compromised, leading to the occurrence of such abnormal movements (PLM). Exogenous L-DOPA, seemingly, would reinstate this balance, reducing abnormal movements of the lower limbs.[29]

The results demonstrate that the two types of intervention were efficient in reducing PLM in paraplegic individuals. A significant reduction in the frequency of PLM was observed for the two treatments when compared to basal levels, but there was no significant difference between treatments. Dopaminergic agonists are only recommended for patients who do not respond to physical exercise.

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