Impact of neuromuscular electrical stimulation on functional capacity of patients with chronic kidney disease on hemodialysis

Impacto da estimulação elétrica neuromuscular na capacidade funcional de pacientes com doença renal crônica submetidos à hemodiálise

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Abstract

Introduction: Literature shows that patients undergoing hemodialysis present poor physical conditioning and low tolerance to exercise. They may also suffer from respiratory dysfunctions. The purpose of this study was to evaluate the effects of neuromuscular electrical stimulation on pulmonary function and functional capacity of patients with chronic kidney disease on hemodialysis. **Methods:** Forty adult patients with chronic kidney disease on hemodialysis were prospectively studied and randomized into two groups (control n = 20 and treatment n = 20). The treatment group underwent bilateral femoral quadriceps muscles electrical stimulation for 30 minutes during hemodialysis, three times per week, for two months. The patients were evaluated by pulmonary function test, maximum respiratory pressures, maximum one-repetition test, and six-minute walk test (6MWT), before and after the treatment protocol. **Results:** The treatment group presented increased maximum inspiratory (MIP) ($p = 0.02$) and expiratory pressures (MEP) ($p < 0.0001$), muscular strength in maximum one-repetition test ($p < 0.001$), and distance covered in the 6MWT ($p = 0.03$), and decreased systolic blood pressure ($p < 0.001$) and respiratory frequency ($p < 0.001$) when compared with the control group. **Conclusion:** Electrical neuromuscular stimulation had a positive impact on pulmonary function and functional capacity, leading to better physical performance in patients on hemodialysis.

Keywords: exercise therapy; kidney failure, chronic; physical therapy modalities; renal dialysis.

Resumo

Introdução: Pacientes submetidos à hemodiálise apresentam baixo condicionamento físico além de serem acometidos por disfunções respiratórias. Objetivamos avaliar os efeitos da estimulação elétrica neuromuscular na função pulmonar e capacidade funcional de pacientes com doença renal crônica em hemodiálise. **Método:** 40 adultos com doença renal crônica em hemodiálise foram estudados prospectivamente e randomizados em dois grupos (controle n = 20 e tratamento n = 20). O grupo tratamento realizou protocolo com estimulação elétrica neuromuscular em quadríceps femoral por 30 minutos durante a hemodiálise, três vezes por semana, durante dois meses. Todos pacientes realizaram espirometria, pressões respiratórias máximas, teste de uma repetição máxima e teste da caminhada dos seis minutos (TC6), antes e após o período de acompanhamento. **Resultados:** O grupo tratamento apresentou aumento da pressão inspiratória máxima com $p = 0,02$ na comparação entre grupos e $p < 0,001$ para a pressão máxima expiratória. O teste de uma repetição máxima e a distância percorrida no TC6 apresentaram-se maiores após o protocolo no grupo de tratamento com $p < 0,001$ e 0,03 respectivamente. Houve diminuição da pressão arterial sistólica ($p < 0,001$) e frequência respiratória ($p < 0,001$) após a estimulação elétrica quando comparado ao grupo controle. **Conclusão:** A estimulação elétrica neuromuscular teve impacto positivo sobre a função pulmonar e a capacidade funcional levando ao melhor desempenho físico em pacientes em hemodiálise.

Palavras-chave: diálise renal; doença renal crônica; modalidades de fisioterapia; terapia por exercício.

Introduction

Patients with chronic kidney disease (CKD) undergoing dialysis suffer from various symptoms and signs that characterize the uremic syndrome, which affects virtually all organ systems, including the pulmonary, cardiovascular and musculoskeletal.[1] It is reported that patients on hemodialysis (HD) have deconditioning and low tolerance for physical activities. This, although not fully understood, seems to be related to muscular atrophy, myopathies and malnutrition.[2,3]

The neuromuscular electrical stimulation (NMES) is used on patients suffering from chronic obstructive pulmonary disease and heart failure. The results are promising, showing improvement in functional capacity of this patients.[4-6] As patients suffering from CKD and on hemodialysis present similar symptoms of other chronic diseases that directly affect the functional capacity, the use of NMES could be beneficial to them. Therefore, the objective of this study was to evaluate the effects of NMES on the pulmonary function and functional capacity of patients with chronic kidney disease on hemodialysis.

Materials and methods

This is an original, randomized clinical study on patients with CKD undergoing hemodialysis, conducted at the dialysis unit of the public and university hospital. The study protocol was approved by the Ethics Committee in Research of the Institution (protocol number 146/09) and patients signed informed consent forms to participate.

The sample size (theorem of Cochran) in this study was determined as 40 individuals for simple random sampling, using a confidence interval of 95% and 5% error for infinite sample and all the patients they were recruited in the Dialysis Service.

Inclusion criteria: patients aged 18 or older, hemodynamically stable and on hemodialysis for more than six months. Exclusion criteria: patients who required any emergency or elective surgery during the study; those who presented acute heart or lung disease, skin rashes, metallic implants, tumors, infections, *diabetes mellitus* or hypoesthesia in the region that the neuromuscular electrical stimulation would be applied; those who practiced physical activities three times a week or more; and those who presented physical or cognitive changes that would not enable the completion and collecting of results in the proposed tests.

At admission and agreement to participate, patients were randomized into two groups by means of opaque, sealed envelopes: group control and treatment. The patients of both groups were evaluated before and after two months.

The evaluation and reevaluation were done before the hemodialysis session, and we took care of never evaluating the same patient twice in 48 hours, i.e., between the sessions period, and consisted of the following tests: pulmonary function test forced vital capacity (FVC), volume expired in 1 second (FEV_1), FEV_1/FVC, forced expiratory $flow_{25/75\%}$ ($FEF_{25/75\%}$), peak expiratory flow (PEF), maximum respiratory pressures [maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP)], peak flow, one-repetition-maximum test (1RM) and six-minute walking distance (6MWT).[7-12]

Pulmonary function test was carried with the spirometer *Koko (PDS Instrumentation)*, in sitting position, using nose clip. The calculation of the predicted values was given by age, gender and height according to equation Pereira *et al*.[7]

Maximum respiratory pressures (MIP and MEP) and peak flow were performed as recommended by the respiratory muscle testing statement.[8] We taken three measurements for every variable tested and the larger measure was analyzed.

1RM test was performed in sitting position with no support. First, the movement without load was trained, starting with knee's 90 degree flexion followed by full extension. Then, using an ankle bracelet weighting half kilogram, were prompted the same trained action. While there is no compensatory movement during the trained action, we add another half kilogram to the ankle bracelet for each completed action. The test is stopped when any adjustment was observed and the measure taken was the ankle bracelet weigh for last completed action before compensation.[10]

The 6MWT consists of a 6 minute free walk, as fast as possible, across a flat surface with 30 m length scaled at each meter. Once reached the 6 minute, the total distance walked is recorded.[11] Additionally to the walked length, the Borg scale measure is taken.

The laboratory parameters was taken from peripheral blood samples on the evaluation and reassessment days, including analysis of serum albumin, creatinine, hemoglobin and urea. The evaluation and reassessment rate of removal of urea (clearance) (Kt/V) were calculated from medical records.

Patients randomized for treatment group made protocol were submitted to the NMES (Neurodyn II, Ibramed, Amparo, Brazil), on the quadriceps muscle bilaterally during hemodialysis for 24 sessions (eight weeks). The protocol was performed three times a week for 30 minutes. The parameters used were based on the systematic review by Sillen *et al*.:[6] pulse width within 350 microseconds, frequency of 50 Hz for two seconds if bearable, and resting for ten seconds. The intensity of the electrical current was determined by the tolerance of each patient.

The Statistical Package for the Social Sciences (version 13.0) statistical software was used for the data analysis. Differences between groups were assessed with unpaired Student's *t* test or Mann-Whitney test, when appropriate. The paired Student's *t* test was used to compare within-patients variations. We compared proportions of qualitative variables using the chi-square test. A *p*-value lower than 5% ($p < 0.05$) was considered statistically significant.

Results

For this study we had recruited 87 patients and from this total 45 were excluded: 31 by the exclusion criteria, two who denied signing the informed consent form and 12 for other reasons. From the remaining 42 patients, who were randomized to one of the two groups, we had two losses as follow, one in each group: in the control, the patient did not complete all evaluation exams; and in the treatment, the patient had to undergo abdominal surgery for hernia correction. Therefore, the study was completed with 20 patients who did not have NMES (control group) and other 20 patients who were submitted to the NMES protocol (treatment group).

The baseline characteristics of the patients (n = 40) were not significantly different between groups in relation to age, height and duration of hemodialysis (Table 1).

Control group presented 52.9% for males individuals and treatment 47.1%. The comparison between groups did not present evidence of statistical difference ($p > 0.50$).

The etiology of CKD in group control was chronic glomerulonephritis in 11 patients, hypertensive nephrosclerosis in seven, and cystic kidney disease in the other two. In group treatment there was chronic glomerulonephritis in 12 patients, hypertensive nephrosclerosis in seven and an unknown etiology in one patient.

In relation to laboratory tests, serum albumin and urea and Kt/V showed no statistically significant difference between groups either at the time of the initial evaluation or the revaluation. At the time of revaluation, serum creatinine showed higher average levels for group treatment than control. The hemoglobin values, on the other hand, were statistically different in both evaluations, demonstrating that control had higher levels than treatment (Table 2).

There was no statistically significant difference in the comparison of pulmonary function test (PFP) between groups. The evaluation mean value of FEV_1 in control group was 1.95(SD0.52) and decreased to a mean 1.82(SD0,47) in reevaluation, and so the comparison between them showed the same significance for FEV_1 ($p = 0.00$), with the highest averages for treatment.

The outcome of the groups in the measurement of maximal respiratory pressures and peak expiratory flow showed a significant difference for MIP ($p = 0.02$) and MEP ($p < 0.001$), with higher average levels for both in treatment group in relation to control. As for the 1RM test, comparing the outcome between groups showed a significant difference, with higher average levels for treatment group (Table 3).

In the analysis of the outcome of the groups for the 6MWT, there was a decrease in SBP ($p < 0.001$) and f ($p < 0.001$), and increased distance ($p = 0.03$) for treatment group (Table 4).

Discussion

The hemodialysis treatment aims to increase the patient survival rate, but should also aim for rehabilitation[13] seeking to restore normal daily activities. Our study demonstrates the positive impact of an NMES protocol performed during HD, and shows that NMES may benefit patients suffering from CKD.

There was no baseline difference between groups as for the duration of hemodialysis and both were on hemodialysis for an average of over three years. Herrero *et al.*[2] reported that patients undergoing HD for a long period presented change in lung function. In the pulmonary function test, treatment group underwent neuromuscular electrical stimulation protocol had better

Table 1 Comparison of the initial profile between 20 patients in group I (control) and 20 patients in group II (treatment)

Variables	Groups	Mean (SD)	Minimum	Maximum	*p*
Age (years)	I	54.65 (19.93)	19.00	83.00	0.15
	II	46.40 (15.43)	26.00	69.00	
Height (m)	I	1.62 (0.70)	1.53	1.75	0.55
	II	1.61 (0.11)	1.49	1.88	
Time on HD (months)	I	46.15 (41.40)	9.00	132.00	0.11
	II	68.80 (46.90)	9.00	180.00	

HD: hemodialysis, *p*: statistically significant. Source: Center for Dialysis.

Table 2 Comparison between groups I (control) and group II (treatment) of laboratory results and weight at the time of evaluation and revaluation

Variables	Groups	Evaluation		Revaluation	
		Mean (SD)	*p*	Mean (SD)	*p*
Kt/V	I	1.38 (0.21)	0.56	1.48 (0.16)	0.15
	II	1.40 (0.17)		1.40 (0.15)	
Creatinine (mg/L)	I	9.95 (1.79)	0.08	9.95 (1.97)	0.01*
	II	11.28 (2.88)		12.24 (3.35)	
Albumin (g/dL)	I	3.58 (0.40)	0.65	3.67 (0.41)	0.36
	II	3.53 (0.37)		3.78 (0.30)	
Hg (g/dL)	I	11.86 (1.59)	0.01*	11.60 (1.47)	0.01*
	II	10.53 (1.62)		10.49 (1.17)	
Urea (mg/dL)	I	137.80(27.28)	0.16	132.78(29.56)	0.18
	II	151.18(31.57)		146.66(35.80)	
Weight (kg)	I	60.83 (10.48)	0.76	61.88 (9.58)	0.22
	II	59.75 (12.33)		60.40 (12.24)	

Kt/V: Rate of removal of urea (clearance); Hg: Hemoglobin; * Statistically significant. Source: Center for Dialysis.

Table 3 Comparison of maximum pressures, MEP, peak flow and one maximal repetition test (1RM) between the moments of assessment and reassessment in group I (control) and group II (treatment)

Variables	Phases	Group I (control)		Group II (treatment)	
		Mean (SD)	*p*	Mean (SD)	*p*
MIP (cmH_2O)	Evaluation	57.00 (19.84)	0.41	49.80 (12.94)	0.01*
	Revaluation	53.80 (21.26)		58.90 (18.39)	
MEP (cmH_2O)	Evaluation	64.20 (17.24)	0.11	68.80 (17.87)	< 0.001*
	Revaluation	69.80 (23.52)		83.00 (12.57)	
Peak flow (L/min)	Evaluation	304.00 (84.25)	0.15	299.00 (69.50)	0.72
	Revaluation	293.00 (70.79)		296.00 (82.10)	
1RM (kg)	Evaluation	2.00 (0.74)	< 0.001*	1.65 (0.84)	< 0.001*
	Revaluation	1.70 (0.76)		3.03 (1.25)	

MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; * Statistically significant. Source: Center for Dialysis.

performance compared to control group for FEV_1, and we believe that the improvement in respiratory muscle strength indirectly caused by NMES had a positive impact on FEV_1, despite the greater weight gain and lower hemoglobin values of treatment group.

The positive response for FEV_1 is important, since the literature indicates that patients with CKD on hemodialysis have lower values of this parameter, resulting from the retention of uremic toxins, fluid overload and pulmonary fibrosis.[2,14,15]

Table 4 Differences in the six-minute walk test (6MWT) between the phases (evaluation and revaluation) of group I (control) and group II (treatment)

Variables	Phases	Group I (control)		Group II (treatment)	
		Mean (SD)	*p*	Mean (SD)	*p*
SBP (mmHg)	Evaluation	5.50 (8.25)	0.02*	8.20 (10.33)	0.15
	Revaluation	12.00 (9.51)		4.30 (7.52)	
DBP (mmHg)	Evaluation	3.00 (7.32)	0.17	1.80 (8.55)	0.19
	Revaluation	5.50 (7.59)		4.10 (7.77)	
HR (bpm)	Evaluation	27.40 (9.66)	0.05	14.20 (12.89)	0.73
	Revaluation	34.30 (8.48)		15.30 (10.81)	
f (ipm)	Evaluation	7.40 (3.69)	0.05	6.90 (4.38)	0.05
	Revaluation	9.30 (4.21)		3.85 (5.47)	
SpO_2 (%)	Evaluation	-0.70 (0.97)	0.09	-0.50 (1.10)	0.02*
	Revaluation	-0.35 (0.93)		0.70 (1.68)	
Borg	Evaluation	3.50 (2.89)	0.06	3.75 (2.63)	0.46
	Revaluation	4.90 (2.40)		4.35 (2.81)	
Distance (m)	Evaluation	330.00 (68.77)	0.71	350.40 (97.53)	0.02*
	Revaluation	327.20 (53.93)		373.20 (112.94)	

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; f: Respiratory rate; SpO_2: Oxygen saturation; Borg: Scale of effort perception; * Statistically significant. Source: Center for Dialysis.

The improvement in MIP and MEP is probably due to a gain in muscle strength after the NMES protocol. The literature suggests that patients with CKD regularly undergoing HD have decreased pulmonary muscle strength.[16] The main cause for this respiratory muscle strength loss is unknown, but some authors consider that the pathogenesis of this condition is similar to that in peripheral muscles, the causal mechanism of which is uremic myopathy.[17]

The reason underlying the indirect improvement caused by NMES is not clear, and currently there are no studies showing which mechanisms lead the patient to achieve an increase in respiratory muscles after training with neuromuscular electrical stimulation.

The distance walked in the 6MWT is used as an indicator of functional capacity[11] verifying the physical performance of the patients[3]. It was observed that the NMES positively impacted the distance walked, as the treatment group increased its mean, while the control decreased the distance covered. The control group response could be due to the lack of fitness of these patients, probably caused by cardiovascular, respiratory and muscle diseases that can influence the ability to capture, transport and use oxygen.[18]

As for the treatment group, we can infer that the increase in muscle strength achieved in the quadriceps femoral with NMES allowed for a better response to the 6MWT, demonstrated by the increase in the distance walked.

Headley *et al.*[19] demonstrated the improvement of physical performance of HD patients in the 6MWT after a resistance training program for 12 weeks. In our study, the patients achieved positive results in eight weeks. Studies by Parsons *et al.*[1], Simó *et al.*[5] or Xavier *et al.*[20] corroborate our results in relation to distance walked, as they also reported an increase in this variable after a physical exercise protocol in patients with CKD undergoing HD.

The eight weeks of interval training proposed in our protocol is considered minimum time of a rehabilitation program. The hypothesis of different response to longer training was not the objective of this study, as well if the acute effects found in this paper remains into our population after a period of time.

In this study, the 1RM test showed significant results: while the control group had worsening in muscle strength, the group treated with NMES had a significant improvement. The behavior of the control group can be explained by the fact that it is common for patients with CKD on hemodialysis to show a loss in muscle strength, as a result of a compromised muscular system, possibly resulting from uremic myopath.[1,18]

In their study, Adams and Vaziri[21] describe that muscular atrophy present in patients undergoing HD is due to change in the degradation of protein synthesis, causing muscle atrophy. The response of the treatment group could be due to the effect of electrical stimulation on capillarization, which provides an increase in capillary density and perfusion and oxygen supply. These factors contribute to increased aerobic oxidative capacity and resistance to muscle fatigue.[6]

According to Sillen *et al.*[6] and Miyamoto *et al.*,[22] electrical stimulation activates all muscles fibers, and the type II fibers are the first recruited, improving muscle torque and fatigue resistance earlier. We believe that this mechanism occurred in the treatment group of the present study, including the increase in body weight: we attributed that weight gain in treatment group to a lean mass increase.

Another aspect that shows us indirect improvements in muscle strength was the increase in serum creatinine in treatment group after NMES protocol. Serum creatinine is a nutritional parameter in hemodialysis patients,[23,24] and we believe that the increased muscle mass with NMES was shown indirectly by increased creatinine, suggesting the hypothesis of improvement of physical performance by increasing the muscle fibers to neuromuscular electrical stimulation.

The major limitation of the present study concerns absence of direct measure of the muscle mass and protein ingestion. These observations could be related to changes that we observed for creatinine, opening the possibility for a new study that will investigate this hypothesis.

Several researches have been developed to clarify the role NMES in patients with pulmonary disease or peripheral,[4-6,12,25] Vovidtzev *et al.*[25] studied 22 patients with severe COPD who underwent a protocol of NMES and the authors have observed an association between catabolic equilibrium after performing the NMES and improved functional capacity, with increased levels of phosphorylated p70S6K and reduction of atrogin-1, and associated improvement in distance walking and strength of quadriceps.

In a recent study, Sillen *et al.*[26] analyzed, in COPD, the efficiency of a protocol with high (75 Hz) *versus* low (15 Hz) frequency NMES, stating that the two of may benefit patients with respiratory dysfunction. Our study used a frequency of 50 Hz, finding greater strength and distance walked in the group that was treated.

Treatment with NMES is alternative for patients with large functional impairment because it is resembles active exercise. We did not observe any adverses events during or after the sessions. We credit this fact to the choice of a low frequency during NMES. This uses a portable stimulator and skin electrodes to produce only controlled contraction of the muscle.[26]

The present study controlled to evaluate the effects of the method of NMES in patients with CKD on hemodialysis. We conclude that the NMES protocol optimizes the physical condition of these patients, with positive impact on pulmonary function and functional capacity, resulting in improved physical performance in patients with CKD on hemodialysis.

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