ORIGINAL PAPER

Physiotherapy Quarterly (ISSN 2544-4395)
2022, 30(3), 1–6

Neuromuscular electrical stimulation and exercises effect on functional exercise performance and quality of life in cases of liver cirrhosis

DOI: https://doi.org/10.5114/pq.2022.116445

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Abstract

Introduction. Patients with cirrhosis experience severe physical deconditioning, sarcopenia, physical frailty, fatigue, and malnutrition. Exercise capacity is limited owing to inactivity, bed rest, obesity, or cachexia. Limb muscle dysfunction has important consequences for patients with liver cirrhosis because it contributes to exercise limitation and reduces daily activities and social life, leading to a quality of life (QOL) impairment, greater utilization of social and health resources, and a worse prognosis. The study purpose was to compare the effect of neuromuscular electrical stimulation (NMES) and exercises on treatment of patients with liver cirrhosis.

Methods. A total of 60 patients (41 males and 19 females) with liver cirrhosis, aged 35–59 years, were randomly assigned to 2 groups: an NMES group (n = 30) and exercises group (n = 30). The intervention was implemented 3 times per week for 3 months. Exercise performance and QOL were measured before and after the intervention.

Results. Before treatment, there was no significant difference in exercise performance or QOL between the 2 groups; however, after 3 months of intervention, a significant difference in exercise performance was observed between the 2 groups (p = 0.001). Both groups improved their QOL (p = 0.001), but the NMES group improved more than the exercise group.

Conclusions. NMES is an important technique to increase exercise performance and QOL in patients with liver cirrhosis.

Key words: liver cirrhosis, exercise, neuromuscular electrical stimulation, exercise capacity, quality of life

Introduction

End-stage liver disease or cirrhosis studies consistently revealed low muscle mass [1], fatigue and weakness due to malnutrition [2], extreme bodily deconditioning, sarcopenia [3], and physical frailty [4], which can cause exercise limitation [5], resulting in impaired quality of life (QOL) [6].

Patients often undertake sedentary lifestyles because of restricting signs that can cause lower limb weakness, which precipitates a downward spiral of incapacity. Different etiological elements for skeletal muscle disorder encompass low-grade systemic infection, nutritional insufficiency, and/or an imbalance among anabolic and catabolic hormones [7]. Muscle weakness impacts adversely on degrees of bodily function, independence, and QOL [8].

It should also be indicated that limb muscle dysfunction is often related to decreased body weight and greater loss of function, specifically with discounted lean mass (i.e., muscle tissue). Limb muscle disorders also have serious consequences for the patient, as they contribute to exercise difficulty, as well as reduce daily activities and social existence, leading to QOL impairment, increased use of social and health resources, and worse prognosis [9]. Also, hepatic encephalopathy can result from impaired ammonium clearance by the muscle due to muscle atrophy [10]. Fatigue was linked to depression, autonomic dysfunction, and sleep disturbance in end-stage liver disease patients [11].

According to García-Pagàn et al. [12], cirrhosis can be accompanied by cardiac and pulmonary adjustments, including hepatopulmonary syndrome and portopulmonary hypertension, with different complications, such as ascites or oedema, which can affect pulmonary function and workout capability. Furthermore, the underlying liver ailment may have an association with adjustments in fitness, although this has yet to be thoroughly investigated. The design of these studies should receive some additional attention from those interpreting the currently available research on physical activity in patients with liver disease.

Mild exercise (30% of maximum capacity) has been shown to increase portal pressure in individuals with portal hypertension, potentially raising the risk of variceal bleeding afterward. Advanced liver disease complications, such as hepatic encephalopathy, ascites, and portal hypertension, have been linked to an increased risk of adverse outcomes (e.g., variceal haemorrhaging) during exercise [13]. Neuromuscular electrical stimulation (NMES) can be an option for those who are unable to engage in whole-body exercise to improve lower limb muscle strength. The use of NMES seems to be satisfactory for patients and has resulted in improvements in muscle function, exercise capability, and QOL.

To the author's knowledge, there is no previous study on the use of NMES in patients with liver cirrhosis and no research to compare the effects of exercise and NMES in cases of liver cirrhosis.

Subjects and methods

Study design and randomization

A 2-arm cluster randomized controlled trial was performed. Patients were given an identification number when they were admitted. Odd numbers were assigned to group 1, even numbers to group 2. The participants' consent was obtained before starting the treatment, after full explanation of the study details.

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Received: 06.04.2021
Accepted: 12.07.2021

Citation: Youssef MK. Neuromuscular electrical stimulation and exercises effect on functional exercise performance and quality of life in cases of liver cirrhosis. Physiother Quart. 2022;30(3):1–6; doi: https://doi.org/10.5114/pq.2022.116445.

Participants

A total of 70 patients meeting the inclusion criteria were selected to this study from the Department of Internal Medicine, Cairo University Hospitals, Giza, Egypt. Out of these, 5 refused to take part, 2 refused to sign the informed consent, and 3 dropped out of the treatment program; their data were removed from the analysis (Figure 1). Overall, 60 participants (41 males and 19 females) with liver cirrhosis, aged 35–59 years, were randomly assigned to 2 groups: the NMES group (n = 30) and the exercise group (n = 30).

The inclusion criteria were as follows: (1) positive for anti-hepatitis C virus; (2) no antiviral treatment at entry; (3) positive for continual hepatitis or compensated cirrhosis; (4) negative for hepatitis B surface (HBs) antigen; (5) not pregnant; (6) systolic blood pressure of much less than 180 mm Hg or diastolic blood pressure of much less than 110 mm Hg; (7) no ischaemic coronary heart disease or excessive arrhythmia [14].

The exclusion criteria involved: (1) great cardiac disorder (ejection fraction < 60% or records of a coronary artery disorder); (2) persistent renal failure on dialysis; (3) haemoglobin concentration < 11.0 g/l; (4) human immunodeficiency virus contamination; (5) hepatocellular carcinoma; (6) active non-hepatocellular carcinoma associated malignancy; (7) myopathy; (8) any physical impairment or orthopaedic abnormality preventing exercise, or history of liver transplantation [15].

Interventions

Group 1: NMES treatment

Four electrodes were located at the quadriceps femoris muscle mass on each lower limb: 1 electrode positioned at the rectus femoris muscle, 1 electrode at the vastus lateralis muscle, and 2 electrodes used to stimulate the vastus medialis. Two electrodes were located at the calf muscle. A session of NMES with the use of Healthtronics 3-channel model BM 1006 (Taiwan) lasted for 20 minutes, with a symmetrical biphasic rectangular pulse at 75 Hz and a pulse time of 410 seconds. The intensity of electrical current increased gradually until the maximal level tolerated by the patient. The stimulation was performed 3 times per week.

Group 2: exercises

Chair-seated exercises were used within the early stages of the program owing to the fact that the patients were frail adults. Even with the participants seated in a chair, I was able to perform toe and heel raises, knee lifts, and knee extensions. Hip flexions and lateral leg raises were executed while standing upright at the back of the chair and protecting the back of the chair for balance. To reinforce lower extremities, a fixed weight was positioned at the ankle even as the individuals performed strengthening exercises. Weights of 0.50–1.50 kg were used, depending on each participant's strength stage because the resistance regularly elevated. The exercises done using the ankle weights included seated knee flexion and extension and standing knee flexion and extension [16]. These exercises were chosen because the strength of the muscles has an effect on stability, mobility, function, and QOL [17, 18]. Exercises were done 3 times per week for 30 minutes in each session. Each exercise was performed in 3 sets and each set consisted of 10 repetitions.

All participants were instructed about well-balanced diets,

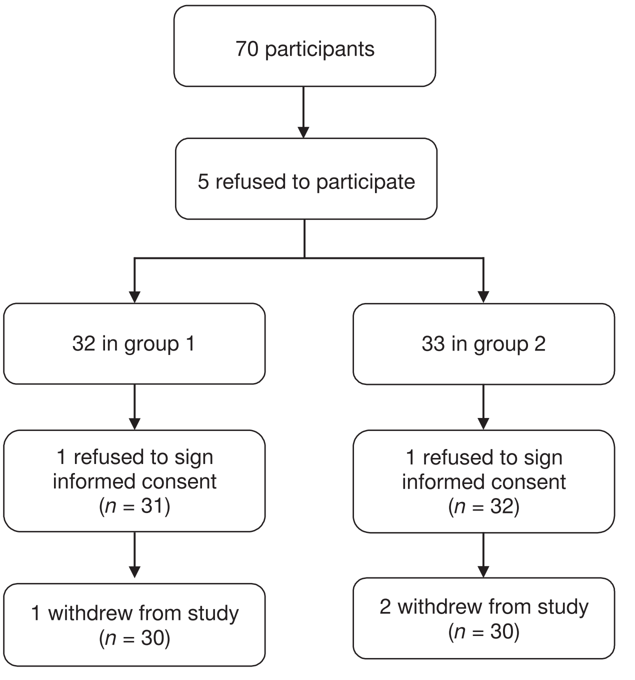

Figure 1. CONSORT flowchart of the study

which include low sodium, high carbohydrates, and high proteins to prevent or slow complications. The patients were recommended to consume enough minerals and vitamins and low fat. The original Borg scale was used to assess the intensity of exercise. An appropriate exercise intensity for persons with chronic diseases is 12–16 on the Borg scale.

Measurements

All participants were evaluated before and after the 3-month treatment with the following tools:

1. Sit-to-stand test (SST). The examined individual was requested to complete as many repetitions as they could in a 30-second interval. The check began with a patient sitting on a 43-cm chair with their palms crossed at the chest. The patient started to stand up and moved back to a sitting position.
2. Balance test. The participant was asked to stand on one chosen lower limb, with the other limb raised off the ground. The patient had to stand barefoot, with their arms located across the chest, each touching the opposite shoulder, with open eyes. The time of preserving one-leg balance was measured. Time less than 5 seconds predicted the risk of fall.
3. Timed up and go test (TUG), used as a check of physical function. TUG provided the time (expressed in seconds) taken by the participant to arise from a chair, walk a distance of 3 m, return to the chair, and sit down again. Time exceeding 14 seconds predicted the risk of fall.
4. The 6-minute walk distance (6MWD), useful capability evaluation. The test was conducted in a 30-m hospital corridor. Patients were asked to walk through it for 6 minutes. Then, they stopped and the distance was measured and recorded in meters.
5. The 2-minute step test (2MST). The number of steps covered in 2 minutes was reported.
6. The Chronic Liver Disease Questionnaire (CLDQ), to assess QOL. There are 29 questions in total, divided into 6 categories (abdominal symptoms, movement, emotional function, exhaustion, systemic symptoms, and worry). The scale ranges from 1 to 7. A higher score indicates better QOL.
7. Short Form Health Survey (SF-36). The test was administered to all patients to evaluate QOL. The scores range from

0 to 100. SF-36 includes 36 items that assess bodily functioning, physical role, bodily pain, and general health, which comprise bodily factor and vitality, social functioning, emotional and mental health. Higher ratings indicate better QOL.

Statistical analysis

Pre- and post-treatment measures were analysed with the Minitab software, version 13.1 (Minitab LLC, State College, USA). All of the data were presented as mean ± standard deviation. To analyse the relationships between the participants' variables, an independent *t*-test was used. The pre- and post-treatment values of exercise efficiency and QOL of each group were compared with a paired *t*-test after the confirmation of normal data distribution with the Shapiro-Wilk test. The independent *t*-test was applied to compare the 2 groups. For all tests, the significance level was set at $p < 0.05$.

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved by the ethical committee of Faculty of Physical Therapy, Cairo University, Egypt (approval No.: P.T. REC/012/002609). ClinicalTrials (www.clinicaltrials.gov) registration number: NCT04629456, registered on November 13, 2020.

Informed consent

Informed consent has been obtained from all individuals included in this study.

Results

There were 60 participants, 41 males (68.4%) and 19 females (31.6%), aged 35–59 years. There was no significant difference in age between the 2 groups ($p = 0.708$). Also, no significant difference was observed in body mass index ($p = 0.940$) or pre- or post-treatment SST scores in both groups ($p = 0.502$ and $p = 0.502$, respectively). There was no significant difference in stability before treatment ($p = 0.123$); after treatment, the difference was highly significant ($p \leq 0.001$). TUG result was not significantly different before treatment ($p = 0.123$), but there was a highly significant difference after treatment ($p \leq 0.001$). Before treatment, there were no significant differences in 6MWD, 2MST, CLDQ, or SF-36 ($p = 0.753$, $p = 0.345$, $p = 0.184$, and $p = 0.660$, respectively), but after treatment, a particularly significant difference was revealed in 6MWD ($p = 0.001$), 2MST ($p \leq 0.001$), CLDQ ($p \leq 0.001$), and SF-36 ($p \leq 0.001$) (Table 1, Figures 2–4).

Table 1. Pre- and post-treatment measures of both groups

Item	Group	Before treatment	After treatment
SST	1	3.96 ± 0.76	7.50 ± 1.10
	2	4.10 ± 0.75	7.86 ± 0.86
p		0.502	0.118
Balance	1	2.96 ± 0.92	10.16 ± 1.85
	2	3.36 ± 1.09	8.50 ± 0.86
p		0.123	≤ 0.001
TUG	1	41.30 ± 4.47	31.06 ± 4.18
	2	42.90 ± 3.80	39.53 ± 1.47
p		0.123	≤ 0.001
6MWD	1	138.77 ± 5.91	162.67 ± 5.71
	2	139.27 ± 4.96	157.53 ± 5.48
p		0.753	0.001
2MST	1	6.63 ± 0.92	12.20 ± 1.47
	2	6.40 ± 0.77	9.90 ± 1.21
p		0.345	≤ 0.001
CLDQ	1	3.10 ± 0.66	5.00 ± 0.64
	2	2.80 ± 0.76	3.56 ± 0.56
p		0.184	≤ 0.001
SF-36	1	28.90 ± 2.99	43.70 ± 4.07
	2	28.56 ± 2.95	36.10 ± 2.83
p		0.660	≤ 0.001

SST – sit-to-stand test, TUG – timed up and go test,
6MWD – 6-minute walk distance, 2MST – 2-minute step test,
CLDQ – Chronic Liver Disease Questionnaire,
SF-36 – Short Form Health Survey

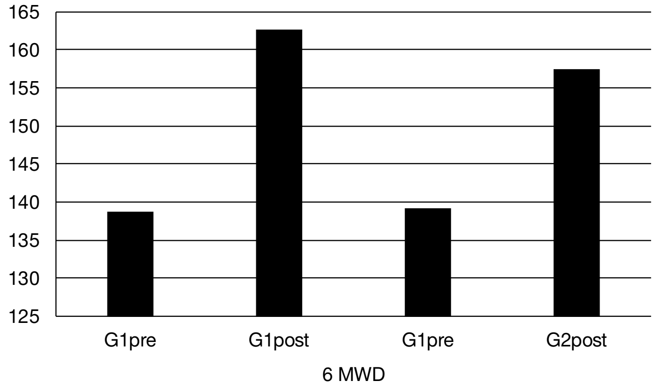

Figure 3. The 6-minute walk distance (6MWD) results

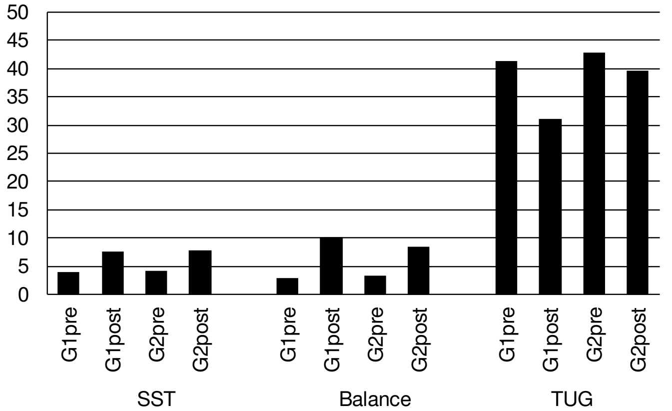

Figure 2. Sit-to-stand test (SST), balance, and timed up and go test (TUG) results

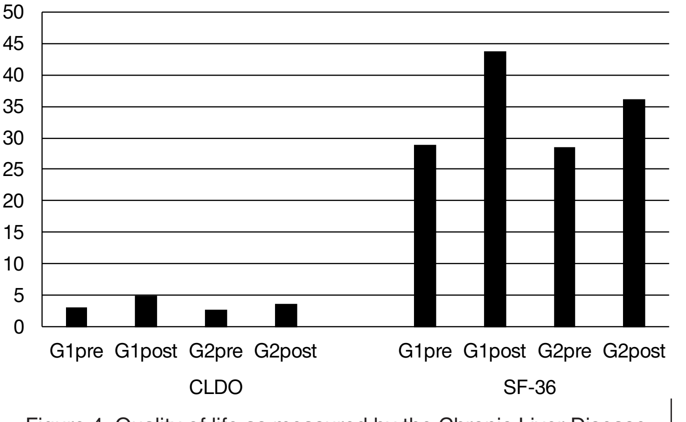

Figure 4. Quality of life as measured by the Chronic Liver Disease Questionnaire (CLDQ) and Short Form Health Survey (SF-36)

Discussion

The outcomes of this study showed a vast improvement in the overall exercising performance and QOL in both groups, with the improvement in the NMES group being higher than that in the exercise group. One of the most surprising findings in the NMES literature is that it is possible to induce increases in power with minimal training intensities [19], which are significantly lower than the intensities required for voluntary training [20]. Similarly, this explains the improvement in the overall performance battery, SST, balance, TUG, 6MWD, and 2MST in the NMES group.

The strengthening of a hypotrophic muscle is more easily accomplished with NMES than with voluntary exercise. Whole activation of a hypotrophic muscle will not be feasible voluntarily, specifically after a lower motor neuron excitability. NMES, on the other hand, may bypass those deficiencies and aim at an increase in motor neuron excitability, both through direct activation of large motor units [21] and through the facilitative effect of cutaneous afferent feedback on big motor neurons [22]. This gives an explanation for the better impact of NMES on the performance battery factor (SST, balance, TUG, 6MWD, 2MST) as it relies on muscle power, and muscle tissues change higher with the aid of NMES than exercises.

The distance walked by chronic liver disease patients was shorter than that walked by healthy subjects, according to Alameri et al. [5]. In contrast to patients with chronic hepatitis B or C infections, 6MWD was found to be lower in cirrhosis patients, exactly as shown in this study: 6MWD results of cirrhotic patients were lower than in normal subjects.

Pu et al. [23] reported significant increases in muscle power, 6MWD, and QOL after 20 weeks of NMES in haemodialysis patients. In this study, after NMES, there was an increase in exercise capacity and capacity to walk the 6MWD test within 3 months, which resulted in an improvement in SF-36 and CLDQ. SST coupled with this improvement in power after NMES, which is explained by enhanced lower limb muscle strength. TUG reflects muscle mass and muscle strength and is also considered a reliable predictor of the onset of sarcopenia [24]. This is in line with the findings of the present study: there was a significant difference in SST and TUG after NMES application.

Motor units are recruited in order to grow in size at some stage in voluntary contraction (the 'size precept'). In turn, percutaneous NMES can activate large type II motor units (muscle fibres) even at quite low stimulation intensities [25]. Muscle intensity was found to be higher after NMES application [26]. When used to maintain lower limb muscle volume, NMES produces excellent performance. It protects the muscle groups of vital patients on bed rest, according to a study that used ultrasound to evaluate muscle tissues [27].

Neder et al. [28] determined that 6-week home-based NMES application enhanced some markers of skeletal muscle strength and endurance in patients with excessive chronic obstructive pulmonary disease. Those useful effects on peripheral muscle function translated into an improved capability to perform whole body exercise and were related to decreased breathlessness in the activities of daily living. Certainly, the usage of NMES allows early mobilization from bed and mobilization from bed to chair in routinely ventilated patients with chronic obstructive pulmonary disease. Similarly to the findings of the current research, the patients were able to get out of bed more easily and engage in more activities of daily life, social support was reduced, and self-sufficiency increased.

Nuhr et al. [29] compared the impact of low- and high-frequency NMES on chronic heart failure sufferers and found that the use of low-frequency NMES (< 50 Hz) increased muscle endurance, while NMES at a frequency > 50 Hz raised muscle strength. The present study demonstrated that CLDQ and SF-36 improved after NMES more than in the exercise group. The score of the 6MWD test, which measures function, was higher after NMES than after physical activities. CLDQ and SF-36 also provided better results in the NMES group.

Gerovasili et al. [30] investigated quadriceps structure after an everyday 55-minute usage of NMES with a frequency of 45 Hz, pulse width of 400 ms, in severely ill patients and observed less atrophy of the quadriceps in comparison with the other group. This suggests that NMES acts as a means to prevent disuse atrophy.

Toshikuni et al. [31] stated that exercise management was a key issue in the control of liver cirrhosis because it might lead to an increase in physical activity, skeletal muscle strength, and exercising ability, in the long run improving QOL and survival. Bodily activity might also prevent and improve sarcopenia in liver cirrhosis patients. Certainly, in studies of the elderly with various chronic illnesses, exercise management has been proven powerful in stopping and reducing sarcopenia. The current study also discovered increased 6MWD, 2MST, CLDQ, and SF-36 results in the exercise group owing to raised muscle strength and performance.

Román et al. [32] implied that after 12 weeks, the exercise group presented advanced exercise capacity, as shown with the 6MWD and 2MST results, increased lower thigh circumference, and progressed QOL; the control group exhibited no great improvement. In the present study, after 3 months of exercises, a considerable difference was observed in SST, balance, TUG, 6MWD, 2MST, CLDQ, and SF-36.

Toshikuni et al. [31] came to the conclusion that light exercise combined with dietary assistance in patients with liver cirrhosis could increase skeletal muscle volume and improve outcomes. Furthermore, the current study revealed that voluntary exercise or NMES implementation was important for liver cirrhosis patients.

Limitations

To generalize the results, further research must include a wide range of patients and a 3-month follow-up to verify if the improvement is maintained or if there is a decline in outcomes after stopping treatment.

Conclusions

Patients with liver cirrhosis present with muscle wasting and limited exercise capacity. Many of them are unwilling or unable to do exercise. NMES is the treatment choice for these patients to prevent muscle wasting, as well as improve muscle strength, endurance, and exercise capacity.

Disclosure statement

The author does not have any financial interest and did not receive any financial benefit from this research.

Conflict of interest

The author states no conflict of interest.

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