Neuromuscular Electrical Stimulator as a Protective Treatment against Intensive Care Unit Muscle Wasting in Sepsis/Septic Shock Patients

Gunes Comba Cebeci[1], Halil Cebeci[2], Mehtap Pehlivanlar Kucuk[3], Ahmet Oguzhan Kucuk[3], Ilkay Koray Bayrak[4] and Fatma Ulger[5]

[1]*Department of Anaesthesiology and Reanimation, Istanbul Eyupsultan State Hospital, Istanbul, Turkey*
[2]*Department of Anaesthesiology and Reanimation, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey*
[3]*Department of Chest Diseases, Division of Intensive Care Unit, Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkey*
[4]*Department of Radiology, Samsun Medical Park, Samsun, Turkey*
[5]*Department of Anaesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayis University, Division of Intensive Care Unit, Samsun, Turkey*

ABSTRACT

Objective: To investigate the efficacy of neuromuscular electrical stimulation (NMES) application in preventing muscle wasting in intensive care unit (ICU) patients diagnosed with sepsis/septic shock.

Study Design: A single-centre, unblinded, parallel-group, prospective, randomised clinical study.

Place and Duration of Study: Ondokuz Mayıs University, Faculty of Medicine Hospital, Level 3 ICU, between October 28th 2018, and October 1st, 2020.

Methodology: Eighty patients from a single centre who were diagnosed with sepsis/septic shock, followed up at level 3 ICU, and met the criteria were included. The patients were evaluated in 2 groups: One who received physiotherapy alone (n=40) and the other who received physiotherapy + NMES (n=40). The development of intensive care unit-muscle wasting was evaluated in patients of both groups. Muscle wasting was identified by anthropometric and ultrasonographic measurements. The day the patients were diagnosed with sepsis was determined as the first day and the bilateral anthropometric and ultrasonographic measurements of the biceps brachii and rectus femoris muscles were obtained on days 3, 7, 14, 21, and 28.

Results: There was no significant difference between the groups in the ultrasonographic and anthropometric measurements on days 1, 3, and 7 ($p>0.005$). However, the ultrasonographic measurements of the group that received physiotherapy + NMES demonstrated a significantly lower loss in the upper extremities on days 14 and 21 compared to the group that received physiotherapy alone ($p=0.003$ and $p=0.028$, respectively). No significant difference was found in the anthropometric measurements.

Conclusion: The NMES, which have been increasingly used as new treatment protocols in the prevention of ICU-AW, yield favourable results in patients with sepsis/septic shock.

Key Words: *Intensive care unit, Acquired weakness, Neuromuscular electrical stimulation, Muscle wasting, Sepsis.*

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INTRODUCTION

A large majority of patients admitted to the ICU after the acute phase of a critical illness exhibit major defects in skeletal muscle strength (weakness) and mass (wasting).[1]

Correspondence to: Dr. Gunes Comba Cebeci, Department of Anaesthesiology and Reanimation, Istanbul Eyupsultan State Hospital, Istanbul, Turkey
E-mail: gunescomba@gmail.com

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Aetiology is multi-factorial; malnutrition, chronic diseases, and immobility. In addition to a limitation in movement, muscle wasting may cause prolonged hospital stay, functional dependence, increased risk of falling, and consequently increased morbidity and mortality.[2,3]

Sepsis and septic shock are considered major factors in the development of myopathy in critically ill patients, which is correlated with increased morbidity rates and ICU length of stay. The underlying pathophysiology is complex, involving increased protein breakdown, mitochondrial dysfunction and muscle inexcitability. Sepsis-induced myopathy is characterised by several histopathological and electrophysiological abnormalities of the muscle and also has clinical conse-

quences such as flaccid weakness and failure to wean from the ventilator.[4]

The most commonly used methods for assessing muscle mass are bioelectrical impedance analysis, anthropometric measurements, and radiological measurements.[2] Ultrasonographic measurement of the thickness of the rectus femoris muscle is a muscle mass measurement method that has been used in recent years.[3,5]

In addition to creating a state of well-being, isometric exercises provide an increase in muscle performance, mass and strength in the management of sarcopenia.[2] Several studies have investigated whether neuromuscular electrical stimulation (NMES) applications can increase the muscle mass and strength in patients who cannot actively exercise. NMES promotes neuronal activation and muscle mass growth.[1]

In the present study, it was aimed to investigate the effects of NMES on muscle wasting in patients with sepsis/septic shock followed in the intensive care unit, accompanied by a physiotherapist.

METHODOLOGY

This single-centre, unblinded, parallel-group, prospective, randomised clinical study was conducted at the Ondokuz Mayıs University, Faculty of Medicine Hospital, Department of Anaesthesiology and Reanimation of a tertiary care centre, between October 28th 2018 and October 1st, 2020. The study protocol was approved by the Ethics Committee of the Ministry of Health, Turkish Medicines and Medical Devices Agency (Date: 23/10/2018; No. 71146310-511.06-E.185120). Prior to the study, all patients were informed about the nature of the study and written informed consent were obtained. The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT04833621).

Initially, a total of 148 patients diagnosed with sepsis/septic shock and hospitalised in the ICU of Ondokuz Mayıs University, Faculty of Medicine Hospital were screened. Of these, 80 were found to be eligible for the study and included.

Inclusion criteria were: age over 18 years, being hospitalised in the ICU, and having a diagnosis of sepsis/septic shock. Exclusion criteria were age under 18 years, being pregnant, having a cardiac pacemaker, having amputated lower extremities, having severe venous insufficiency or major injuries in the lower extremities, having a neuromuscular disease, and being diagnosed with malignancy. Sepsis/septic shock definitions were based on the latest Surviving Sepsis Campaign 2016 guidelines.[6] The day of the diagnosis of sepsis/septic shock was considered the first day of the study for all patients. The group to which the patients would be included in was determined randomly. The patients were divided into groups using the sealed envelope method. The randomisation list was made electronically and letters denoting groups were written in sealed envelopes numbered according to the results (Group NMES, Group CONTROL). A person who was in the ICU at that time and was not related to the study was selected from the envelopes prepared by a person who was not included in the study during the study planning. Eligible patients were assigned by block randomisation with an allocation ratio of 1:1 and divided into two groups: The control group receiving physiotherapy alone (n=40) and the intervention group receiving physiotherapy + NMES (n=40). Patients who died due to sepsis and septic shock related multiple organ failure, DIC, hypotension, and sudden cardiac arrest could not be followed up in the following days.

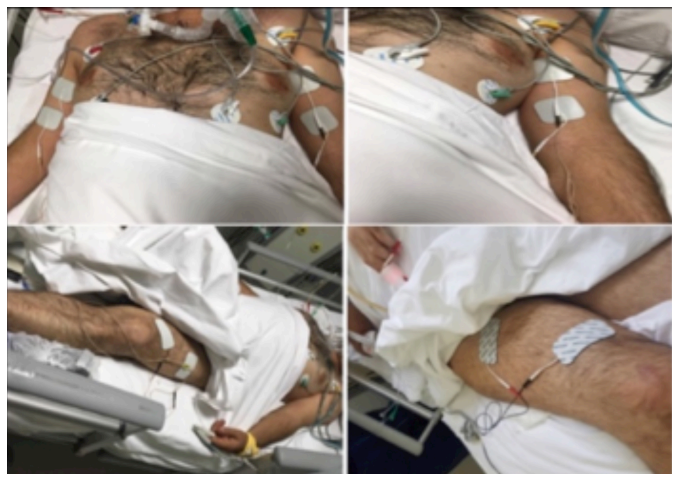

Figure 1a: NMES application.

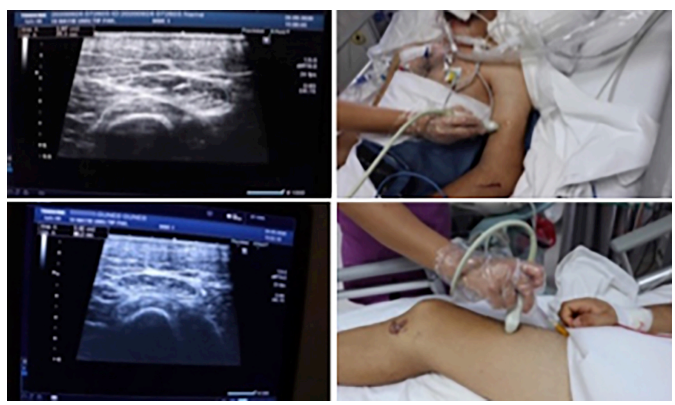

Figure 1b: Ultrasonographic measurements.

All patients were followed up in the ICU for a maximum of 28 days. The patients who met the study criteria were included in the study whether they received or did not receive mechanical ventilation support. The number of days with the need for mechanical ventilation was recorded in intubated patients. The patients were evaluated in two groups. Daily physiotherapy (muscle strengthening) exercises and NMES (Globus Premium 400 neuromuscular stimulator device, Globus Italian Excellence) were applied to one group by a physiotherapist working in the ICU. The electrodes were placed close to the distal and proximal tendon of the muscle group to be applied. 5*5 cm electrodes were used for the biceps brachii muscle and 9*5 cm electrodes were used for the rectus femoris muscle (Figure 1a). Treatment was administered for 55 minutes a day, 5 days a week. Biphasic in practice, 45 Hz. 400 mc second pulse dura-

tion, 12 seconds active (0.8 sec increase, 0.8 sec decrease) impulses were sent for 6 seconds, the impulse intensity was ensured to be visible to the eye and at a level that the patient could tolerate. In the other group (control group), daily physiotherapy exercises (active and passive extremity exercises) alone were performed for 30 min.

The anthropometric measurements of the patients were recorded (arm circumference and thigh circumference) on days 1, 3, 7, 14, 21, and 28 days. The mass of the biceps brachii and rectus femoris muscles were measured (from the same places as anthropometric measurements) ultrasonographically using a linear probe (Mindray; Shenzhen Mindray Bio-Medical Electronics Co., LTD. Hamburg, Germany) by a single radiologist and the patient outcomes were recorded (Figure 1b). Arm circumference and biceps brachii muscle mass measurement from the thickest part of the biceps muscle when the elbow is 90 degrees flexed, thigh circumference and rectus femoris muscle mass measurement; with leg extended (15 cm above the patella) anthropometric and ultrasonographic measurements were made and recorded.

Among the intensive care scoring systems, Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), and Acute Physiology And Chronic Health Evaluation II (APACHE-II) scores were calculated for each patient on the first day of the study.[6] Daily calorie requirement was arranged by the dietitian according to the American Society for Parenteral and Enteral Nutrition (ASPEN).[7]

C-reactive protein (CRP), procalcitonin, lactate, complete blood count (CBC), and biochemistry parameters, routinely followed during the diagnosis and treatment period, were recorded simultaneously with other measurements during follow-up. In addition, whether the patients received positive inotropic/vasopressor support, diuretic needs (the amount in mg), dialysis needs, use of low-molecular-weight heparin, corticosteroids, neuromuscular blockers, daily fluid intake, and daily urine volume were noted. The type of nutrition (enteral or parenteral) was also recorded. The length of ICU stays, duration of intubation and time of extubation, the body weight, and body mass index (BMI) at the final follow-up compared to baseline were recorded.

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Compliance with normal distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The chi-square test and Fisher's exact test were used to compare categorical variables according to the groups. The Mann-Whitney U test was used to compare non-normally distributed data according to the pairwise groups and the independent samples t-test was used to compare normally distributed data. Analysis results mean ± s for quantitative data were presented as deviation and median (minimum- maximum) and frequency (percent) for categorical data. The significance level was taken as $p<0.05$.

RESULTS

A total of 80 patients were included in the study. The intervention group (n=40) received physiotherapy + NMES and the control group (n=40) received physiotherapy alone. The median age was 47 (range: 18 to 85) years in the intervention group and 64 (range: 20 to 82) years in the control group ($p=0.021$). There was no statistically significant difference in the distributions of other quantitative variables between the groups (Table I).

Categorical variables of the groups that did and did not receive NMES are presented in Table I. There was a statistically significant difference in sex distributions ($p=0.036$; Table I).

However, there was no significant difference between the groups in terms of the daily biochemistry values (sodium, potassium, calcium, chlorine, creatinine, blood urea nitrogen, uric acid, and albumin), lactate values, no significant difference in calorie intake, fluid intake and urine output (balance), dialysis needs, and nutrition (enteral/parenteral).

There was no significant difference between the groups at any given time point in the anthropometric measurements of the right and left biceps brachii muscles and the right and left rectus femoris muscles ($p>0.050$). However, there was a significant decrease in the time-dependent measurements of these values ($p<0.001$, Table II).

The ultrasonographic evaluation of the right biceps brachii muscle mass on Days 14 and 21 showed that the patients who received NMES (5.28 cm^2 [range: 1.93 to 9.33 cm^2] and 4.83 cm^2 [range: 1.54 to 9.30 cm^2], respectively; $p=0.003$) had statistically significantly higher median values than those who did not receive NMES (3.32 cm^2 [range: 1.89 to 8.52 cm^2] 3.10 cm^2 [range: 1.12 to 7.56 cm^2], respectively; $p=0.028$, Table III).

The ultrasonographic evaluation of the left biceps brachii muscle mass on days 14 and 21 showed that the patients who received NMES (5.49 cm^2 [range: 1.55 to 9.80 cm^2] and 4.80 cm^2 [range: 1.53 to 8.75 cm^2], respectively; $p=0.009$) had statistically significantly higher median values than those who did not receive NMES (3.43 cm^2 [range: 1.66 to 8.75 cm^2] and 2.89 cm^2 [range: 1.07 to 7.69 cm^2], respectively; $p=0.038$, Table III).

There was no statistically significant difference in the median values of other parameters between the groups at any time point ($p>0.050$; Table I). There was no significant difference in the median values at any given time point in the ultrasonographic measurements of the left and right rectus femoris muscle mass between the groups ($p>0.050$, Figure 2).

DISCUSSION

Muscle wasting is an important cause of morbidity and mortality accompanying the clinical course of patients followed in the ICU setting.[1] The clinical condition known as ICU-AW is associated with many adverse outcomes, particularly a delay in weaning from mechanical ventilation and its effects can persist even years after discharge from the hospital due to impaired physical functions.[1]

Table I: Comparison of quantitative variables and categorical variables according to study groups.

	NMES group	Control group	Test statistic	p-value
Age (years)	48.8 ± 18.86 47 (18 - 85)	58.18 ± 18.17 64 (20 - 82)	U=560	0.021*
Height (cm)	159.16 ± 18.78 160 (52.6 - 180)	158.94 ± 7.39 158 (143 - 178)	U=630.5	0.102
Weight (kg)	69.61 ± 17.57 65.75 (46 - 104)	71.81 ± 18.84 69.9 (40 - 131)	U=718.5	0.433
BMI*** (kg/m^2)	27.72 ± 6.55 26.4 (18.6 - 46.3)	29.46 ± 7.57 28.2 (17.7 - 52.9)	U=681.5	0.254
GCS*****	6.63 ± 2.26 6 (4 - 15)	7.2 ± 2 6 (4 - 11)	U=628	0.076
SOFA**	8.78 ± 2.62 9 (4 - 14)	9.25 ± 3.18 10 (3 - 15)	U=724	0.462
qSOFA	2.53 ± 0.55 3 (1 - 3)	2.63 ± 0.49 3 (2 - 3)	U=732.5	0.448
APACHE II*	23.83 ± 5.83 23 (12 - 38)	25.23 ± 4.82 25 (16 - 38)	t=-1.170	0.245
Temperature (°C)	38.06 ± 0.89 38.2 (35.5 - 39.8)	38.19 ± 0.71 38.3 (36 - 39.5)	U=749	0.622
Length of ICU stay (days)****	31.68 ± 17.64 30 (7 - 80)	26.55 ± 13.81 22.5 (7 - 69)	t=1.447	0.152
Duration of intubation (days)	22.38 ± 14.53 20 (5 - 63)	22.1 ± 15.66 19.5 (2 - 83)	U=767.0	0.751
Gender				
Male	30 (75)	21 (52.5)	χ^2=4.381	0.036*
Female	10 (25)	19 (47.5)		
Comorbidity				
Yes	17 (42.5)	11 (27.5)	χ^2=1.980	0.160
No	23 (57.5)	29 (72.5)		
Inotropic medicine				
Yes	13 (32.5)	18 (45)	χ^2=1.320	0.251
No	27 (67.5)	22 (55)		
******LMWH				
Yes	25 (62.5)	20 (50)	χ^2=1.270	0.260
No	15 (37.5)	20 (50)		
Diuretic				
Yes	15 (37.5)	13 (32.5)	χ^2=0.220	0.639
No	25 (62.5)	27 (67.5)		
Steroid				
Yes	11 (27.5)	6 (15)	χ^2=1.867	0.172
No	29 (72.5)	34 (85)		
Enteral nutrition				
Yes	25 (62.5)	24 (60)	χ^2=0.053	0.818
No	15 (37.5)	16 (40)		
Parenteral nutrition				
Yes	15 (37.5)	9 (22.5)	χ^2=2.143	0.143
No	25 (62.5)	31 (77.5)		
Neuromuscular blocker				
Yes	4 (10)	4 (10.3)	---	0.630[F]
No	36 (90)	35 (89.7)		
Death				
Yes	13 (32.5)	14 (35)	χ^2=0.056	0.813
No	27 (67.5)	26 (65)		
*******Target protein				
Yes	23 (57.5)	16 (40)	χ^2=2.452	0.117
No	17 (42.5)	24 (60)		
Vitamin				
Yes	19 (47.5)	17 (42.5)	χ^2=0.202	0.653
No	21 (52.5)	23 (57.5)		

*t: Two independent samples t-test, U: Mann-Whitney U-test statistic, mean ± SD, median (minimum–maximum), χ2: Chi-square test, F: Fisher's Exact test, frequency (percent). *APACHE II: Acute Physiology and Chronic Health Evaluation II, **SOFA: Sequential Organ Failure Assessment, ***BMI: Body mass index, ****ICU: Intensive care unit, *****GCS: Glaskow Coma Scale, ******LMWH: Low-molecular-weight heparin. ******* (Is the target protein amount reached?).*

It has been demonstrated that sepsis is associated with involuntary loss of muscle mass and that severe neuromuscular dysfunction is associated with ICU-AW.[8,9] In the present study, the application of physiotherapy + NMES yielded a better response in upper extremity muscle groups (biceps brachii) than in lower extremity muscle groups (rectus femoris) compared to the physiotherapy application alone in patients diagnosed with sepsis/septic shock.

The major risk factors for muscle wasting are immobilisation, multiple organ failure, and systemic inflammatory response syndrome, among many other conditions.[1,4,8]

Table II: Anthropometric measurement of the right, left biceps brachii muscle and right, left rectus femoris muscle.

		NMES Group	Control Group	Test statistic	p-value
Anthropometric measurement of the right biceps brachii muscle (cm)	Day 1	30.03 ± 5.39 29.25 (23 - 43)[c]	30.6 ± 5.78 30 (18 - 49)[c]	U=703	0.350
	Day 3	29.49 ± 5.4 28.75 (23 - 42)[c]	29.64 ± 5.9 29 (17 - 48)[bc]	U=749.5	0.626
	Day 7	28.58 ± 5.38 27.75 (21 - 41)[bc]	28.3 ± 5.84 28 (16 - 47)[abc]	U=791.5	0.935
	Day 14	27.37 ± 5.24 26.5 (19 - 40)[ab]	26.76 ± 6.18 26 (17.5 - 45)[ab]	U=417.5	0.635
	Day 21	26.6 ± 5.6 26 (17.5 - 37)[ab]	25.91 ± 6.87 24.5 (17 - 44)[a]	U=149	0.522
	Day 28	25.08 ± 5.54 25 (16.5 - 36)[a]	25.28 ± 9.49 24 (17 - 48)[a]	U=53.5	0.738
Anthropometric measurement of the left biceps brachii muscle (cm)	Day 1	29.64 ± 5.58 28 (21.5 - 4335)[d]	28.99 ± 7.06 29 (2 - 48)[c]	U=797	0.977
	Day 3	29.09 ± 5.6 27.75 (21.5 - 42)[cd]	27.98 ± 7.24 27.5 (2 - 47)[bc]	U=772	0.787
	Day 7	28.18 ± 5.65 26.55 (21 – 41.5)[bcd]	27.19 ± 5.59 27 (16.5 - 45)[abc]	U=742.5	0.579
	Day 14	26.89 ± 5.48 25.5 (19 - 40)[abc]	25.64 ± 5.67 25 (17.5 - 43)[ab]	U=388.5	0.366
	Day 21	26.58 ± 5.71 26 (17 - 38)[ab]	25.06 ± 5.98 24 (17 - 41)[a]	U=137	0.314
	Day 28	25.12 ± 5.26 25 (16.5 - 36)[a]	28.22 ± 20.59 22 (17 - 82)[a]	U=46	0.403
Anthropometric measurement of the left rectus femoris muscle (cm)	Day 1	50.3 ± 7.77 49.5 (33 - 69)[c]	51.79 ± 9 49.5 (35 - 79)[d]	U=760.5	0.703
	Day 3	48.44 ± 10.52 48.75 (3 - 66)[c]	51.04 ± 8.63 48 (38 - 79)[cd]	U=733	0.645
	Day 7	48 ± 7.67 47.5 (29.5 - 66)[bc]	48.89 ± 9.24 47 (31 - 77)[bcd]	U=799.5	0.996
	Day 14	45.48 ± 8.25 46 (27 - 64)[ab]	47.38 ± 8.87 45 (35 - 75)[abc]	U=423	0.695
	Day 21	44.55 ± 8.8 45.5 (25 - 62)[ab]	44.97 ± 9.74 43 (32.5 - 72)[ab]	U=168	0.951
	Day 28	41.08 ± 8.81 40.5 (24 - 56)[a]	42.22 ± 12.58 38 (31 - 71)[a]	U=53.5	0.738
Anthropometric measurement of the right rectus femoris muscle (cm)	Day 1	50.6 ± 7.76 49.75 (33 - 70)[c]	51.66 ± 10.07 49.5 (29 - 82)[d]	U=774.5	0.806
	Day 3	49.71 ± 7.56 49 (32 - 67)[c]	50.79 ± 9.22 48.75 (32 - 80)[cd]	U=781	0.855
	Day 7	48.08 ± 7.78 47.5 (29 - 66)[bc]	48.89 ± 9.16 47 (30 - 78)[bcd]	U=796	0.969
	Day 14	45.5 ± 8.45 45 (27 - 64)[ab]	47.16 ± 9.05 45 (35 - 77)[abc]	U=419.5	0.657
	Day 21	44.3 ± 9.22 45.75 (25 - 61)[a]	45.15 ± 10.42 43 (32.5 - 76)[ab]	U=163.5	0.843
	Day 28	41.27 ± 8.83 42 (24 - 56)[a]	41.89 ± 13.14 37 (30 - 73)[a]	U=48.5	0.504

U: Mann-Whitney U test statistic, a-d: There is no difference between times with the same letter mean ± s. deviation, median (minimum-maximum).

Malnutrition can also cause a decrease in muscle mass by affecting protein synthesis.[8] These variables are crucial and confounding factors that may affect the interpretation of findings. In this study, no significant difference was observed between the groups in terms of fluid-electrolyte and albumin levels, steroid use, and fluid balance of the patients with sepsis.

The use of physiotherapy is encouraged to prevent muscle weakness and wasting since early rehabilitation/mobilisation treatments have functional consequences in preventing the development of ICU-AW in ICU patients.[10] Physiotherapy practices, *albeit* limited, are maintaining their relevance along with physical activity in ICU patients, and they contribute to the patient's improvement in both clinical and post-intensive care processes. The NMES application attempts to find its place among these treatment protocols.[11-13] It is well known that long-term ICU stay is one of the main risk factors for ICU-AW.[11] The evaluation of the patients revealed that there was no difference in the first seven days in anthropometric and ultrasonographic measurements of both groups. Although, there was a significant time-dependent decrease in the anthropometric measurements of the upper and lower extremities, the results were statistically similar between the groups. Gruther *et al*. measured the quadriceps femoris muscle in 17 pilot patients who were evaluated with ultrasonography at the beginning and on day 28.[14] In another study group consisting of 101 cases, the same procedure was performed randomly during the ICU stay. The comparison of the results revealed that the quadriceps femoris muscle thickness had a significant negative correlation with the length of stay in the ICU in both groups.

Table III: Comparison of the right and left biceps brachii muscle ultrasonographic measurement results (cm^2).

		NMES group	Control group	Test statistic	p
Ultrasonographic measurement of the right biceps brachii muscle (cm^2)	Day 1	6.61 ± 2.53 6.39 (2.05 - 12)^{c}	6.1 ± 2.34 5.8 (2.66 - 11.63)^{d}	U=719,5	0.439
	Day 3	6.16 ± 2.53 6/13 (2 - 11.05)^{bc}	5.48 ± 2.33 5.03 (1.88 - 11.41)^{cd}	U=679,5	0.246
	Day 7	5.59 ± 2.18 5.45 (1.92 - 10.05)^{bc}	4.82 ± 2.21 4.39 (1.8 - 10.76)^{bcd}	U=629,5	0.101
	Day 14	5.42 ± 2.09 5.28 (1.93-9.33)^{ab}	3.89 ± 1.86 3.32 (1.89 - 8.52)^{abc}	U=251	0.003*
	Day 21	4.8 ± 2.23 4.83 (1.54 - 9.3)^{a}	3.2 ± 1.85 3.1 (1.12-7.56)^{ab}	U=98	0.028*
	Day 28	4.95 ± 2.5 5.5 (1.06 - 8.7)^{a}	3.08 ± 1.68 2.8 (1.02 - 5.75)^{a}	U=34	0.102
Ultrasonographic measurement of the left biceps brachii muscle (cm^2)	Day 1	6.55 ± 2.23 6.45 (2.3 - 11.58)^{d}	5.82 ± 2.4 5.26 (2.19 - 12.76)^{d}	U=648	0.144
	Day 3	6.03 ± 2.28 6.13 (2.27 - 10.35)^{cd}	5.36 ± 2.38 4.88 (1.83 - 12.55)^{cd}	U=630	0.102
	Day 7	5.39 ± 1.96 5.25 (2.2 - 10.12)^{bcd}	4.7 ± 2.31 4.33 (0.03 - 11.48)^{bcd}	U=613,5	0.073
	Day 14	5.18 ± 2.06 5.49 (1.55 - 9.8)^{abc}	3.92 ± 1.86 3.43 (1.66 - 8.75)^{abc}	U=273	0.009*
	Day 21	4.77 ± 2.12 4.8 (1.53-8.75)^{ab}	3.28 ± 1.9 2.9 (1.07-7.69)^{ab}	U=102	0.038*
	Day 28	4.88 ± 2.32 5.62 (1.4 - 7.9)^{a}	3.17 ± 1.87 2.5 (0.72 - 6.33)^{a}	U=35	0.117

U: Mann-Whitney U test statistic, a-d: There is no difference between times with the same letter mean ± s. deviation, median (minimum maximum).

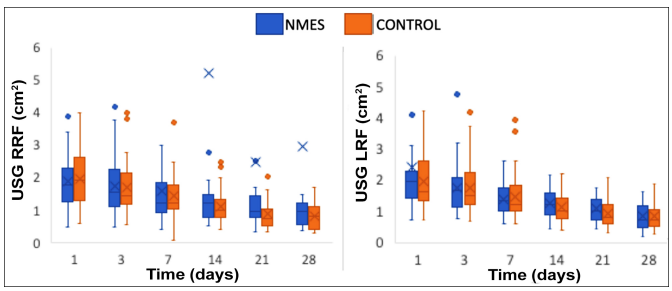

Figure 2: Ultrasonographic measurement of the right rectus femoris muscle (USG RRF) and left rectus femoris muscle (USG LRF).

It has been demonstrated in the literature that the muscle groups that are primarily affected by muscle wasting are in the lower extremities and that these muscles are more active than the upper extremity muscles but volume loss becomes more prominent in the lower extremity muscle group with ageing.[8] In the study of Takashi *et al*. in which they examined 1559 patients, muscle wasting in different muscle groups was evaluated by ultrasound, taking into account the age and gender variables and similar results were found in the study.[15]

The difference in the muscle mass measurements by ultrasonography between the lower and upper extremities in the study can be explained by these two reasons. However, it is thought that the desired response to NMES treatment could not be obtained due to the more pronounced loss of lower extremity muscles.

Gender is a significant risk factor for sepsis, while sex hormones have been shown to have natural advantages and protective effects on women in septic conditions and men are disadvantageous in sepsis cases due to androgens' reduction of cell-mediated immune responses.[16] Although, the male gender was statistically more common in the NMES applied group in the study, it is thought that this situation is not reflected in the clinical outcome.

Review of the literature reveals some studies showing that NMES applications prevent and reduce the development of ICU-AW and on the contrary, there are some reports demonstrating that it does not prevent ICU-AW.[17-19] The NMES treatment was applied to the upper and lower extremity muscle groups in the same frequency of treatment sessions. The measurement of upper extremity muscle thickness showed that muscle loss was significantly lower in the NMES-applied group than in the physiotherapy alone group. Although, there was no significant difference between the groups in the anthropometric arm circumference measurements in the comparison of the upper extremities, the muscle loss was less pronounced in the NMES-applied group in the ultrasonographical measurements of the biceps brachii muscle performed on days 14 and 21. The difference between the upper extremity and the lower extremity results can be explained by the lower extremity muscles being more sensitive to the development of ICU-AW.[8]

The main limitation of the study was that the patients diagnosed with sepsis/septic shock were followed under sedation and mechanical ventilation. This was reflected in their Glasgow Coma Score (GCS) and the initial mean GCS of the patients in both groups was low (GCS 6). Due to the low long-term survival rate in the patients with sepsis/septic shock, 28-day patient follow-up was very difficult. Another limitation in the study is the difficulties in patient selection. Since patients diagnosed with sepsis/septic shock were randomly assigned to groups, the age factor of patients could not be standardised. In the 2010 European Sarcopenia Study Group in Elderly Patients (EWGSOP), age is stated as another risk factor for sarcopenia.[20] In a review, Richard *et al*. reported

that advanced age (decreased protein production) and sepsis (decreased protein production, increased proteolytic activity, impaired glycemic index) were the risk factors for ICU-AW.[21] These variables were similar in the groups included in the present study, except for age. The median age of the patients was 47 years in the physiotherapy + NMES group and 64 years in the physiotherapy alone group (p=0.021). Mitchell *et al*. reported in their study that muscle strength loss was >75 years.[22] Although, the mean age of the experimental group was 47 years, this effect was minimal, since the median age in both groups was <75 years in the study. However, it is important to standardise the age factor when designing future studies.

In addition, the age, gender, comorbidities, hospitalisation diagnoses, and different treatment protocols of the patients hospitalised in the ICU differ. Although most of the variables in groups did not differ significantly between groups, new studies can be planned for larger patient groups, especially by standardising age and gender variables.

It was specially designed so that the physiotherapist treating both groups was the same person. Because it was important that the physical therapy standard was maintained. Although, it is questionable that the physiotherapist is not blind, that he applied more effective treatment to the experimental group, it should be expected that he has no interest in this study and this is unethical. In addition, an observer who did not have a conflict of interest with the work in the intensive care unit observed the treatment practices of the physiotherapist.

With the increasing diagnosis and treatment methods in parallel with the today's technological developments, the survival period of critically ill patients in the ICU is extended.[23] However, many concomitant problems and bring about predisposition also arise that need to be solved. Intensive care unit-acquired weakness is also one of them and it is thought to affect at least 50% of patients hospitalised in the ICU setting. It has been demonstrated that different muscle groups can respond differently to NMES treatment protocols and some muscle groups are unresponsive. Further, large-scale, prospective, randomised studies are needed to examine muscle groups affected by individual differences, clinical courses and many other controllable or uncontrollable conditions.

CONCLUSION

NMES used as new treatment protocols in the prevention of ICU-AW, yield favourable results in patients with sepsis/septic shock.

DISCLOSURE:
It is not part of any work in progress.

PATIENTS' CONSENT:
Consents of the patient/guardian were obtained prior to writing the article.

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The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
GCC: Conceptualisation, methodology, software, data collection, data interpretation, writing.
HC: Data collection, data interpretation.
MPK: Conceptualisation, methodology, software, formal analysis, data collection, data interpretation, writing, original draft, review and editing, supervision.
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IKB: Data collection.
FU: Conceptualisation, methodology, software, data collection, data interpretation, writing, original draft, review and editing, supervision.
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