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

Sir,

We have read with interest the article titled 'Neuromuscular Electrical Stimulator (NMES) as a Protective Treatment against Intensive Care Unit (ICU) Muscle Wasting in Sepsis/Septic Shock Patients' by Cebeci *et al*.[1] They have reported a decrease in muscle wasting in biceps brachii in patients who received a combination of ultrasound therapy and NMES. This is an important finding which has the potential to help prevent and manage muscle wasting in patients admitted to ICU for various conditions. This, in turn, can possibly lead to better recovery, functional and mobility outcomes.

We performed a critical analysis of the article using Critical Appraisal Skills Programme (CASP) Randomised Controlled Trials Checklist (http:// casp-uk.net/wpcontent/uploads/2020/10/CASP_RCT_Checklist_PDF_Fillable_Form.pdf) and would like to highlight some points that need attention and further clarification.

According to the Consolidated Statement for Reporting of Randomized Trial (CONSORT) reporting guidelines, the CONSORT diagram is a mandatory requirement for the publication of a randomised controlled trial (RCT). This was missing from this article.[1]

The protocol for the research article was registered in ClinicalTrials.gov, Trial number NCT04833621. The published protocol mentioned "single centre, prospective, cross-over, double blinded trial" but in the published manuscript, that study design is mentioned as "parallel group, un-blinded" trial. This is deviation from the published protocol and needs to be explained.

The control group had more female patients than the intervention group and it was statistically significant.[1] Chlan *et al.* concluded that female gender, increased age, and length of ventilator support contribute to decreased grip strength in patients admitted to ICU, irrespective of the severity of illness.[2] Moreover, the female gender is an independent risk factor to develop ICU-acquired weakness (AW).[3] This might be a potential confounding factor which can affect the results.

The median age of the control group was significantly more than the intervention group.( 58.18 ± 18.17 *vs.* 48.8 ± 18.86 years).[1] Sarcopenia increases with aging and co-existence of sarcopenia in ICU patients can result in more loss of muscle mass and it can affect the treatment outcome in both groups.[3] Body mass index was more in the control group, which even though statistically insignificant, can still predispose patients to sarcopenic obesity; which, when combined with the disparity in age as well, can confound the results of this study. A baseline assessment of sarcopenia with equal distribution in both groups would have been a better approach to handling this confounding factor in the study.

Change in appendicular lean mass in both groups can be an important outcome measure to see the effectiveness of NMES in this population of people for future studies.[4]

ICU-AW affects lower limbs more than the upper limb and proximal more than distal muscles.[1,3] Authors found no difference in loss of muscle mass in the rectus femoris muscle in both groups. This raises the question whether the decrease in muscle wasting in biceps brachii in intervention was clinically significant or not. This can be answered by conducting studies with longer follow-up and functional assessments of patients with ICU-AW, which can point out the clinical utility of NMES in these patients.

We feel that this article is a good contribution to the ICU-related rehabilitation interventions literature and more studies should be conducted on a larger scale to address other unanswered questions.

**COMPETING INTEREST:**
The authors declared no competing interest.

**AUTHORS' CONTRIBUTION:**
MTK: Study concept and design, Initial draft writing, literature search, and final approval
FAR: Draft writing, Critical revision of the manuscript, and final approval.

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*Muhammad Tawab Khalil and Farooq Azam Rathore*

*Department of Rehabilitation, Armed Forces Institute of Rehabilitation Medicine, Rawalpindi, Pakistan*

*Correspondence to: Dr. Muhammad Tawab Khalil, Department of Rehabilitation, Armed Forces Institute of Rehabilitation Medicine, Rawalpindi, Pakistan*
*E-mail: tawabkhalil2013@gmail.com*

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## AUTHOR'S REPLY

Sir,

First of all, thank you for your valuable comments and positive review. Following is the reply to your comments on our study.

Our study is arranged according to the CONSORT diagram and we present it in the appendix.

Our study was organised and carried out in 2 groups as a single centre, prospective, parallel and double-blind from the planning stage, and ethics committee approval was obtained in this way. As we mentioned in our article, treatment was performed by a single physiotherapist. Although the radiologist who made the measurements was not aware of the study groups, we stated this situation as "unblinded" in our article in line with the criticism made because the physiotherapist who applied the treatment knew the patient groups. This has already been mentioned in the limitations of the study.

First of all, thank you for mentioning this important issue. In our article, we intentionally kept this particular aspect concise to maintain focus on the main subject. It is one of the issues that must be clarified. Sepsis is defined as life-threatening organ dysfunction due to infection.[1] Gender is an important risk factor in sepsis. According to Kizilarslan *et al*., while the female gender is considered a risk factor, there are also studies in the literature showing that the female gender is protective in sepsis.[2,3] Sex hormones have been shown to have a natural advantage and protective effect on women in septic conditions. On the other hand, it has been shown that the male gender is disadvantaged in sepsis, as androgens reduce cell--mediated immune responses in addition to reduced immunological and cardiovascular responses.[3] Since the patients we included in the study were diagnosed with sepsis/septic shock, we could not differentiate our patients in terms of gender. Therefore, there is a statistically significant difference between the distributions of gender according to NMES groups in our study (p=0.036). While, 75% of those who received NMES were males, 52.5% of those who did not receive it were males. We think that the results of our study were not affected because the male gender was proportionally higher in both groups.

According to the report published by EWGSOP (European Working Group on Sarcopenia in Elderly Patients) in 2010, another risk factor for sarcopenia is age.[4] In the EWGSOP statement, it was stated that the incidence of sarcopenia increased in people over 65 years of age. In the review published by Richard et al. in 2010, it was stated that advanced age (decreased protein production) and sepsis (decreased protein production, increased proteolytic activity, impaired glycemic index, *etc*.) are risk factors for ICU-AW.[5] In our study, a statistically significant difference was found between the median age of the patients according to the NMES groups (p=0.021). While the median age of those who received NMES was 47 years, the median age of those who did not receive NMES was 64 years; the median age in both groups was <65 years. It is thought that the age factor was not a factor in the clinical course in our study. Your views on sarcopenic obesity are valuable, but, as stated in the limitations, it was very difficult to follow our patients for a long time with sepsis/septic shock.

Definitely, more detailed studies should be planned by determining the subgroups and parameters related to the subject.

In our study, no statistically significant difference was found in the lower extremity measurements (both anthropometric and ultrasonographic) in the groups that received and did not receive NMES treatment. There are studies in the literature showing that the primary affected muscle group in sarcopenia is the lower extremities.[6] In addition, there are studies showing that lower extremity muscles are more active than upper extremity muscles in daily life and that muscle volume loss is more in the lower extremity muscle group with ageing.[7] The difference in muscle thickness measurements made by ultrasonography between the lower and upper extremities in our study can be explained by these two reasons. We think that we could not get the response we expected to NMES treatment because the loss in the lower extremity muscles was more pronounced. As you have emphasized, future studies will be important in terms of illuminating the subject.

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*Gunes Comba Cebeci*

*Department of Anaesthesiology and Reanimation, Istanbul Eyupsultan State Hospital, Istanbul, Turkey*

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