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Original Article

Effect of early bed cycling on muscle strength and cellular immune factors in patients with intensive care unit-acquired weaknesses - a protocol for a randomized controlled clinical trial

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Abstract: In the intensive care unit (ICU), patients often experience restricted mobility due to their critical condition, potentially leading to negative effects on both muscle strength and immune function. Previous research has highlighted the beneficial effects of early mobilization among patients, regardless of mechanical ventilation status. Hence, early bed cycling serves as a potential facilitator for early mobilization and is considered a feasible intervention for critically ill patients within the ICU. To mitigate this concern, we propose a randomized controlled clinical trial aiming to assess the efficacy of early bed cycling for patients undergoing mechanical ventilation and analgosedation. The study will encompass 56 participants randomly assigned to either the treatment or control group, each consisting of 28 patients. Participants in both groups will receive health education. However, the control group will not receive any therapeutic intervention throughout the study. In contrast, the experimental group will undergo passive bed cycling of their lower extremities for 20 minutes at a rate of 30 revolutions per minute. Primary outcomes will focus on changes in the rectus femoris muscle area and thickness, evaluated using ultrasound, interleukin-6 (IL-6), IL-10, and nitric oxide (NO) production function. Secondary endpoints will encompass the modified Barthel index score, Medical Research Council total score at 1, 2, and 4 weeks following the final treatment session, participants' mechanical ventilation duration, rate of extubation in the second week, 28-day survival rate, and occurrence of adverse reactions. Any encountered side effects will be duly documented. Statistical analysis will be employed to compare patient outcomes between the treatment and control groups.

Keywords: ICU-AW, IL-6, bed cycling, exercise, cellular immune factors

Introduction

Intensive Care Unit-Acquired Weakness (ICU-AW) is a critical complication frequently observed in critically ill patients. These individuals often necessitate mechanical ventilation and analgosedation due to their unstable condition [1]. Immobility significantly impacts muscle degradation and systemic weakness. Prolonged immobility triggers considerable muscle tissue breakdown, resulting in a reduction of muscle mass by up to 30% within merely ten days. This breakdown primarily manifests in decreased muscle fibre size, culminating in systemic muscle weakness that affects the entire body. Furthermore, immobility not only induces localized muscle weakness but also precipitates widespread muscle weakness and dysfunction throughout the body. The incidence of ICU-AW in patients with sepsis ranges from 60% to 100%. Immediate repercussions of ICU-AW encompass delayed ventilator weaning, prolonged ICU stays, and extended hospitalization. Long-term consequences involve post-discharge limitations in performing daily activities and a diminished quality of life [2-4]. Patients

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frequently endure systemic inflammation due to shock, trauma, sepsis, or the critical illness itself. Notably, pro-inflammatory cytokines exacerbate muscle protein degradation in this context [5]. Interleukin (IL)-6, among hundreds of other cytokines, chemokines, and growth factors, operates as a mediator of both innate and adaptive immune responses [6, 7]. Additionally, IL-6 exerts endocrine and metabolic effects on various organs, including the liver, adipose tissue, intestines, pancreas, and skeletal muscle. However, under certain pathological conditions, IL-6 may induce muscle atrophy [8]. In the context of skeletal muscle tissue, IL-6 might stimulate satellite cell proliferation and their integration as new myonuclei into existing muscle fibers. While the direct correlation between these phenomena remains incompletely established in vivo, exercises and anti-IL-6 receptor-based approaches have been recognized as potentially beneficial therapeutic strategies in combating muscle wasting associated with chronic inflammatory conditions [9-11].

Mobilization has demonstrated the potential to improve outcomes among critically ill adults, leading to notably reduced stays in the ICU and hospital, along with enhanced functional recovery [12, 13]. While certain reports suggest that implementing an exercise protocol did not significantly reduce the duration of mechanical ventilation or hospital stays, there were considerable reductions in post-hospital care costs and marked improvements in quality of life [14, 15]. A particular study observed a significant enhancement in muscle strength post-intervention through passive cycling [16]. Furthermore, other studies propose that employing passive bed cycling could augment anti-inflammatory processes and bolster the immune response in critically ill patients, thereby mitigating muscle degradation and the onset of ICU-AW [14]. A progressive mobilization strategy, ranging from passive and active range of motion exercises to dangling, standing, lift transfer to a chair, and ambulation, has been advocated as an approach to mitigate muscle weakness post-critical illness [17]. Consequently, there exists a necessity to develop straightforward yet potent interventions specifically targeting ICU-AW to prevent and treat this condition effectively.

We endeavoured to investigate the efficacy of a customized passive bed cycling program in averting muscle degradation, rectifying the imbalance of cellular immune factors, and mitigating the onset of ICU-AW. Our hypothesis posited that initiating bed cycling at an early stage would prove more effective in preserving muscle strength and mass, fostering a reduction in IL-6 levels, and amplifying insulin activity along with glucose uptake in muscles.

Material and methods

Study design

This parallel-group, randomized, and single-blinded (outcome assessors) prospective clinical trial was designed to assess the efficacy of early bed cycling for patients undergoing mechanical ventilation and analgosedation. The flow of the study is illustrated in **Figure 1**.

Participants will be randomly assigned to either the treatment group or the control group at a 1:1 ratio using a blocked randomization table. This table will encompass all potential combinations of a limited series of figures arranged in random order, ensuring equal probability for patients to be allocated to treatment or control groups. The sequence of interventions within each block will undergo randomization. This iterative process will continue across successive blocks until all participants have been randomized. Furthermore, both outcome evaluators and statistical analysts will remain blinded, devoid of involvement in any aspect of the trial's design or treatment procedures.

Participants

The study will target patients undergoing mechanical ventilation, invasive sedation, and will recruit individuals from Shanghai General Hospital, affiliated with Shanghai Jiaotong University and Shanghai Sunshine Rehabilitation Center. The inclusion criteria were: 1) volunteered to participate in this trial after being informed of the objectives, procedures, treatments, and potential risks; 2) age ≥18 years; 3) patients undergoing mechanical ventilation and invasive sedation; 4) intubated for a minimum of 24 hours; 5) adequate cardiac reserve (evidenced by < 20% heart rate variability at rest), maintaining systolic blood pressure within the range of 90 to 180 mmHg, pre-

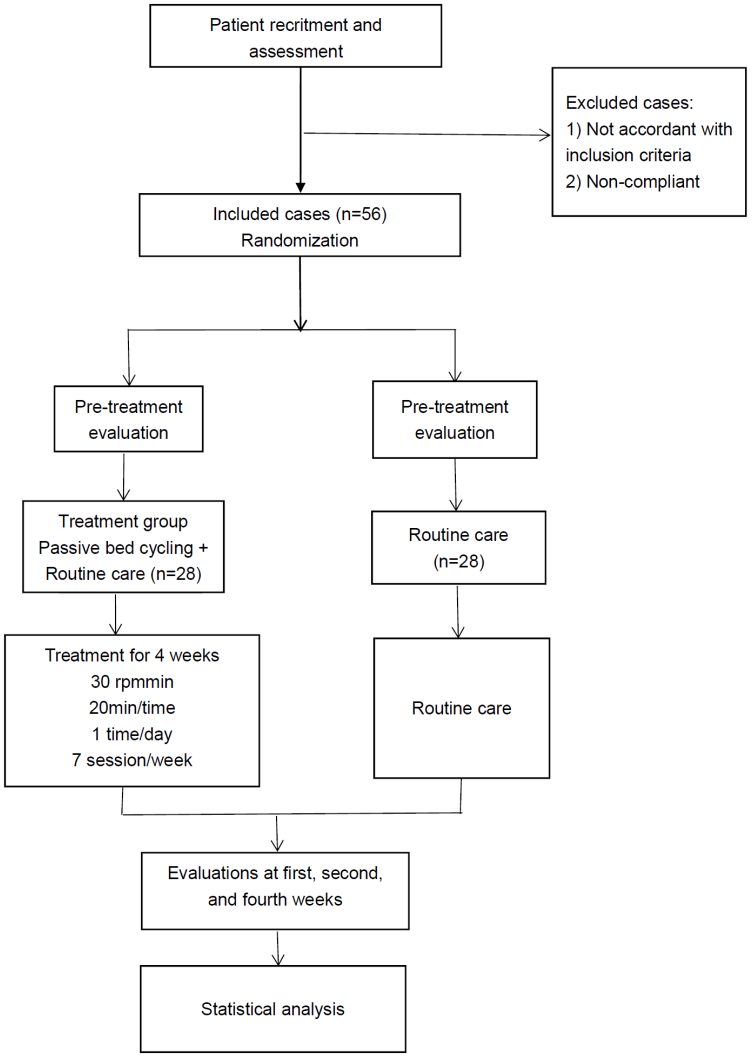

Figure 1. Flow chart of this study.

senting a normal electrocardiogram, peripheral capillary oxygen saturation exceeding 90%, a fraction of inspired oxygen below 60%, hemoglobin levels above 7 g/dL, and a platelet count exceeding 20,000 cells/mm^3 [18]. The exclusion criteria were: 1) pre-existing neurological and muscular disorders, encompassing brain and spinal cord injuries; 2) limb disability and limb instability fractures; 3) malignant tumors; 4) ongoing active bleeding.

The elimination criteria were: 1) choose to leave the clinical trial due to personal reasons; 2) encounter severe adverse events necessitating withdrawal from the trial; 3) fail to fully engage in the treatment or follow-up sessions, or 4) demonstrate non-compliance with the treatment regimen or inability to furnish necessary evaluation-related information.

Ethics approval and consent to participate

This trial was structured by the guidelines stipulated by Consolidated Standards of Reporting Trials (CONSORT 2010) (refer to **Figure 1**), Standards for Reporting Interventions in Controlled Trials of Non-Pharmacologic Treatment [19], as well as the Standard Protocol Items-Recommendations for Interventional Trials (SPIRIT) statement and the SPIRIT checklist [20]. The study was also approved by the Ethics Committee of the Institute of Shanghai General Hospital [(2023)094].

Intervention

Participants in both the control and treatment groups will receive health education and concomitant care and intervention when required. In the treatment group, participants will receive additional passive bed cycling therapy for 20 minutes at a speed of 30 revolutions per minute once daily during hospitalization. If a severe adverse event occurs, the intervention will be halted.

The health education aim is to elucidate the participants about their condition and present circumstances, fostering a positive attitude while providing prompt feedback regarding the stability of their vital signs. Our strategy involves redirecting their focus, facilitating visits from their family members, addressing psychological barriers, and alleviating any fears they may have.

The concomitant care and intervention: In cases of severe symptoms among participants in both groups, medications from the first-aid kit will be administered. Comprehensive documentation of medicine type, dosage, and usage

will be meticulously recorded on diary cards for subsequent analysis. Furthermore, individuals managing complex chronic conditions necessitating ongoing medication and essential treatment will have their diseases, medications, and therapies documented. Continuous 24/7 monitoring of all ICU patients will be conducted by registered nurses, while ICU doctors will assess patients every 6 hours. In the event of hemodynamic instability, such as arrhythmias or hypotension caused by passive bed cycling, immediate medical attention from ICU doctors will be sought for patient treatment.

Discontinuation of the Intervention: The intervention will be halted in instances of severe adverse events.

Outcome measures

Baseline Information: Demographic data (including center location, name, age, gender, address, telephone number, and employment status) and medical data (including diagnosis, medication history, and APACHE II rating forms) were collected utilizing a standardized survey.

Primary Outcome Measures include: 1) the average changes in both the area and thickness of the rectus femoris muscle evaluated using ultrasound examination; 2) serum IL-6, IL-10, and nitric oxide (NO) production function before and after the therapeutic intervention [21].

Secondary Outcome Measures were: modified Barthel index (MBI) [22] and Medical Research Council (MRC) [23] scores at 1, 2, and 4 weeks following the final treatment session, participants' mechanical ventilation duration, rate of detachment in the second week, 28-day survival rate, and occurrence of adverse reactions.

Sample size calculation

Sample size calculation was performed using SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA). The mean change in the primary outcome before and after treatment will serve as the efficacy evaluation indicator in the sample size calculation. Prior study findings demonstrated a mean ultrasound-measured muscle thickness change of 0.45±0.1 [24] and an average ultrasonic intensity of muscle alteration of 25±3 [25] after muscle mass and function loss. To detect a significant difference with 80% power, a 0.05 alpha value, and an acceptable delta value of 0.2, each group will necessitate a sample size of at least 23 participants. Considering a potential 20% dropout, each group will require 28 participants.

Randomization and blinding

Participants will be randomly assigned (at a 1:1 ratio) to either the treatment group or the control group using a blocked randomization table. This table will encompass all potential combinations of a limited series of figures arranged in random order, ensuring equal probability for patients to be allocated to treatment or control groups. The sequence of interventions within each block will undergo randomization. This iterative process will continue across successive blocks until all participants have been randomized. Furthermore, both outcome evaluators and statistical analysts will remain blinded, devoid of involvement in any aspect of the trial's design or treatment procedures.

Statistical analysis

The statistical analysis will be performed using R Software (v4.2.0) and SPSS (23.0, IBM Corp., New York, USA). The primary analysis will be conducted based on the intention-to-treat set, which included all initially assigned participants. Normally distributed data will be expressed as means ± standard deviations and non-normally distributed continuous data as medians with interquartile ranges. Categorical variables are presented as numbers and percentages. Differences between groups will be compared using a t-test, F-test, Kruskal-Wallis H-rank sum test, and χ^2 test accordingly. Ultrasound data will undergo analysis via a mixed-effect model. Cox regression analysis will be conducted to identify outcome-related factors. Statistical significance will be set at $P < 0.05$.

All data required for the primary statistical analysis will be collected by the fourth week of treatment. In instances of missing data, an analysis of the assumed missing data mechanism will be performed, employing a multiple adjustment approach. Following the primary analysis, a sensitivity analysis will be executed on diverse datasets to evaluate the influence of missing

data on the outcomes. A comprehensive statistical analysis plan will be independently developed.

Discussion

This protocol proposed a bed cycling plan for patients undergoing mechanical ventilation and invasive sedation in the ICU. The primary outcome measures include the area and thickness of the rectus femoris muscle and serum IL-6, IL-10, and nitric oxide (NO) production function, while the secondary outcome measures include MBI and MRC scores and other clinical parameters.

Few studies have addressed the impact of bed cycling on long-term inflammation in critically ill patients. Kho enrolled 360 ICU patients undergoing invasive mechanical ventilation and found that adding early in-bed cycling did not improve physical function 3 days after discharge from the ICU [26]. Existing research suggests that exercise induces anti-inflammatory effects through IL-10 and IL-6 induction. Exercise has been explored as a potential regulator of inflammation and muscle function. The collective evidence showing a significant decrease in IL-6 concentration from baseline to the end of the intervention, coupled with the absence of notable changes after the rest period post-intervention, implies that passive exercise not only lacks adverse effects on inflammation but might also contribute to reducing IL-6 levels [27]. While passive exercise appears to reduce IL-6 levels, further investigation is warranted to comprehend the clinical significance of such reductions. Cytokine values could serve as valuable indicators in elucidating the physiological basis behind the benefits of mobilization in critically ill adults.

In the initial stages of critical illness, many patients are deeply sedated during mechanical ventilation. Ultrasound, a cost-effective, reproducible, and noninvasive imaging technique, can assess multiple muscle groups. Extensive research in the ICU setting has focused on ultrasound evaluation of peripheral skeletal muscles for ICU-acquired weakness (ICU-AW) [28]. This study protocol utilizes muscular ultrasound to evaluate muscle strength by observing the muscle's cross-sectional area, layer thickness, and echo intensity based on grayscale and penetration angle. We contend that muscular ultrasound can accurately identify pathological changes associated with ICU-AW [29]. Our study aims to determine whether this treatment will affect the rectus femoris muscle area, thickness, and MBI and MRC total scores over the long term following the final treatment.

However, this study still possesses several limitations. First, it is hard for clinicians to communicate with patients, and the experience and feelings during the examination are hard to evaluate directly; second, this study only included participants undergoing mechanical ventilation and invasive sedation, therefore the most suitable cycling parameters should be further screened.

For preventing ICU-AW, further research is imperative to establish the safety and efficacy of early bed cycling in ICU patients, the correlation between muscle strength, cellular immunity, and cycling treatment also requires further analysis.

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Disclosure of conflict of interest

None.

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References

[1] Mitobe Y, Morishita S, Ohashi K, Sakai S, Uchiyama M, Abeywickrama H, Yamada E, Kikuchi Y, Nitta M, Honda T, Endoh H, Kimura S, Sakano S and Koyama Y. Skeletal muscle index at intensive care unit admission is a pre-

dictor of intensive care unit-acquired weakness in patients with sepsis. J Clin Med Res 2019; 11: 834-841.
[2] De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, Outin H and Sharshar T; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med 2007; 35: 2007-2015.
[3] Ali NA, O'Brien JM Jr, Hoffmann SP, Phillips G, Garland A, Finley JC, Almoosa K, Hejal R, Wolf KM, Lemeshow S, Connors AF Jr and Marsh CB; Midwest Critical Care Consortium. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 2008; 178: 261-268.
[4] Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS and Cheung AM; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011; 364: 1293-1304.
[5] Vollenweider R, Manettas AI, Häni N, de Bruin ED and Knols RH. Passive motion of the lower extremities in sedated and ventilated patients in the ICU - a systematic review of early effects and replicability of Interventions. PLoS One 2022; 17: e0267255.
[6] Belizário JE, Fontes-Oliveira CC, Borges JP, Kashiabara JA and Vannier E. Skeletal muscle wasting and renewal: a pivotal role of myokine IL-6. Springerplus 2016; 5: 619.
[7] Feng B, Zhou T, Guo Z, Jin J, Zhang S, Qiu J, Cao J, Li J, Peng X, Wang J, Xing Y, Ji R, Qiao L and Liang Y. Comprehensive analysis of immune-related genes for classification and immune microenvironment of asthma. Am J Transl Res 2023; 15: 1052-1062.
[8] Pelosi L, Berardinelli MG, Forcina L, Ascenzi F, Rizzuto E, Sandri M, De Benedetti F, Scicchitano BM and Musarò A. Sustained systemic levels of IL-6 impinge early muscle growth and induce muscle atrophy and wasting in adulthood. Cells 2021; 10: 1816.
[9] Argilés JM, Busquets S and López-Soriano FJ. The pivotal role of cytokines in muscle wasting during cancer. Int J Biochem Cell Biol 2005; 37: 2036-2046.
[10] Argilés JM, Anker SD, Evans WJ, Morley JE, Fearon KC, Strasser F, Muscaritoli M and Baracos VE. Consensus on cachexia definitions. J Am Med Dir Assoc 2010; 11: 229-230.
[11] Weber-Carstens S, Deja M, Koch S, Spranger J, Bubser F, Wernecke KD, Spies CD, Spuler S and Keh D. Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. Crit Care 2010; 14: R119.
[12] Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB and Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009; 373: 1874-1882.
[13] Jiang B, Liu H, Liu Y, Tian Y, Nie M, Jing W and Du A. Development of an early mobilization practice for critically ill patients in intensive care units: a Delphi method study. Am J Transl Res 2024; 16: 3875-3885.
[14] Amidei C and Sole ML. Physiological responses to passive exercise in adults receiving mechanical ventilation. Am J Crit Care 2013; 22: 337-348.
[15] Storch EK and Kruszynski DM. From rehabilitation to optimal function: role of clinical exercise therapy. Curr Opin Crit Care 2008; 14: 451-455.
[16] Llano-Diez M, Renaud G, Andersson M, Marrero HG, Cacciani N, Engquist H, Corpeño R, Artemenko K, Bergquist J and Larsson L. Mechanisms underlying ICU muscle wasting and effects of passive mechanical loading. Crit Care 2012; 16: R209.
[17] França EE, Ribeiro LC, Lamenha GG, Magalhães IK, Figueiredo TG, Costa MJ, Elihimas UF Júnior, Feitosa BL, Andrade MD, Correia MA Júnior, Ramos FF and Castro CM. Oxidative stress and immune system analysis after cycle ergometer use in critical patients. Clinics (Sao Paulo) 2017; 72: 143-149.
[18] Schulz KF, Altman DG and Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332.
[19] França EET, Gomes JPV, De Lira JMB, Amaral TCN, Vilaça AF, Paiva Júnior MDS, Elihimas Júnior UF, Correia Júnior MAV, Forgiarini Júnior LA, Costa MJC, Andrade MA, Ribeiro LC and De Castro CMMB. Acute effect of passive cycle-ergometry and functional electrical stimulation on nitrosative stress and inflammatory cytokines in mechanically ventilated critically ill patients: a randomized controlled trial. Braz J Med Biol Res 2020; 53: e8770.
[20] Griffiths RD and Hall JB. Intensive care unit-acquired weakness. Crit Care Med 2010; 38: 779-787.
[21] Mirón Mombiela R, Facal de Castro F, Moreno P and Borras C. Ultrasonic echo intensity as a new noninvasive in vivo biomarker of frailty. J Am Geriatr Soc 2017; 65: 2685-2690.
[22] Chen K, Shu S, Yang M, Zhong S and Xu F. Meridian acupuncture plus massage for children with spastic cerebral palsy. Am J Transl Res 2021; 13: 6415-6422.

[23] Corner EJ, Wood H, Englebretsen C, Thomas A, Grant RL, Nikoletou D and Soni N. The Chelsea critical care physical assessment tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. Physiotherapy 2013; 99: 33-41.

[24] Rustani K, Kundisova L, Capecchi PL, Nante N and Bicchi M. Ultrasound measurement of rectus femoris muscle thickness as a quick screening test for sarcopenia assessment. Arch Gerontol Geriatr 2019; 83: 151-154.

[25] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleza-Jeric K, Laupacis A and Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013; 346: e7586.

[26] Kho ME, Berney S, Pastva AM, Kelly L, Reid JC, Burns KEA, Seely AJ, D'Aragon F, Rochwerg B, Ball I, Fox-Robichaud AE, Karachi T, Lamontagne F, Archambault PM, Tsang JL, Duan EH, Muscedere J, Verceles AC, Serri K, English SW, Reeve BK, Mehta S, Rudkowski JC, Heels-Ansdell D, O'Grady HK, Strong G, Obrovac K, Ajami D, Camposilvan L, Tarride JE, Thabane L, Herridge MS and Cook DJ. Early in-bed cycle ergometry in mechanically ventilated patients. NEJM Evid 2024; 3: EVIDoa2400137.

[27] Winkelman C. Inactivity and inflammation in the critically ill patient. Crit Care Clin 2007; 23: 21-34.

[28] De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphaël JC, Outin H and Bastuji-Garin S; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002; 288: 2859-2867.

[29] Formenti P, Umbrello M, Coppola S, Froio S and Chiumello D. Clinical review: peripheral muscular ultrasound in the ICU. Ann Intensive Care 2019; 9: 57.