Comparison between a standard and a modified early mobilization protocol on oxidative stress and inflammatory parameters in patients with sepsis

Comparação entre um protocolo de mobilização precoce padrão e um modificado sobre estresse oxidativo e parâmetros inflamatórios em pacientes com sepse

Danielle Cristina Alves Oliveira [1]
Fabiane Valentini Francisqueti-Ferron [2]
Marina Melo Coelho [1]
Ana Karla de Loiola Gomes Lima [1]
Gabriela Oliveira [1]
Artur Junio Togneri Ferron [2]
Camila Renata Correa [2]
Carlos Fernando Ronchi [1]

[1] Universidade Federal de Uberlândia (UFU), Uberlândia, MG, Brazil
[2] Universidade Estadual Paulista (Unesp), Botucatu, SP, Brazil

Date of first submission: June 13, 2024
Last received: February 12, 2025
Accepted: April 30, 2025
Associate editor: Ana Paula Cunha Loureiro

***Correspondence:** fernando.ronchi@ufu.br

Abstract

Introduction: Oxidative stress is considered a promoter of negative outcomes, including severe myopathy, especially in critical care patients. Early mobilization is the application of physical activity as early as possible to avoid the deleterious bed rest effects. **Objective:** To evaluate the effect of early mobilization protocol on oxidative stress and inflammatory parameters in patients with sepsis. **Methods:** Prospective study conducted in critical patients divided in control group (CG) and intervention group (IG). Lactate, procalcitonin, Medical Research Council sum score, inflammatory and oxidative stress parameters were obtained before and after protocol. Statistical comparisons among groups for continuous variables were performed using parametric and non-parametric tests. **Results:** EM increased Medical Research Council sum score and reduced lactate (IG: initial 5.40 ± 3.44, final 2.02 ± 0.92; CG: initial 4.64 ± 4.99, final 1.90 ± 0.90, $p > 0.05$); procalcitonin (IG: initial 43.30 ± 39.20, final 8.01 ± 8.13; CG: initial 33.10 ± 33.70, final 14.00 ± 14.80, $p > 0.05$); oxidative stress (protein carbonylation: IG: initial 4.82 ± 1.00, final 3.52 ± 0.82, $p < 0.05$; CG: initial 3.32 ± 0.86, final 2.54 ± 0.49, $p > 0.05$; malondialdehyde: IG: initial 5.57 ± 1.77, final 2.72 ± 1.30, $p < 0.05$; CG: initial 3.84 ± 2.61, final 4.84 ± 2.11, $p > 0.05$); and inflammation (TNF-α IG: initial 6.14 ± 2.28, final 4.85 ± 1.10, $p < 0.05$; CG: initial 7.98 ± 3.37, final 7.08 ± 3.33, $p > 0.05$). **Conclusion:** It is possible to conclude that the modified early mobilization protocol used in this study was effective to reduce oxidative stress and inflammation in sepsis patients.

Keywords: Early mobilization. Physiotherapy. Oxidative stress. Critical care. Sepsis.

Resumo

Introdução: *O estresse oxidativo é considerado um promotor de resultados negativos, incluindo miopatia grave, especialmente em pacientes em tratamento intensivo. Mobilização precoce é a aplicação de atividade física precoce para evitar os efeitos deletérios da imobilidade no leito.* ***Objetivo:*** *Avaliar o efeito do protocolo de mobilização precoce no estresse oxidativo e parâmetros inflamatórios em pacientes com sepse.* ***Métodos:*** *Trata-se de um estudo prospectivo conduzido em pacientes críticos divididos em grupo controle (GC) e grupo intervenção (GI). Lactato, procalcitonina, pontuação de soma do* Medical Research Council*, parâmetros de estresse inflamatório e oxidativo foram obtidos antes e depois da aplicação do protocolo. Comparações estatísticas entre os grupos para variáveis contínuas foram realizadas usando testes paramétricos e não paramétricos.* ***Resultados:*** *A mobilização precoce aumentou o escore do* Medical Research Council *e reduziu o lactato (GI: inicial 5,40 ± 3,44, final 2,02 ± 0,92; GC: inicial 4,64 ± 4,99, final 1,90 ± 0,90, p > 0,05), procalcitonina (GI: inicial 43,30 ± 39,20, final 8,01 ± 8,13; GC: inicial 33,10 ± 33,70, final 14,00 ± 14,80, p > 0,05), estresse oxidativo (carbonilação de proteínas: GI: inicial 4,82 ± 1,00, final 3,52 ± 0,82, p < 0,05; CG: inicial 3,32 ± 0,86, final 2,54 ± 0,49, p > 0,05; malondialdeído: GI: inicial 5,57 ± 1,77, final 2,72 ± 1,30, p < 0,05; CG: inicial 3,84 ± 2,61, final 4,84 ± 2,11, p > 0,05); e inflamação (TNF-α GI: inicial 6,14 ± 2,28, final 4,85 ± 1,10, p < 0,05; CG: inicial 7,98 ± 3,37, final 7,08 ± 3,33, p > 0,05).* ***Conclusão:*** *É possível concluir que o protocolo de mobilização precoce modificado usado neste estudo foi eficaz para reduzir o estresse oxidativo e a inflamação em pacientes com sepse.*

Palavras-chave: *Mobilização precoce. Fisioterapia. Estresse oxidativo. Cuidados intensivos. Sepse.*

Introduction

Sepsis is an organic dysfunction lead by an unregulated response to an injury. It may be characterized by an increase of two points in Sequential Organ Failure Assessment score and is one of the main death causes in severe patients.[1,2]

There are around 15 to 17 million patients with sepsis a year worldwide, which contribute to more than 5 million deaths annually. In Brazil, a study showed an increase in the number of cases of this syndrome in recent years.[3]

Many factors contribute to this trend, such as the increase in population, as well as life expectancy, which rose from 65.3 years in 1990 to 71.5 years in 2013, increasing the susceptible population of people with advanced age, chronic diseases and immunosuppressed people.[3] Recently a meta-analysis reported an estimated mortality rate of 26.7% among sepsis patients.[4] Sepsis has long-term effects that go beyond the acute stage of the disease. Survivors frequently suffer from chronic physical, mental, and cognitive deficits that lower their quality of life and increase their need for medical treatment. Sepsis has a significant financial impact due to the high expenses of acute care, long-term rehabilitation, and lost productivity.[5]

In this context, oxidative stress, resulted from the imbalance between reactive species and antioxidant systems, is considered a greatest promoter of a systemic inflammatory response, biomolecules oxidation, progressive and irreversible mitochondrial failure, energy depletion, hypoxia, leading to negative outcomes, including septic shock and multiple organ dysfunction, as severe myopathy and neuropathy, leading to intensive care unit-acquired weakness (ICU-AW).[6]

ICU-AW is a common condition in sepsis patients and plays an important role in prolonged ICU stays. This condition is characterized by generalized weakness, fatigue, atrophy, and a delay in weaning from mechanical ventilation due to diaphragmatic muscle weakness.[7] Therefore, researchers have been investigating possible interventions to reduce oxidative stress and inflammation in sepsis patients.

An important intervention to reduce ICU-AW is early mobilization (EM), which consists in the application of physical activity as early as the 2nd to 5th day after the onset of critical illness or injury in order to avoid the deleterious effects of bed rest.[8,9] One of the main benefits of EM it is the effectiveness preserving muscle mass, since in just seven days of rest muscle strength is reduced by 10 - 30%, leading to an additional loss of 20% each week. Within this context, EM is a method to preserve muscle strength and mass, improving blood flux, stimulating anti-inflammatory cytokines synthesis, increasing insulin activity and glucose uptake by muscle and, mainly, stimulating the nuclear factor erythroid 2-related factor 2 (NRF2), which acts in antioxidants endogenous synthesis.[10]

The European Respiratory Society and European Society of Intensive Care Medicine establishe a sequence

of basic exercises that are used in most ICUs.[11] However, considering that in healthy people exercises with moderate intensity are able to improve the antioxidant response,[12] it would be interesting to investigate if the increment in the standard protocol would improve oxidative stress and inflammatory parameters also in sepsis patients. It is important to emphasize that to our knowledge there are no studies about the effect of EM on oxidative stress parameters in sepsis patients. Based on this, the hypothesis of this study is that EM protocols are beneficial to reduce oxidative stress and synthesis of proinflammatory cytokines in sepsis patients. Thus, this study aimed to evaluate the effect of a standard and modified EM protocol on oxidative stress and inflammatory parameters in patients with sepsis admitted in ICU.

Methods

This is a prospective study conducted with patients admitted to the Adult Intensive Unit Care of the Clinical Hospital of Uberlandia - Universidade Federal de Uberlândia (HC-UFU). Ethics committee of UFU approved all procedures involving human patients (protocol No. 2.319.451). Written informed consent was obtained from all patients or their responsible.

Patients with 18 years old or more were eligible for enrollment, under mechanical ventilation, sepsis diagnosis with protocol being opened within 48 hours since ICU admission. Exclusion criteria included patients diagnosed with traumatic brain injury, spinal cord injury, hemodynamically unstable and/or with any alteration that prohibit the exercises performance.

Groups

Eighteen patients were included in the study and randomly divided into intervention group (IG), with 8 volunteers, and control group, (CG) with 10 volunteers. Patients were randomly assigned to which group they would be in. Before each attendance, patients were evaluated for heart and respiratory rates, vasoactive drugs used, body temperature, hemodynamic stability, blood pressure, platelet concentration, absence of arrhythmia and peripheral oxygen saturation. Patients had their vital data constantly monitored and no intervention needed to be interrupted by changes in normal values.

Initially, all patients were submitted to an evaluation form containing demographic and hospitalization data, such as age, gender, clinical diagnosis and medications in use. In addition, the initial and final Medical Research Council sum score (MRC-SS) was evaluated. MRC-SS is a strength scale applied bilaterally to six muscle groups of the upper and lower limbs, with the strength rating for each group from 0 (plegia) to 5 (strength normal), resulting in a total score ranging from 0 to 60.[13] Also, lactate and procalcitonin values were collected during the follow-up period, according to tests requested by the department doctors.

CG was submitted to daily assessment and care by the unit's physiotherapists, which included changes in decubitus and position in bed, passive mobilization, active-assisted and free active exercises, training in activities of daily living and mobility, sitting, standing, static gait, transfer from bed to chair and walking. The procedures were carried out for approximately 10 minutes in the morning and afternoon.

Research team attended IG during seven days. The EM protocol applied in IG was developed as follow: 30 minutes of electrical stimulation by Neurodin® III device, which was applied to quadriceps femoris, with a frequency of 40-45 Hz, pulse duration of 400 μs, being 12s on and 6s off, and the intensity necessary for visible muscle contraction, ten minutes of cycle ergometer in the lower limbs and kinesiotherapy for ten minutes. Exercise's progression was improved according to the daily assessment of the patient's condition, starting passively during the sedation period and evolving according to the level of consciousness and muscle strength, including passive, assisted and active exercises, sitting, transference, orthostatism and walking.

The istitution (HC-UFU) uses ILAS-based protocol,[14] where patient is identified and the 3- and 6-hour package is started, which was performed on patients in both groups. All intervention started within 48h after opening this protocol. Blood procedures for lactate and procalcitonin were obtained by ICU routine exams, which were collected from all patients under sepsis investigation following the hospital protocol. Volunteers had 10 ml of venous blood collected for evaluation of inflammatory and oxidative biomarkers before and after protocol intervention. All patients received usual care and no medication was added or removed due to study protocol. Samples were collected on day 1 and day 7 of intervention and stored in biorepositories until analysis.

Plasma protein carbonyl concentration

Carbonylated proteins were measured by an unspecific method that uses DNPH (2,4-dinitrophenylhydrazine derivatizing agent) and photometric detection of any modified protein by carbonylation. Briefly, 100 µl of plasma was mixed with 100 µL DNPH (10 mM in HCl 2M) and incubated for 10 minutes at room temperature. Then, added 50µL of NaOH (6M) and incubated again for 10 minutes. The analysis was performed in 450 nm in a microplate reader Spectra Max 190 (Molecular Devices®, Sunnyvale, CA, USA) and the results obtained by sample absorbance and molar extinction coefficient (22000 M^{-1} cm^{-1}). The final result was expressed in nmol/mg protein.[15]

Plasma malondialdehyde levels

Malondialdehyde (MDA) level was used to evaluate the lipid peroxidation. Briefly, 250 µL of plasma was mixed with 750 µL of 10% trichloroacetic acid for protein precipitation. Samples were centrifuged (3000 rpm; 5 min; Eppendorf Centrifuge 5804-R, Hamburg, Germany) and the supernatant removed. Thiobarbituric acid (TBA) was added 0.67% in ratio (1:1) and the samples heated for 15 min at 100 °C. MDA reacts with TBA in the ratio 1:2 MDA-TBA, absorbed at 535 nm. After cooling, the reading at 535 nm was performed on Spectra Max 190 microplate reader (Molecular Devices, Sunnyvale, CA, USA). The MDA concentration was obtained by the molar extinction coefficient (1.56×10^5 M^{-1} cm^{-1}) and the absorbance of the samples and the final result expressed in nmol/g protein.[16]

Plasma inflammatory markers

Plasma tumoral necrosis factor-alpha (TNF-α) and interleukin-1 (IL^{-1}) were measured using the ELISA (enzyme-linked immunosorbent assay) method, using commercial kits from R&D System, Minneapolis, MN, USA.

Statistical analysis

Data are expressed as mean ± standard deviation or as median (including the lower and upper quartiles). Statistical comparisons between groups for continuous variables were performed using the Student's t-test for parameters with a normal distribution. If data were not normally distributed, comparisons between groups were made using Mann-Whitney U-test. Comparison intra-group between pre- and post-intervention was performed by paired t-test. Correlation among the variables was evaluated by Pearson correla-tion. Data analysis was performed using SigmaStat soft-ware for Windows v3.5 (Systat Software Inc., San Jose, CA, U.S.A.). P-values less than 0.05 were considered sta-tistically significant.

Results

Twenty-two patients were included after opening sepsis protocol. However, two were excluded because they were hemodynamically unstable, one was discharged from ICU during the intervention period, and one had clinical condition worsening. Eighteen patients enrolled and were randomly divided into two groups (IG = 8; CG = 10). All patients finished the protocol, without any complications (Figure 1). Table 1 shows the general characteristics of patients. There was no difference for age and sedation time between the groups.

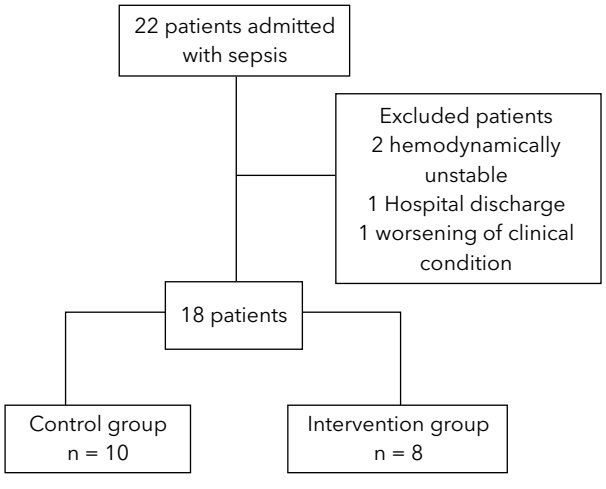

Figure 1 - Flow diagram of studied patients.

Table 2 presents initial and final MRC-SS, lactate, procalcitonin, inflammatory and oxidative stress parameters. Initial MRC-SS was similar in both groups, since patients were under sedation. However, IG showed an increase in MRC-SS and reduction in lactate and procalcitonin. No effects were observed in CG. It is possible to verify that IG presented a reduction in TNF-α, protein carbonylation and MDA levels. Moreover, the levels of MDA in IG were also lower compared to CG final level.

Table 1 - General characteristics of patients

Characteristics	Intervention group (n = 8)	Control group (n = 10)	p-value
Gender (%)			
Male	75.00	60.00	-
Female	25.00	40.00	-
Age - median (range)	55.53 (37.5 – 58.5)	62.51 (36.0 – 71.0)	0.424
Education (%)			
Elementary school incomplete	20.00	33.33	-
Elementary school complete	20.00	16.67	-
High school incomplete	0.00	16.67	-
High school complete	40.00	33.33	-
Higher education complete	20.00	0.00	-
Marital status (%)			
Married	60.00	83.33	-
Single	20.00	16.67	-
Divorced	20.00	0.00	-
Average income (%)			
1 to 3 minimum salaries	100	83.33	-
Above 4 minimum salaries	0.00	16.67	-
Admission diagnosis (%)			
Stab wound	20.00	0.00	-
Pancreatitis	20.00	16.67	-
Acute abdomen	40.00	50.00	-
Cholecystectomy	0.00	33.33	-
Appendicitis	20.00	0.00	-
Need for tracheostomy	20.00	16.67	-
Sepsis type (%)			
Sepsis	0.00	33.33	-
Septic shock	100	66.60	-
Infectious focus (%)			
Pulmonary	20.00	0.00	-
Abdominal	80.00	100	-
Simplified Acute Physiology Score (%)*	72.00 ± 13.00	50.00 ± 33.00	0.337
Intensive care unit (days)*	17.20 ± 9.20	19.66 ± 17.31	0.782
Sedation time (days)*	4.43 ± 2.64	4.00 ± 2.13	0.766
Hospital time (days)*	47.60 ± 29.24	60.50 ± 29.72	0.489
Mechanical ventilation time (days)*	10.40 ± 5.85	10.66 ± 17.47	0.975

Note: *Data presented as mean ± standard deviation.

It is possible to note that modified protocol was effective to increase MRC sum score in IG (Figure 2A). No difference was observed for CG (Figure 2B) and for the final moments among groups (Figure 2C). Pearson correlation is presented in Figure 3. There were correlations among final procalcitonin and final MRC-SS (Figure 3A), final lactate and TNF-α (Figure 3B), final lactate and MDA (Figure 3C), final TNF-α and final MDA (Figure 3D). These results shows that lactate can be a simple marker to indicate inflammation and oxidative stress conditions in sepsis patients. It also demonstrates that reducing procalcitonin is important to improve MRC-SS.

Table 2 - Initial and final MRC-SS, lactate, procalcitonin levels, inflammatory and oxidative stress parameters

	Intervention group (n = 8)	Control group (n = 10)	p-value*
Initial MRC-SS	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.314
Final MRC-SS	36.50 (0.00 – 54.00)	18.50 (0.00 – 44.00)	0.545
p-value**	0.019	0.063	
Inicial lactate (mmol/L)	5.40 ± 3.44	4.64 ± 4.99	0.719
Final lactate (mmol/L)	2.02 ± 0.92	1.90 ± 0.90	0.261
p-value**	0.017	0.127	
Inicial procalcitonin (ng/mL)	43.3 ± 39.2	33.10 ± 37.10	0.397
Final procalcitonin (ng/mL)	8.01 ± 8.13	14.00 ± 14.80	0.448
p-value**	0.024	0.214	
Initial TNF-α (pg/mL)	6.14 ± 2.28	7.98 ± 3.37	0.142
Final TNF-α (pg/mL)	4.84 ± 1.10	7.08 ± 3.33	0.055
p-value**	0.049	0.571	
Inicial IL^{-1} (pg/mL)	3.13 ± 3.64	4.16 ± 3.44	0.213
Final IL^{-1} (pg/mL)	4.87 ± 2.76	3.77 ± 0.62	0.228
p-value**	0.268	0.741	
Inicial PC (nmol/mg protein)	4.82 ± 1.00	3.32 ± 0.86	0.004
Final PC (nmol/mg protein)	3.52 ± 0.82	2.54 ± 0.49	0.007
p-value**	0.048	0.051	
Initial MDA (nmmol/mg protein)	5.57 ± 1.77	3.84 ± 2.61	0.136
Final MDA (nmmol/mg protein)	2.72 ± 1.30	4.84 ± 2.11	0.005
p-value**	0.011	0.183	

Note: *Student t-test for independent samples. **Paired t-test (initial vs final). MRC-SS = Medical Research Council sum score; IL-1 = interleukin-1; TNF-α = tumoral necrosis fator alpha; PC = protein carbonylation; MDA = malondialdehyde.

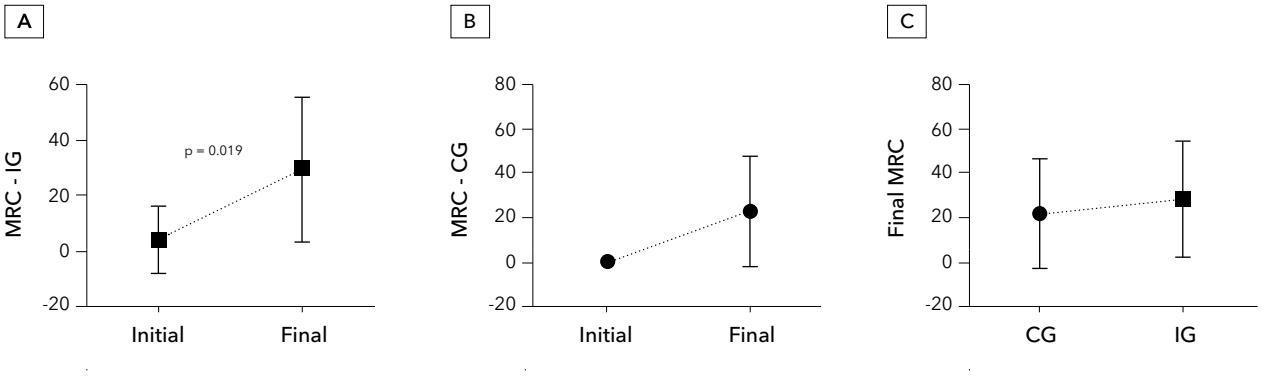

Figure 2 - Medical Research Council (MRC) sum scores (initial and final).

Note: Initial and final moment were compared by paired T test; Comparison between final moments of intervention (IG) and control (CG) groups was performed by Student's t-test; $p < 0.05$ as significant.

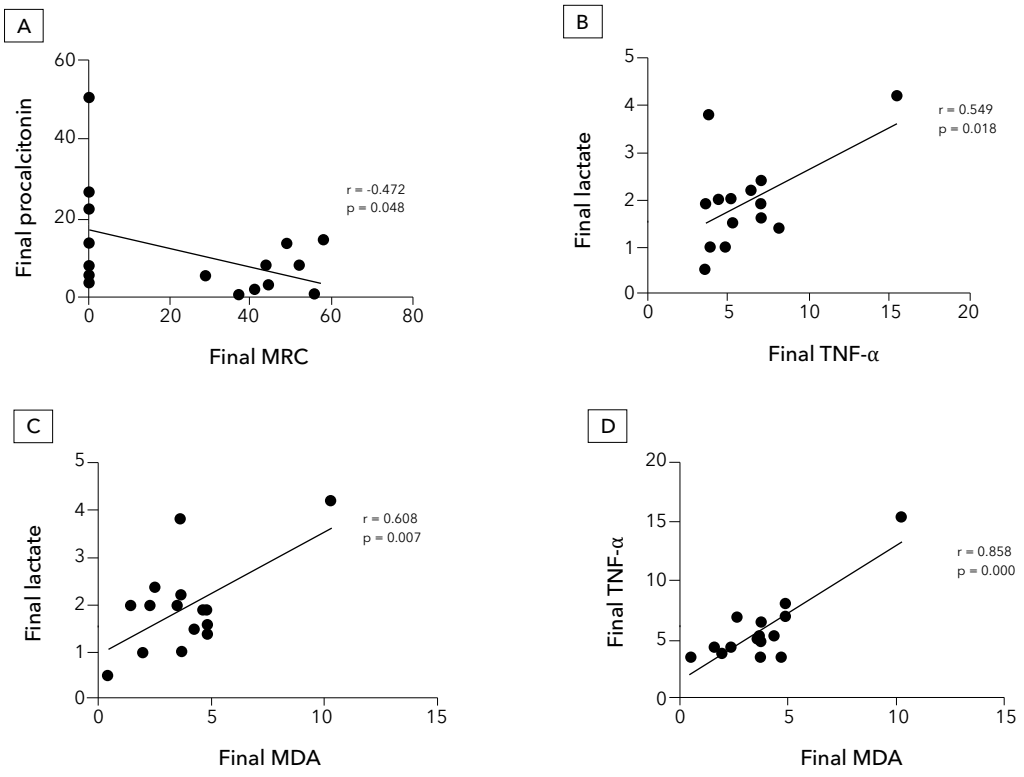

Figure 3 - Pearson correlation among the variables.

Note: MDA = malondialdehyde; MRC = Medical Research Council; TNF-α = tumoral necroses factor alpha.

Discussion

The aim of this study was to evaluate the effect of a standard and modified EM on oxidative stress and inflammatory parameters in patients with sepsis admitted in ICU. According to our results, modified protocol of EM was more effective than the standard to reduce inflammation and oxidative stress in sepsis patients. It is important to emphasize that there is a lack of studies evaluating the effects of EM on oxidative stress and inflammatory parameters.

In healthy adults, skeletal muscles represent about 40–50% of total body mass, being important for several vital physiological functions, including both locomotion and breathing. However, skeletal muscle mass loss on sick patients, as sepsis, is named cachexia and is characterized by progressive muscle mass loss with or without fat mass loss, reducing individual's quality of life, and it is associated with increased morbidity and mortality.[17]

Muscle weakness is a frequent problem in critical ill patients and is known as intensive care unit acquired weakness. Even though different types of diseases can induce cachexia, one important common feature of these conditions is plasma levels alteration of several soluble factors (termed "atrophic factors"), among them: transforming growth factor type beta (TGF-β), myostatin, glucocorticoids, TNF-α, and interleukin 1 and 6 (IL-1 and IL-6). These molecules are able to modulate different mechanisms involved in the loss of mass and function of skeletal muscle, as well as diaphragmatic muscles which is very important in critical patients.[18,19]

Our results shows that the modified EM protocol was effective to reduce TNF-α, which can be a protective factor against cachexia. Some interleukins, such as IL-6, are also an important signaling molecule during exercise, being acutely released from working muscle

fibers with increased exercise duration, intensity, and muscle glycogen depletion, which could explain the acutely increase in IL-1 in IG.[20]

Moreover, reduction in TNF-α level is a promisor result that can avoid some complications common in sepsis patients. There are reports that cytokines, TNF-α and IL-1 are capable of activating target immune cells to produce additional inflammatory mediators, which results in a improving immune responses.[21] During sepsis development, TNF-α can act as a principal inflammatory cascade activator, leading to clinical manifestations, such as disseminated intravascular coagulation, hypotension and organ failure. Thus, TNF-α is considered a potential target for the sepsis treatment.[22]

One of the main stresses of cachexia is the reduction of muscle strength, caused by several mechanisms, including oxidative stress. Oxidative stress is able to cause mitochondrial dysfunction, increase ubiquitin proteasome system activity and myonuclear apoptosis, decreases protein synthesis pathway, and deregulate autophagy, which are conditions involved in cachexia-skeletal muscle atrophy.[19] MDA is result from lipid peroxidation due oxidative stress. It is one of several products formed during the degradation of cellular membrane phospholipids and is one of the toxic species that can disrupt protein structure and function in several organs, including muscle. In particular, oxidative injury to lipids within plasma and mitochondrial membranes can alter permeability and impair membrane-bound receptors and enzymes. Since aldehydes are released into the blood when cells are damaged by lipid peroxidation, serum MDA has been considered as an indirect marker of oxidative stress.[23] Moreover, there are some studies reporting that sepsis patients non-survivors at 30 days showed persistently higher MDA serum levels during the first week than survivors, reflecting a state of lipid hyperoxidation.[24] Lipid peroxidation process accompanied by excess production of MDA has been well documented and reinforce the impression that lipid peroxidation is a harmful event that accompany all cases of systemic inflammation and sepsis. Thus, circulating MDA may be considered a biomarker of worst prognosis. Our results showed that the modified protocol was more effective to reduce the MDA levels, which can be a protector factor in sepsis patients against negative outcomes.

Protein carbonyl groups are early markers of protein oxidative damage. Severe sepsis is associated with early protein oxidation and free oxygen radicals, which may contribute to respiratory muscle failure, and respiratory muscle failure is one of the most important causes of death in patients with sepsis and/or septic shock.[25,26] Moreover, protein oxidation, including protein carbonylation, was demonstrated to modify enzyme activity and DNA binding of transcription factors, while also result in proteolytic degradation.[25] Studies conducted by Costa et al.[27,28] showed that serum protein carbonyl concentrations were higher in patients with septic shock who died during ICU stay[27] and that protein carbonyl, but not malondialdehyde concentration, is associated with ICU mortality in patients with septic shock.[28] Our results show that the modified EM protocol reduced the protein carbonyl levels in sepsis patients. The connection between protein oxidation and protein proteolysis is potentially clinically relevant since the prevention of protein oxidation may reduce proteolysis, which helps to preserve vital physiological functions and accelerate recovery.[26]

Both biomarkers, procalcitonin and lactate, provide diagnostic and prognostic information in ICU sepsis patients, especially when looking at biomarker kinetics.[29] In patients who are susceptible to sepsis, measurement of lactate and procalcitonin levels provide information on the monitoring and severity of the condition and disease progression.[30] Our results show that the modified protocol reduced the levels of both lactate and procalcitonin, indicating an improvement in sepsis conditions. Furthermore, procalcitonin levels were negatively associated with MRC-SS, demonstrating that it can be considered an indirect marker of muscle strength loss.

Muscle weakness and dysfunction were reported in 25% of ICU patients and a major factor influencing both short-term and long-term clinical outcome.[31] The muscular atrophy process begins within 72 hours and may be associated with loss of muscle mass and muscle loss within 10 days after bed rest in healthy individuals and nutritious muscles. Therefore, interventions aiming to improve functional recovery may not only minimize or improve physical function, but may also affect cognitive processes and emotional health.[32] This study showed that the EM protocol increased MRC-SS in these group of sepsis patients, with greater strength increase in those submitted to the protocol. This results might suggest an improvement in oxidative stress and inflammation by early mobilization, as some studies have already shown that these conditions play an important role in muscle atrophy in critical ill patients.[33]

Implementation of EM in critical care is possible in most patients; however, some limitations are a challenge for the multidisciplinary team. In the present study, the most important limitation was the number of patients, not being possible to include a larger number that could express better the findings, as well as improve statistical analysis. However, even with reduced number of patients included in this study, it was possible to see very positive effects when an EM protocol was applied. Therefore, more studies including a larger number of patients are necessarily to confirm the beneficial effects of EM protocols on oxidative stress and inflammatory parameters in sepsis patients.

Conclusion

In summary, this study showed that the modified EM protocol could have had an effect reducing procalcitonin, lactate, inflammation and oxidative stress, and increasing muscle strength in these sepsis patients. From a therapeutic perspective, the development of oxidant state modulators and inflammation, as EM, could be useful for the severe sepsis treatment. Thus, it is possible to conclude that the modified EM protocol used in this study may have positive effects on oxidative stress and inflammation in these sepsis patients.

Acknowledgements

The authors acknowledge the Laboratory of Nanobiotechnology and adult Intensive Care Unit from UFU, as well as Botucatu Medical School Experimental Unit (UNIPEX) staff for their assistance. Any findings, conclusion, recommendations or opinions expressed in this publication are those of the authors and do not necessarily reflect the views of Universidade Estadual Paulista or UFU.

Authors' contributions

DCAO, FVF, AJTF, CRC and CFR contributed to literature search, study design, data collection, analysis of data, manuscript preparation, and review of manuscript. MMC, AKLGL and GO participate in literature search, data collection and review of manuscript.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315(8):801-10. https://doi.org/10.1001/jama.2016.0287

2. Instituto Latino-Americano de Sepse. Sepse: um problema de saúde pública. Brasília: CFM; 2015. 90 p.

3. Lobo SM, Rezende E, Mendes CL, Oliveira MC. Mortality due to sepsis in Brazil in a real scenario: the Brazilian ICUs project. Rev Bras Ter Intensiva. 2019;31(1):1-4. https://doi.org/10.5935/0103-507X.20190008

4. Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med. 2020;46(8):1552-62. https://doi.org/10.1007/s00134-020-06151-x

5. La Via L, Sangiorgio G, Stefani S, Marino A, Nunnari G, Cocuzza S, et al. The Global Burden of Sepsis and Septic Shock. Epidemiologia (Basel). 2024;5(3):456-78. https://doi.org/10.3390/epidemiologia5030032

6. Duran-Bedolla J, Montes de Oca-Sandoval MA, Saldaña-Navor V, Villalobos-Silva JA, Rodriguez MC, Rivas-Arancibia S. Sepsis, mitochondrial failure and multiple organ dysfunction. Clin Invest Med. 2014;37(2):E58-69. https://doi.org/10.25011/cim.v37i2.21087

7. Coelho CW, Jannig PR, Souza AB, Fronza Jr H, Westphal GA, Petronilho F, et al. Exercise training prevents skeletal muscle damage in an experimental sepsis model. Clinics (Sao Paulo). 2013;68(1):107-14. https://doi.org/10.6061/clinics/2013(01)oa17

8. Cameron S, Ball I, Cepinskas G, Choong K, Doherty TJ, Ellis CG, et al. Early mobilization in the critical care unit: A review of adult and pediatric literature. J Crit Care. 2015;30(4):664-72. https://doi.org/10.1016/j.jcrc.2015.03.032

9. Santos F, Mandelli PGB, Ostrowski VR, Tezza R, Dias JS. Relação entre mobilização precoce e tempo de internação em uma unidade de terapia intensiva. Rev Eletr Gestao Saude. 2015;6(2):1394-407. https://periodicos.unb.br/index.php/rgs/article/view/2955

10. França EET, Gomes JPV, Lira JMB, Amaral TCN, Vilaça AF, Paiva Jr MDS, et al. 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(4):e8770. https://doi.org/10.1590/1414-431x20208770

11. Machado AS, Nunes RD, Rezende AAB. Intervenções fisioterapêuticas para mobilizar precocemente os pacientes internados em unidades de terapia intensivas: Estudo de Revisão. Amaz Sci Health. 2016;4(2):41-6. https://www.ojs.unirg.edu.br/index.php/2/article/view/1252

12. Williams NC, Killer SC, Svendsen IS, Jones AW. Immune nutrition and exercise: Narrative review and practical recommendations. Eur J Sport Sci. 2019;19(1):49-61. https://doi.org/10.1080/17461391.2018.1490458

13. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of medical research council sum score and handgrip strength in the intensive care unit. Muscle Nerve. 2012;45(1):18-25. https://doi.org/10.1002/mus.22219

14. Instituto Latino Americano de Sepse. Roteiro de implementação de protocolo assistencial gerenciado de sepse. São Paulo: ILAS; 2019. 39 p.

15. Mesquita CS, Oliveira R, Bento F, Geraldo D, Rodrigues JV, Marcos JC. Simplified 2,4-dinitrophenylhydrazine spectrophotometric assay for quantification of carbonyls in oxidized proteins. Anal Biochem. 2014;458:69-71. https://doi.org/10.1016/j.ab.2014.04.034

16. Samarghandian S, Farkhondeh T, Samini F, Borji A. Protective effects of carvacrol against oxidative stress induced by chronic stress in rat's brain, liver, and kidney. Biochem Res Int. 2016;2016:2645237. https://doi.org/10.1155/2016/2645237

17. Hyatt HW, Powers SK. Mitochondrial dysfunction is a common denominator linking skeletal muscle wasting due to disease, aging, and prolonged inactivity. Antioxidants (Basel). 2021;10(4):588. https://doi.org/10.3390/antiox10040588

18. Barker G, Leeuwenburgh C, Brusko T, Moldawer L, Reddy ST, Guirgis FW. Lipid and lipoprotein dysregulation in sepsis: clinical and mechanistic insights into chronic critical illness. J Clin Med. 2021;10(8):1693. https://doi.org/10.3390/jcm10081693

19. Ábrigo J, Elorza AA, Riedel CA, Vilos C, Simon F, Cabrera D, et al. Role of oxidative stress as key regulator of muscle wasting during cachexia. Oxid Med Cell Longev. 2018;2018:2063179. https://doi.org/10.1155/2018/2063179

20. Nash D, Hughes MG, Butcher L, Aicheler R, Smith P, Cullen T, et al. IL-6 signaling in acute exercise and chronic training: Potential consequences for health and athletic performance. Scand J Med Sci Sports. 2023;33(1):4-19. https://doi.org/10.1111/sms.14241

21. Nedeva C, Menassa J, Puthalakath H. Sepsis: Inflammation is a necessary evil. Front Cell Dev Biol. 2019;7:108. https://doi.org/10.3389/fcell.2019.00108

22. Lv S, Han M, Yi R, Kwon S, Dai C, Wang R. Anti-TNF-α therapy for patients with sepsis: A systematic meta-analysis. Int J Clin Pract. 2014;68(4):520-8. https://doi.org/10.1111/ijcp.12382

23. Weiss SL, Deutschman CS. Elevated malondialdehyde levels in sepsis - something to "stress" about? Crit Care. 2014;18(2):125. https://doi.org/10.1186/cc13786

24. Lorente L, Martín MM, Borreguero-León JM, Solé-Violán J, Ferreres J, Labarta L, et al. Sustained high plasma plasminogen activator inhibitor-1 levels are associated with severity and mortality in septic patients. Thromb Res. 2014;134(1):182-6. https://doi.org/10.1016/j.thromres.2014.04.013

25. Barreiro E. Role of protein carbonylation in skeletal muscle mass loss associated with chronic conditions. Proteomes. 2016;4(2):18. https://doi.org/10.3390/proteomes4020018

26. Abu-Zidan FM, Plank LD, Windsor JA. Proteolysis in severe sepsis is related to oxidation of plasma protein. Eur J Surg. 2002;168(2):119-23. https://doi.org/10.1080/11024150252884359

27. Costa NA, Gut AL, Pimentel JAC, Cozzolino SMF, Azevedo PS, Fernandes AAH, et al. Erythrocyte selenium concentration predicts intensive care unit and hospital mortality in patients with septic shock: A prospective observational study. Crit Care. 2014;18(3):R92. https://doi.org/10.1186/cc13860

28. Costa NA, Gut AL, Azevedo PS, Fernandes AAH, Polegato BF, Cunha NB, et al. Protein carbonyl, but not malondialdehyde, is associated with ICU mortality in patients with septic shock. J Intensive Care Med. 2019;34(8):669-73. https://doi.org/10.1177/0885066617710218

29. Braun N, Schuetz P, Baruti R, Amin D. Procalcitonin or lactate clearance, or both, for risk assessment in patients with sepsis? Results from a prospective US ICU patient cohort. Crit Care. 2015;19(Suppl 1):P59. https://doi.org/10.1186/cc14139

30. Sofijanova A, Bojadzieva S, Shuperliska E, Jordanova O. Is procalcitonin and lactate a early markers for sepsis in newborns in the ICU. Health Sci J. 2020;14(6):768. https://tinyurl.com/3ta9k3ef

31. Connolly BA, Jones GD, Curtis AA, Murphy PB, Douiri A, Hopkinson NS, et al. Clinical predictive value of manual muscle strength testing during critical illness: An observational cohort study. Crit Care. 2013;17(5):R229. https://doi.org/10.1186/cc13052

32. Seo B, Shin WS. Effects of functional training on strength, function level, and quality of life of persons in intensive care units. Phys Ther Rehabil Sci. 2019;8:134-40. https://doi.org/10.14474/ptrs.2019.8.3.134

33. Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. Int J Mol Sci. 2010;11(4):1509-26. https://doi.org/10.3390/ijms11041509

Data Availability Statement

Research data is not available.