PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:
CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

Tese de Doutorado

EFEITOS DA MOBILIZAÇÃO PRECOCE NA MORFOLOGIA MUSCULAR DE PACIENTES CRÍTICOS EM VENTILAÇÃO MECÂNICA INVASIVA NA UNIDADE DE TERAPIA INTENSIVA

Laura Jurema dos Santos

Porto Alegre

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UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

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A Deus, por guiar meus passos.

Aos meus pais, por sempre me apoiarem em todos os momentos da minha vida.

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“Human felicity is produced not as much by great pieces of good fortune that seldom happen, as by little advantages that occur every day”

Benjamin Franklin

SUMÁRIO

LISTA DE ABREVIATURAS

Body mass index (BMI)
Chronic obstructive pulmonary disease (COPD)
Conventional Group (CG)
Estimulação Elétrica Neuromuscular (EENM)
Extracorporeal Membrane Oxygenation (ECMO)
Free and informed consent form (FICF)
Functional Electrical Stimulation (FES)
Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS)
Fundo de Incentivo à Pesquisa e Eventos (FIPE)
Hospital de Clínicas de Porto Alegre (HCPA)
Intensive care unit (ICU)
Intervention Group (IG)
Invasive mechanical ventilation (IMV)
Length of fascicle (FL)
Mechanical ventilation (MV)
Medical Research Council (MRC)
Nosocomial Infection Control Committee (NICC)
Pennation angle of fascicles (PA)
Revolutions per Minute (RPM)
Systolic Blood Pressure (SBP)
Thickness of vastus lateralis muscle (VLMT)
Universidade Federal do Rio Grande do Sul (UFRGS)

1. INTRODUÇÃO

Pacientes na Unidade de Terapia Intensiva (UTI) estão expostos à imobilização prolongada, o que gera perda de massa muscular.[1] A redução de tecido contrátil, por sua vez, tem forte associação com o comprometimento da capacidade de produção de força.[2] Segundo Sibinelli e cols.[3], o sistema musculoesquelético é projetado para se manter em movimento, sendo que são necessários apenas 7 dias de repouso no leito para reduzir a força muscular em 30%, levando à perda adicional de 20% da força restante a cada semana. Em média, 46% dos pacientes internados na UTI, que foram expostos a fatores de risco para fraqueza muscular, desenvolvem tal complicação.[4] Nos casos de sepse, essa taxa de incidência pode variar entre 70% e 100%.[1]

Diversas intervenções com mobilização progressiva têm sido recomendadas como abordagem para minimizar a fraqueza muscular após um quadro crítico.[5] A mobilização é uma forma de preservar a força e a massa muscular, melhorando o fluxo sanguíneo, estimulando a produção de citocinas anti-inflamatórias e aumentando a atividade da insulina e captação de glicose no músculo.[6]

Um dos recursos que vem apresentando grande utilidade em hospitais é o cicloergômetro, que é um aparelho estacionário que promove rotações cíclicas em membros inferiores e/ou superiores e pode ser utilizado para realizar exercícios passivos, ativos e resistidos.[7] Um estudo da década de 90 com indivíduos saudáveis demonstrou que o exercício com cicloergômetro preserva a espessura do músculo anterior da coxa durante a imobilização prolongada.[8] Posteriormente, este recurso mostrou-se viável para pacientes sedados, imobilizados, com doença crítica severa no qual mesmo o movimento passivo pôde desempenhar um papel na preservação da arquitetura muscular.[9] Apesar dos seus potenciais benefícios, a avaliação rigorosa e o uso do cicloergômetro como terapia de reabilitação para pacientes internados têm sido limitados.[7]

Este é o primeiro estudo controlado randomizado que avaliou a hipótese de que a mobilização precoce com cicloergômetro passivo preserva a

morfologia dos extensores de joelho de pacientes sob ventilação mecânica (VM) internados na UTI. Esperamos que por meio de mobilização passiva um estresse mecânico no tecido contrátil fosse gerado e houvesse, consequentemente, a manutenção na excursão e espessura muscular do quadríceps. Isto porque tais pacientes encontram-se em grande fragilidade tecidual e que, mesmo um estímulo tensional ao invés de uma contração, fosse capaz de preservar o tecido.

2. REVISÃO DA LITERATURA

2.1 Fraqueza Muscular Adquirida na UTI

Fraqueza muscular adquirida na UTI é definida como uma fraqueza clinicamente detectável na qual nenhuma etiologia plausível, além da doença crítica, pode ser reconhecida.[10] Está associada ao desmame prolongado, à reabilitação tardia, ao aumento do tempo de internação e à mortalidade,[11-16] com déficits na capacidade física e funcional que persistem até 5 anos após a admissão na UTI.[17] Sua ocorrência varia substancialmente dependendo do caso do paciente e do método de diagnóstico utilizado.[10] De Jonghe e cols.[13] encontraram um taxa de 25% de fraqueza muscular adquirida na UTI nos pacientes que receberam ventilação mecânica por pelo menos sete dias. Estudos com pacientes sépticos e falência de múltiplos órgãos evidenciaram incidências que variam de 70% até 100%.[1,18]

Os fatores de risco incluem resposta inflamatória sistêmica e sepse, medicações como corticosteroides e agentes bloqueadores neuromusculares, controle glicêmico inadequado, imobilismo, hipoalbuminemia, disfunção orgânica severa e disordens eletrolíticas.[19,20] O progresso técnico e científico da terapia intensiva tem aumentado consideravelmente a sobrevivência do paciente crítico, proporcionando aumento no tempo de exposição a fatores etiológicos para fraqueza neuromuscular com impacto direto na funcionalidade e qualidade de vida após a alta hospitalar.[21,22] Miopatia e polineuropatia do doente crítico são doenças neuromusculares que se desenvolvem após a sua admissão e resultam em fraqueza adquirida na UTI, com efeitos adversos tanto em resultados a curto como a longo prazo, incluindo retardo no desmame da

ventilação mecânica, aumento no tempo de permanência na UTI e no hospital, aumento da mortalidade e incapacidade a longo prazo.[23]

2.2 Perda de massa muscular na UTI

A associação da VM prolongada com os efeitos do imobilismo resulta em perda das fibras musculares, acarretando significativa redução da força muscular respiratória e periférica.[13] Assim, o tempo de imobilidade será determinante na gravidade da disfunção contrátil pelas mudanças nas propriedades intrínsecas das fibras musculares.[15]

Durante o tratamento na UTI, uma grande parte dos pacientes críticos internados em VM desenvolvem perda de massa muscular grave e fraqueza dos músculos dos membros devido ao desenvolvimento de miopatia, neuropatia ou uma combinação de ambos.[24] Em estudo com pacientes graves publicado no JAMA recentemente, Puthucheary e cols.[25] concluíram que a perda de massa muscular ocorreu rápida e precocemente durante a primeira semana de internação na UTI e foi mais grave entre aqueles com falência de múltiplos órgãos em comparação com a falha de um único órgão.

Dentre as alterações decorrentes da estada na UTI e do uso de VM, a perda de massa muscular é um dos problemas mais comuns com os quais pacientes são confrontados.[26] Um estudo recente[27] descobriu por meio de ultrassom que a perda de massa muscular nestes pacientes é consideravelmente maior do que em todas as outras populações de pacientes, especialmente nas primeiras 2 a 3 semanas.[28-30]

2.3 Avaliação do Paciente Crítico

O *Medical Research Council* (MRC), escore usado na avaliação da força muscular periférica, consiste em seis movimentos avaliados bilateralmente, com grau de força muscular para cada movimento entre 0 (paralisia total) e 5 (força muscular normal), sendo que a pontuação total varia de 0 (tetrapareia completa) a 60 (força muscular normal).[31] Para os pacientes cooperativos, o MRC demonstra-se bastante reprodutível e com alto valor preditivo em vários estudos sobre disfunção neuromuscular no paciente crítico.[32,33] É o mais

conhecido e utilizado sistema de classificação de força muscular em todo o mundo, contudo a dinamometria também vem ganhando espaço no ambiente da terapia intensiva com objetivo de avaliar a força de contração voluntária máxima à beira do leito.[34]

O reconhecimento e o diagnóstico da disfunção neuromuscular adquirida na UTI podem ser difíceis em pacientes sob ventilação mecânica quando estes estão sedados e inábeis para cooperar com os testes de avaliação.[35] A fraqueza muscular apresenta-se de forma difusa e simétrica, acometendo a musculatura esquelética periférica e respiratória, com variável envolvimento dos reflexos tendinosos profundos e da inervação sensorial.[35] No entanto, distinguir fraqueza muscular verdadeira de falta de motivação ou incapacidade de completar uma tarefa é um desafio, e o uso de testes de força muscular nos primeiros estágios da doença crítica torna-se limitado.[36,37] Métodos volitivos para mensuração da força muscular, enquanto clinicamente atraentes, estão restritos a pacientes alertas, acordados e com cognitivo preservado para serem capazes de produzir esforços máximos.[38]

Mais recentemente, o ultrassom vem demonstrando grande utilidade clínica para avaliar a mudança na arquitetura dos músculos esqueléticos periféricos durante a doença crítica, no entanto a técnica ainda necessita de padronização de protocolos no ambiente da terapia intensiva.[24] A atenção recente tem incidido sobre a utilidade do ultrassom para acompanhar a trajetória de perda de massa muscular em pacientes criticamente enfermos.[39] A estratificação de risco dos pacientes com perda de massa muscular periférica é vital para otimizar a manejo clínico, incluindo a implementação da cinesioterapia, reabilitação e outras intervenções terapêuticas.[40]

Os princípios da técnica do ultrassom neuromuscular foram descritos anteriormente,[41,42] com diferenças ultrassonográficas evidentes entre músculo esquelético saudável e doente[43,44] e um número de características da arquitetura do músculo esquelético periférico incluindo a área da secção transversa, o ângulo de penação, a espessura muscular e a ecogenicidade.[45] Além disso, o ultrassom tem vantagens pragmáticas e clínicas: é amplamente disponível nas UTIs, portátil, simples e rápido de executar.[24] Também é

independente de esforço, livre de radiação ionizante, pode ser realizado à beira do leito e, com treinamento, pode ser implementado por profissionais não especializados.[24]

Atualmente, não existe um padrão-ouro para a mensuração da arquitetura dos músculos esqueléticos periféricos usando o ultrassom. São necessários mais estudos para determinar a uniformidade da aplicação técnica. Os estudos apresentam detalhes mínimos sobre a marca e modelo do equipamento, especificação da sonda, configurações de aquisição de imagem e descrição precisa da posição do paciente e localização do músculo para a avaliação. Sendo assim, o ultrassom está ganhando espaço como ferramenta para avaliar alterações na arquitetura dos músculos esqueléticos periféricos durante a doença crítica. Padronização de protocolos detalhados irão melhorar a validade externa para a realização de estudos futuros e permitir uma futura metanálise e investigação de fatores associados com alteração da arquitetura dos músculos esqueléticos periféricos durante a doença crítica.

2.4 Mobilização Precoce do Paciente Crítico

A mobilização precoce em pacientes críticos tem um forte precedente histórico, existindo relatos de sua utilização como um recurso terapêutico no restabelecimento funcional de soldados feridos em batalhas durante a II Guerra Mundial.[46] Posteriormente, a sedação profunda e o repouso no leito foram práticas comuns na rotina de cuidados para a maioria dos pacientes ventilados mecanicamente.[46] Já, na literatura atual, há uma nova tendência no manejo do paciente em VM incluindo redução da sedação profunda e ampliação da abordagem de mobilização e do treinamento físico-funcional o mais precoce possível nestes pacientes.[47]

Apesar da mobilização precoce no paciente crítico não ser algo recente, seus resultados mais robustos começaram a surgir por volta do ano de 2007. O estudo de Bailey e cols.[48] teve como protocolo o posicionamento de sentar na cama e na cadeira associado à deambulação e observou que essa rotina mostrou-se segura em pacientes sob VM, proporcionando melhora no *status* funcional e prevenção de complicações neuromusculares. Este foi um dos

primeiros estudos que conseguiu correlacionar mobilização precoce com redução de mortalidade na UTI.[48] No entanto, cabe salientar que o desenho do estudo foi mais adequado para responder a hipótese sobre a segurança e viabilidade do que redução na mortalidade (para isso seria necessário um ensaio clínico randomizado).

Desde então, a mobilização precoce vem sendo parte do processo de reabilitação de pacientes críticos, cada vez mais defendida na prevenção e tratamento da fraqueza muscular adquirida na UTI e comprometimentos relacionados à funcionalidade.[49-51] Os primeiros programas estruturados de reabilitação têm demonstrado a redução da permanência na UTI e no hospital,[52-54] bem como melhora da capacidade funcional no momento da alta hospitalar, com níveis mais elevados de mobilização alcançados quando a reabilitação é liderada por fisioterapeutas em comparação com enfermeiros.[55] Mobilização precoce e estruturada também tem sido associada com menor incidência de *delirium*,[55] incremento de parâmetros respiratórios e de força muscular periférica em comparação com os pacientes que não recebem fisioterapia.[52] Não há um consenso descrevendo o nível de mobilidade para os pacientes em terapia intensiva que pode ser utilizado à beira do leito de uma maneira rápida, fácil e confiável.[56,57] Uma série de estudos têm demonstrado que a fisioterapia precoce na UTI reduz custos, permanência na UTI e no hospital e melhora a qualidade de vida do paciente crítico.[53-55,58]

Publicado no Lancet em 2009, o estudo dos autores Schweickert e cols.[55] é contemporâneo ao estudo com cicloergômetro passivo publicado pelo grupo de Gosselink.[58] A diferença é que este estudo se propôs a verificar se a fisioterapia convencional (mobilização passiva, ativo-assistida, ativo-resistida, sentar e caminhar) seria eficaz, já que Gosselink e cols. haviam obtido bons resultados com um equipamento (cicloergômetro). Este estudo apresentou um adequado delineamento e desfechos interessantes, sem tecnologias, mostrando que a Fisioterapia utilizando apenas técnicas convencionais é capaz de obter resultados favoráveis.

De acordo com Stiller,[59] a intervenção fisioterapêutica que compreende a mobilização precoce é benéfica para pacientes de UTI adulto, tendo efeito

positivo sobre a capacidade funcional, podendo também reduzir a permanência na UTI e no hospital, devendo ser implementada como prioridade em todas as UTIs. Os resultados do estudo recente de McWilliams e cols.[60] demonstram como a criação de um protocolo pode melhorar a assistência aos pacientes. Além disso, faz-nos refletir que a maioria das UTIs brasileiras estão a frente dos países de 1º mundo, já que atualmente a presença de Fisioterapeutas aqui é de, no mínimo, 18 horas, diariamente. Temos, portanto, que incorporar a cultura da mobilização no nosso cotidiano e seguir o exemplo deste estudo, focando na qualidade da assistência.

A força tarefa da *European Respiratory Society and European Society of Intensive Care Medicine* estabeleceu uma hierarquia de atividades de mobilização na UTI, baseada numa sequência de intensidade do exercício: mudança de decúbitos e posicionamento funcional, mobilização passiva, exercícios ativo-assistidos e ativos, uso de cicloergômetro na cama, sentar na borda da cama, ortostatismo, caminhada estática, transferência da cama para poltrona, exercícios na poltrona e caminhada.[51] Recomenda, ainda, que o fisioterapeuta deve ser o profissional responsável pela implantação e gerenciamento do plano de mobilização.[51]

Tais atividades são demonstradas como seguras e viáveis, devendo ser iniciadas o mais precocemente possível, ou seja, logo após a estabilização dos maiores desarranjos fisiológicos como as situações de choque não controlado. Uma equipe bem treinada e motivada é fundamental para realizar estas atividades com segurança e eficiência.[46,47,51]

A monitorização durante e após o exercício é mandatória e recomenda-se a avaliação das variáveis cardiovasculares (frequência cardíaca e pressão arterial) e respiratórias (padrão muscular ventilatório do paciente e sincronia do paciente com o ventilador quando em VM, saturação periférica de oxigênio e freqüência respiratória), além de observar o nível de consciência e verificar as dosagens de sedativos e drogas vasoativas.[47,61] Pacientes com instabilidade hemodinâmica, que necessitam de altas frações inspiradas de oxigênio e altos níveis de suporte ventilatório, não são recomendados para atividades de mobilização mais agressivas.[46,51,61]

Sabe-se que o *status* fisiológico do paciente crítico pode flutuar consideravelmente ao longo do dia.[62] Além disso, administração de sedação, sessões intermitentes de hemodiálise e avaliações e preparações para desmame da VM podem dificultar a realização dos exercícios físicos, o que exige a elaboração de um planejamento individualizado e com maior flexibilidade possível, baseando-se no *status* fisiológico que o paciente apresenta na hora da atividade.[62] O conhecimento da reserva funcional cardiorrespiratória, neurológica, músculoesquelética e a independência funcional prévia do paciente a internação na UTI são essenciais para potencializar a eficácia do treinamento físico que não deve ter intensidade nem abaixo, nem acima dos limiares do paciente, oferecendo segurança ao procedimento.[63,64]

Um estudo de caso publicado no *American Journal of Critical Care* em 2014 sugere que pacientes submetidos à terapia de substituição renal contínua podem ser mobilizados de forma segura e, portanto, não devem ser automaticamente excluídos dos programas de mobilização.[65] Da mesma forma, fisioterapia ativa, incluindo deambulação, pode ser alcançada de forma segura e confiável também em pacientes com *Extracorporeal Membrane Oxygenation* (ECMO) quando houver uma equipe multidisciplinar experiente.[66] Tais achados demonstram o quanto a mobilização precoce pode ser segura e viável, podendo ser iniciada em menos de 72 horas do início da VM, no entanto sabe-se que ainda se faz necessária a educação da equipe destacando-se indicações, contraindicações, cuidados, entre outros.

Estratégias que visam minimizar imobilização prolongada durante a doença crítica podem prevenir o desenvolvimento de complicações neuromusculares.[67] A introdução de tecnologias relacionadas com a reabilitação, como estimulação elétrica neuromuscular (EENM) e cicloergômetro, vem ganhando destaque para manter/melhorar a massa e força muscular, bem como a funcionalidade em pacientes de UTI.[67] Estes recursos podem ser utilizados desde a fase aguda da doença crítica, quando a sedação e imobilização podem limitar a capacidade dos pacientes de participar em

intervenções ativas.[67] No entanto, a aplicação dessas tecnologias na UTI requer ainda uma avaliação mais aprofundada para confirmar a eficácia.[67]

Estimulação Elétrica Neuromuscular

Em pacientes incapazes de realizar contração muscular voluntária como nos pacientes críticos em fase aguda, a EENM é um recurso frequentemente utilizado por fisioterapeutas para melhora da função muscular através da estimulação de baixa voltagem de nervos motores periféricos, proporcionando contração muscular passiva e aumento da capacidade muscular oxidativa, podendo representar uma alternativa de treinamento físico mais suave.[32,68,69] A aplicação desta técnica tem sido consistentemente associada com aumento de massa, força e endurance muscular em uma grande gama de situações clínicas que apresentam fraqueza muscular por desuso e inervação muscular anormal.[70,71] Quando combinada com o programa de exercícios físicos, melhora significativamente a força muscular comparada com o uso do programa de exercícios isoladamente.[72,73] A melhor forma de EENM de acordo com a corrente utilizada e a demonstração de estudos morfológicos, correlacionando a melhora na tolerância ao exercício com as mudanças musculares após a EENM em comparação com o exercício convencional, precisa ser determinada no paciente crítico, particularmente naqueles que evoluem com doença neuromuscular do doente crítico.[74]

Uma revisão sistemática realizada em 2013 investigou os efeitos da EENM na prevenção de fraqueza muscular adquirida na UTI forneceu evidências de que a adição de terapia com EENM ao tratamento convencional é mais eficaz do que se ambos forem realizados independentemente. No entanto, os autores ressaltam que há provas inconclusivas sobre a eficácia da EENM para a preservação da massa muscular em pacientes de UTI.[75] Em uma segunda revisão publicada no mesmo ano observou-se que a EENM parece preservar a massa muscular e força nos participantes de longa permanência na UTI e naqueles com menor acuidade. No entanto, nenhum desses benefícios foram observados quando a eletroestimulação começou antes de sete dias de

internação ou em pacientes com maior acuidade, concluindo que a eletroestimulação é uma intervenção promissora, porém há evidências conflitantes para a sua eficácia quando administrada de forma aguda, ressaltando que os resultados medidos são heterogêneos com amostras de pequenas dimensões.[76] Uma terceira revisão sistemática publicada recentemente concluiu que a EENM pode gerar bons resultados quando usada para preservar a massa muscular e força de pacientes críticos na UTI, sendo reforçada por uma pequena metanálise apresentada.[77]

Cicloergômetro

O efeito positivo da carga passiva na função da fibra muscular apóia fortemente a importância da fisioterapia precoce e mobilização em pacientes de UTI profundamente sedados e sob ventilação mecânica.[78] O estudo com cicloergômetro de Burtin e cols.[58] concluiu que treinamento com exercícios precoces promove um incremento na capacidade funcional, funcionalidade e força muscular no momento da alta hospitalar. Em um estudo clínico com 5 pacientes, Griffiths e cols.[9] observaram que três horas de mobilização passiva contínua de forma diária, através de cicloergômetro apropriado para realização deste tipo de mobilização, reduziu a atrofia de fibras e perda de proteínas quando comparado com o alongamento passivo por cinco minutos duas vezes ao dia. Em estudo recente, a mobilização precoce com cicloergômetro em pacientes críticos sedados e em ventilação mecânica foi considerada segura e não foi associada a alterações hemodinâmicas, respiratórias e metabólicas significativas, mesmo naqueles com agentes vasoativos.[7] No entanto, ainda não foi investigado se o cicloergômetro passivo tem efeito positivo na morfologia muscular de pacientes críticos.

Futuramente contaremos com os resultados do estudo EARTH-ICU (*ClinicalTrials.gov Identifier: NCT01787045*) que tem como base a *Cliniques Universitaires Saint-Luc - Université Catholique de Louvain,* sob coordenação do Professor Pierre-François Laterre na Bélgica. A pesquisa tem como objetivo verificar as alterações metabólicas musculares em pacientes com

sepse/choque séptico/Disfunção Múltipla de Órgãos e Sistemas, submetidos a um protocolo de mobilização precoce.

Diante do exposto nesta revisão da literatura, o MoVe-ICU Group se propôs a investigar os efeitos da mobilização precoce na morfologia muscular de pacientes críticos em ventilação mecânica. Nesse sentido, foram desenvolvidos dois projetos de pesquisa com os seguintes objetivos: (1) analisar os efeitos do cicloergômetro passivo na morfologia do quadríceps e do diafragma e, (2) analisar os efeitos da estimulação elétrica neuromuscular na morfologia do abdominal e peitoral de pacientes críticos em ventilação mecânica. Os protocolos e seus resultados seguem ao longo desta tese de doutorado.

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4. HIPÓTESE

✓ O uso do cicloergômetro passivo preserva a espessura e arquitetura do quadríceps durante o período que o paciente encontra-se em ventilação mecânica invasiva na UTI

5. OBJETIVOS

Geral

Avaliar e comparar os efeitos do cicloergômetro passivo na morfologia do quadríceps femoral de pacientes críticos em ventilação mecânica invasiva na Unidade de Terapia Intensiva.

Específicos

- Avaliar e comparar os efeitos do cicloergômetro passivo e da fisioterapia convencional na espessura muscular transversal do quadríceps de pacientes críticos em ventilação mecânica invasiva na Unidade de Terapia Intensiva
- Avaliar e comparar os efeitos do cicloergômetro passivo e da fisioterapia convencional na arquitetura muscular do vasto lateral de pacientes críticos em ventilação mecânica invasiva na Unidade de Terapia Intensiva
- Avaliar e comparar os efeitos do cicloergômetro passivo e da fisioterapia convencional no tempo de internação na UTI, no hospital e em ventilação mecânica, bem como quanto a taxa de sucesso na extubação e mortalidade
- Avaliar e comparar os efeitos do cicloergômetro passivo e da fisioterapia convencional nos parâmetros musculares entre pacientes sépticos e não sépticos

Outros

- Avaliar e comparar os efeitos do cicloergômetro passivo e da fisioterapia convencional sobre a mobilidade

diafragmática de pacientes críticos em ventilação mecânica invasiva na Unidade de Terapia Intensiva

- Avaliar e comparar os efeitos da EENM associada a fisioterapia convencional sobre a espessura muscular do reto do abdomem e peitoral comparada a EENM placebo associada a fisioterapia convencional de pacientes submetidos à ventilação mecânica invasiva

ARTIGO I

Early mobilization with a passive cycle ergometer for critical patients on invasive mechanical ventilation in the Intensive Care Unit (MoVe-ICU study): study protocol for a randomized controlled trial

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ABSTRACT

Background: Patients in Intensive Care Units (ICU) are often exposed to prolonged immobilization which, in turn, plays an important role in neuromuscular complications. Exercise with a cycle ergometer is a treatment option that can be used to improve the mobility of patients on invasive mechanical ventilation (IMV), in order to minimize the harmful effects of immobility.

Methods/Design: A single blind randomized controlled trial (the MoVe ICU study) will be conducted to evaluate the effects on the muscle morphology of the knee extensors and diaphragm in critical patients on IMV of early mobilization with a cycle ergometer. A total of 32 patients (age > 18 years) will be recruited for this study from among those admitted to the intensive care department at the Hospital de Clínicas de Porto Alegre. Eligible patients will have been on IMV for at least 24 to 48 hours, will have spent maximum of 1 week in hospital and will not exhibit any characteristics restricting lower extremity mobility. These subjects will be randomized to receive either conventional physiotherapy or conventional physiotherapy with an additional cycle ergometer intervention. The intervention will be administered passively for 20 minutes, at 20 revolutions per minute (rpm), once per day, throughout the time the patients remain on IMV. Outcomes will be cross-sectional quadriceps thickness, length of fascicle, pennation angle of fascicles, thickness of vastus lateralis muscle, diaphragm thickness and excursion of critical ICU patients on IMV measured with ultrasound, baseline and after seven days of protocol.

Discussion: The MoVe ICU study will be the first randomized controlled trial to test the hypothesis that early mobilization with a cycle ergometer can preserve the morphology of knee extensors in critical patients on IMV in ICUs.

Trial registration: NCT02300662

Keywords: intensive care, early ambulation, clinical trial

BACKGROUND

Patients in Intensive Care Units (ICU) are often exposed to prolonged immobilization, which can play an important role in neuromuscular complications.[1,2] Bed rest results in skeletal muscle weakness, progressing to muscle atrophy and losses of 3-11% of muscle mass during the first 3 weeks of immobility.[3] This loss of muscle mass and muscle weakness, in turn, are the result of acquired myopathy, polyneuropathy or a combination of the two.[4] The prevalence of acquired polyneuropathy among patients in intensive care settings is in the range of 58% to 96%.[5] Notwithstanding, recent evidence suggests that muscle weakness can be present within hours of starting invasive mechanical ventilation (IMV) and is evident in 25-100% of patients ventilated for more than 7 days.[6] Among these patients, muscle weakness is associated with increased length of hospital stay and higher mortality and with impaired functional status that can still be detected years after hospital discharge, compromising patients' quality of life.[7,8]

The combination of prolonged mechanical ventilation (MV) and the effects of immobility causes significant changes to muscle fibres, reducing both respiratory and peripheral muscle strength.[9] While this muscle weakness has multifactorial aetiology, early mobilization of patients in ICUs can help to keep the atrophy, loss of muscle mass and loss of physical conditioning associated with bed rest to a minimum.[2] One resource that has proved to be of great utility in hospitals is the cycle ergometer, which is a stationary piece of equipment designed to enable cyclical rotations of lower and/or upper extremities and can be used to perform passive, active and resisted exercises.[10]

Treatment with the cycle ergometer has been shown to improve quadriceps strength, functional status and 6-minute walking results at hospital discharge. Although this therapy is widely used in outpatient settings with the objective of improving rehabilitation of patients with chronic pulmonary disease, few studies have assessed its effects in hospital settings, particularly in ICUs.[11-13]

This article provides a detailed description of the background, target population and methodology of the MoVe ICU study, an RCT investigating the effects of early mobilization of critical care patients on IMV using the cycle ergometer.

METHODS/DESIGN

Study objectives

The primary objective of this study will be to evaluate the effects of early mobilization of critical care patients on invasive mechanical ventilation using the cycle ergometer. Secondary objectives will be to analyze and compare the effects of cycle ergometer therapy on length of fascicle, pennation angle of fascicles, thickness of vastus lateralis muscle, diaphragm thickness and excursion, time on mechanical ventilation, extubation success and length of stay in the ICU and hospital across conventional and intervention groups.

Study design and setting

This is a single blind RCT that will be conducted by the intensive care and physiotherapy departments at the Hospital de Clínicas de Porto Alegre (HCPA) - Universidade Federal do Rio Grande do Sul (UFRGS). Patients will be allocated at random either to receive conventional physiotherapy or the cycle ergometer intervention in addition to conventional physiotherapy. Randomization will be accomplished using the www.randomization.com website.

This study is financed by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) research funding agency and will be conducted in accordance with the principles laid out in the Helsinki Declaration and with Good Clinical Practices. Procedures will be in accordance with National Health Council (Conselho Nacional de Saúde) Resolution number 466/12 . The HCPA Ethics Committee has approved the study (CEP HCPA n° 10-0530) and informed consent will be obtained in writing from all patients who take part.

Study population

Patients of both sexes aged ≥ 18 years will be recruited from among those admitted to the HCPA intensive care unit and put on invasive mechanical ventilation IMV for at least 24 to 48 hours after transfer from the emergency department or wards, no more than 1 week after admission. Exclusion criteria will include neuromuscular diseases causing motor deficits, such as strokes, multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis and Guillain Barré syndrome. Patients will also be excluded in the event of the following: extubation less than 48 hours after enrolment on the study; haemodynamic instability (noradrenaline > 0.5 mc/kg/min for arterial blood pressure > 60 mmHg); complications during the protocol such as pneumothorax, deep vein thrombosis or pulmonary embolism; Shilley catheter in the femoral vein; reintubation; delayed weaning (3 failed spontaneous ventilation tests); body mass index (BMI) > 35 kg/m^2; or emergence of eschar in the calcaneus area during the protocol.

Recruitment and informed consent

The sample will be selected by one investigator who will conduct a search once a day for eligible individuals using the HCPA's computerized system. The electronic patient records will then be used to provide data on identification, medical diagnosis and current clinical conditions, to check for compatibility with the inclusion criteria. When a patient is selected, the person responsible for them will be invited to sign a Free and Informed Consent Form (FICF).

Baseline assessment and follow up measurements

Ultrasonography

After 24 to 48 hours on IMV and once study enrolment is complete, each participant will undergo an ultrasonographic assessment during which knee extensor morphology and thickness and excursion of the diaphragm muscle will be assessed.

Ultrasonography will be conducted on the first day of enrolment and within 24 hours of extubation by a previously trained researcher blinded to the outcome.

Measurement of muscle thicknesses

For measurement of muscle thickness using ultrasound, subjects will be positioned lying down in decubitus dorsal and a 7.5 MHz linear array ultrasound probe (SONOSITE) will be used to conduct analyses in B mode. The probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin.[14]

Criteria for probe placement: Initially, marks will be made to indicate the length of the segment and used to determine its midpoint. The position for image acquisition will be determined using atomic parameters. A map of the region will be drawn on transparent laminated paper using a permanent pen in order to guarantee that subsequent images are taken from the same position. The map will show bony protuberances, birthmarks and the outline of the probe, in order to maintain the same probe angle, with relation to the frontal plane.[14]

Acquisition of images: Once landmarks have been identified, a cross-sectional image will be acquired in which it is possible to view the quadriceps musculature. Muscle thickness will then be assessed by taking ultrasound measurements from the external bony margin of the femur to the internal margin of the upper aponeurosis of the rectus femoris muscle. This measurement will then be used to assess the cross-sectional muscle thickness of the vastus intermedius and the rectus femoris muscles simultaneously.[15]

Architecture of vastus lateralis muscle

Muscle architecture will be assessed by acquiring ultrasound images at the points on the respective muscle bellies with the greatest contractile tissue content.

Criteria for probe placement: Marks will be made to indicate the length of the segment and used to determine the lower two thirds and to mark a point over the vastus lateralis muscle belly. All subjects will be positioned in decubitus dorsal with the lower segment extended and no hip rotation.

Acquisition of images: For image acquisition, the probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin. The probe will then be positioned longitudinally with respect to the muscle belly. This image will be used to determine muscle architecture parameters such as: 1) length of fascicle (FL); 2) pennation angle of fascicles (PA) and 3) thickness of vastus lateralis muscle (VLMT).[16]

Thickness of Diaphragm

Ultrasound measurement of the thickness of the diaphragm muscle will be conducted with patients lying in decubitus dorsal. The probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin.

Criteria for probe placement: The probe will be positioned perpendicular to the diaphragm in the intercostal space over the tenth rib at the anteroaxillary line.[17]

Acquisition of images: For image acquisition the probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin. The probe will then be positioned perpendicular to the diaphragm and the image will be acquired for measurement of the thickness at the end of the inspiration.[17]

Excursion of the Diaphragm

Subjects will be positioned for assessment of diaphragm excursion lying down in decubitus dorsal. The probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin.

Criteria for probe placement: The probe will be positioned using the anatomic window for liver analysis between the medioclavicular line and the anterior axillary line, in the cranial direction. The probe will therefore be positioned medially, cranially and dorsally in such a way that the ultrasound beam transects the posterior third of the diaphragm.[18,19]

Acquisition of images: Inspiratory and expiratory diaphragmatic excursion images will be acquired with the ultrasound machine in M Mode. Inspiratory excursion will be defined as the vertical height measured from the base at the start of inspiration to the apex of inclination at the end of inspiration. Expiratory excursion will be defined as the vertical height from the apex of inspiration until the base returns.[18,19]

Conventional physiotherapy

Conventional physiotherapy (respiratory and motor therapies) will be provided by professionals from the department twice a day, for 30 minutes. The protocol will include upper and lower extremity functional diagonals from the proprioceptive neuromuscular facilitation method (two series of 10 repetitions for each bilateral diagonal), manual bronchial hygiene exercises, such as vibrocompression, manoeuvres with a manual resuscitator (bag squeezing) and aspiration of secretions when necessary.

During these sessions, all groups will be monitored for heart and respiratory rates, mean arterial blood pressure, peripheral oxygen saturation and mechanical ventilator parameters. Arterial blood gas analysis values will also be noted.

After extubation, the patient will once more be assessed using the same instruments and will continue to receive conventional respiratory and motor physiotherapy until discharge from the ICU.

Intervention

The patients will be divided into two groups: an intervention group (IG) and a conventional group (CG). In addition to conventional physiotherapy, the intervention group will also undergo sessions with a cycle ergometer (a Cajumoro® Flexmotor simple lower extremities model fitted to the bed). Subjects will be administered 20 minutes of exercise on the cycle ergometer[11], at 20 cycles per minute, once per day for as long as they remain on IMV. Patients will be in decubitus dorsal during the cycle ergometer sessions with their heads elevated by 30 degrees. The protocol will be terminated if there are signs of haemodynamic instability (noradrenaline > 0.5 mc/kg/min for a mean arterial

blood pressure of > 60 mmHg) or if a tracheostomy is performed. Patients will be followed until extubation or death.

Before and after administration of the cycling sessions, the ergometer will be cleaned according to the unit's routine procedures and the criteria defined by the hospital's Nosocomial Infection Control Committee (NICC – HCPA). Before starting the exercises, the entire procedure will be briefly explained to each patient, irrespective of their level of consciousness or degree of sedation. The areas around patients' ankles will be protected with sterile compresses in order to minimize contact with the apparatus and will be bound to the pedals using adhesive bindings in such a manner that the ankle joint remains as close as possible to 90 degrees. The passive movement of the cycle ergometer will execute alternate flexions and extensions of the patients' knee and hips bilaterally for 20 minutes consecutively. All procedures will be overseen by one of the researchers.

The protocol will be administered between 24 and 48 hours after starting IMV, once per day until the patient is extubated. Exercises will be performed during the afternoon shift, before the conventional physiotherapy sessions. Supplementary measurements taken will be thigh circumferences, measured with a tape measure bilaterally at the mid point of the length of the thigh (between the anterior superior iliac spine and the upper margin of the patella) and 10 cm and 20 cm above and below this point.

Blinding

In order to preserve the secrecy of the randomization sequence, this will be generated by an independent evaluator, away from the data collection setting and unaware of the study, who will be contacted by telephone after enrolment of each patient, at the point at which they are ready to start the protocol.

All ultrasonographic examinations will be conducted by the same examiner, who will be blinded to which group each patient belongs and to the data analysis.

Endpoints

The primary outcome will be cross-sectional quadriceps thickness of critical ICU patients on IMV. Secondary outcomes will be length of fascicle, pennation angle of fascicles, thickness of vastus lateralis muscle, diaphragm thickness and excursion. Time on mechanical ventilation, extubation success and length of stay in the ICU and hospital will also be analyzed.

Education and monitoring

All of the professionals involved will be duly and fully informed about the study procedures. The research team will hold a monthly meeting at which instruments and data collection procedures will be discussed. Additional information will be provided in writing. The study procedures will be monitored by an independent researcher who will also conduct periodic monitoring visits.

Sample size calculation

The sample size calculation was based on a pilot study with 10 patients. To achieve an effect size of 1.2 standard errors between groups as cross-sectional thickness of the quadriceps muscle, significance level of 5% and power of 85% and 2 repeated measures (initial and final), the sample size estimated by the WinPepi versão 11.43 statistical program was of 14 patients in each group.

Statistical analyses

Continuous variables were described by mean and standard deviation and categorical variables as absolute and relative frequencies. To compare means between groups, the t-Student test for independent samples will be applied. In the intra-group comparisons, the t-Student test for paired samples will be used. To evaluate the effect of group on change of muscle parameters, the model of Generalized Estimating Equations (GEE) will be conducted with a Bonferroni adjustment. In assessing the association between continuous variables, the tests of Pearson linear correlation or Spearman will be applied. To control for confounding factors (body mass index, duration of protocol and duration of MV), analysis of covariance (ANCOVA) will be used. The

significance level is 5 % ($p \leq 0.05$) and the analysis will be performed using SPSS version 17.0.

DISCUSSION

It is becoming ever more widely recognized that physical training is an important component of caring for critical patients who require IMV and one that can improve pulmonary and muscular function and functional independence, accelerating the recovery process and reducing the time spent on IMV and in the ICU.[20] The potentially beneficial effects of early mobilization of critical patients who are immobile in bed are related to the theory of the calf muscle pump and muscle training. Physical exercise increases lower extremity muscle tone and, as a consequence, during muscle contractions there is increased ejection capacity, improving both venous return and muscle perfusion.[21,22]

Patients who are on mechanical ventilation are immobilized in bed and this can lead to muscle weakness rates of up to 25%, can be associated with increased mortality and higher oxygen demand and can present challenges for weaning from ventilation.[11,23,24] Intensive care unit-acquired weakness can be cause by a range of factors, such as inflammatory response and medications, and also because the cardiovascular system undergoes changes when patients spend prolonged periods lying down, including increased cardiovascular work and heart rate and changes to cardiac output, which in turn can lead to retention of liquids, causing oedema.[25]

Immobility in bed and the underlying critical disease lead to greater loss of muscle mass, particularly from the lower extremities, when compared with healthy individuals. [2] Delayed weaning can cause patients to develop pressure sores and worsens patients' physical fitness at the time of discharge from the ICU.[11,23-25] In contrast, patients who are subject to intervention soon after admission to the ICU preserve a greater proportion of their physical capacity and functionality and achieve shorter hospital stays, although implementation of early mobilization in hospitals remains a challenge.[26,27]

In one controlled clinical trial,[28] it was found that an early mobilization protocol was safe and easy to administer and led to shorter ICU stays and reduced expenditure when compared with patients given routine care. The members of the intervention group spent less time in bed, had shorter ICU stays

and spent less time in hospital.[28] The authors also observed that 3 hours of continuous passive mobilization using a cycle ergometer reduced fibre atrophy and protein loss, when compared with passive stretching for 5 minutes twice a day.

A study with healthy volunteers administered a cycling exercise test to exhaustion and then used ultrasound to assess quadriceps, finding that the pennation angle and the thickness of the vastus lateralis muscle both increased.[28] The first randomized clinical trial to study the use and efficacy of a cycle ergometer with critical care patients demonstrated that one regular session of exercise daily was feasible and safe and should be administered early on in the ICU stay. The intervention improved functional capacity and muscle strength and brought forward hospital discharge in the patients who took part in that study.[11]

It is now clear that the role of physiotherapy in the ICU and techniques employed are the subject of much research. A review of the recent literature showed that motor physiotherapy has proven beneficial for critical patients, reducing the time spent in the ICU and hospital. Its effects on functional capacity were also positive, leading to the conclusion that early mobilization should be implemented in all ICUs.[29]

Trial status

Recruiting since May 2013.

Abbreviations

Invasive mechanical ventilation (IMV)
Intensive care unit (ICU)
Mechanical ventilation (MV)
Chronic obstructive pulmonary disease (COPD)
Hospital de Clínicas de Porto Alegre (HCPA)
Universidade Federal do Rio Grande do Sul (UFRGS)
Fundo de Incentivo à Pesquisa e Eventos (FIPE)
Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS)
Body mass index (BMI)
Free and informed consent form (FICF)

Length of fascicle (FL)

Pennation angle of fascicles (PA)

Thickness of vastus lateralis muscle (VLMT)

Intervention Group (IG)

Conventional Group (CG)

Nosocomial Infection Control Committee (NICC)

Revolutions per Minute (RPM)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LJS, FAL, ASD and SRRV developed the study design. TB, AS, AMDA and WSN made substantial contributions to the design of the trial. LJS, TB, ASD and SRRV drafted the manuscript. All authors provided input to revisions of the manuscript and have read and approved the final manuscript.

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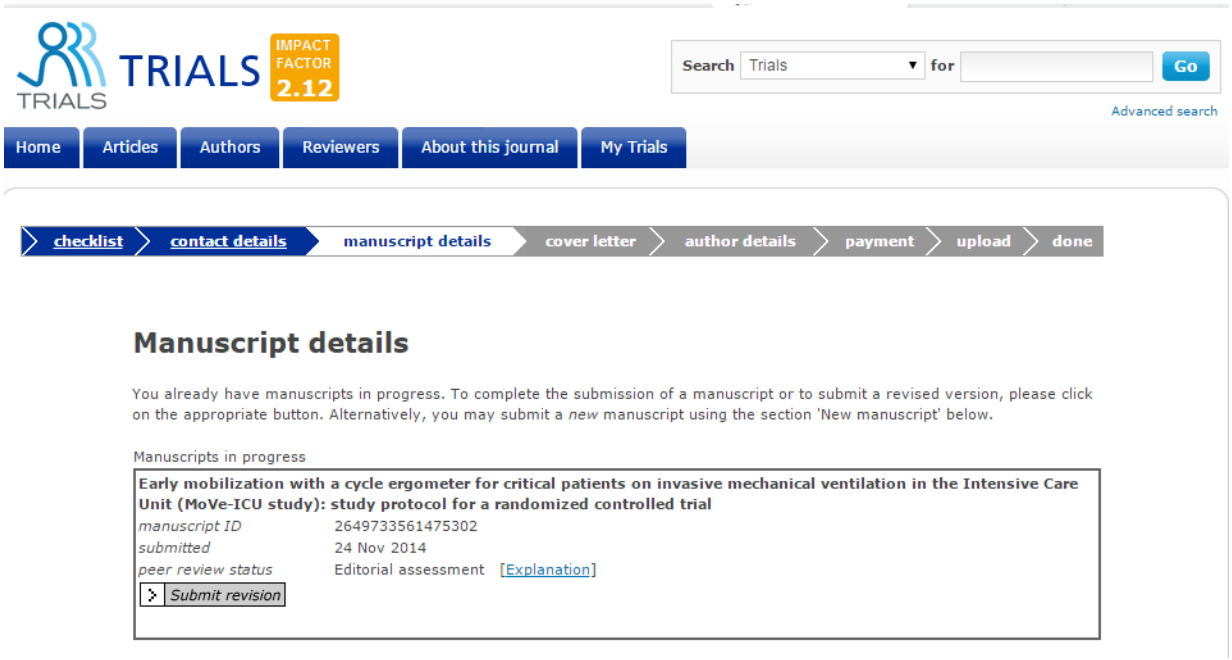
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ARTIGO II

Early mobilization using a cycle ergometer on quadriceps muscle morphology in mechanically ventilated critically ill patients in the intensive care unit: A randomized controlled trial

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The authors report no conflicts of interest.

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ABSTRACT

Objective: To evaluate and compare the effects of early mobilization using a bedside cycle ergometer with conventional physical therapy on the thickness and architecture of the quadriceps muscle in critically ill patients receiving invasive mechanical ventilation (IMV). **Design:** Single-blind randomized controlled trial. **Setting:** Intensive care unit (ICU) at Hospital de Clínicas de Porto Alegre, Brazil. **Patients:** Forty-two patients receiving IMV for 24 to 48 hours who were hospitalized for no longer than 1 week and had no restriction of lower limb movements. **Interventions**: After randomization, passive cycling exercise for the lower extremities was performed once daily for 20 minutes, at 20 revolutions per minute, until extubation or day 7 of the protocol plus conventional physical therapy in the intervention group. Bronchial hygiene maneuvers and passive exercises for the upper and lower extremities were performed twice daily for 30 minutes in both groups. **Measurements and Main Results:** Thirty-two patients were included in the final analysis: 18 in the intervention group (52.3 ± 22.7 years) and 14 in the conventional group (56.1 ± 23.0 years). The interaction group*time showed no difference in the cross-sectional thickness of the quadriceps muscle ($p = 0.100$) or in the vastus lateralis fascicle length ($p = 0.712$), pennation angle ($p=0.603$) and muscle thickness ($p=0.552$) as assessed by ultrasound before and after the protocol. **Conclusion:** There was preservation of muscle thickness and architecture in the acute phase of ICU stay. However, the addition of exercise using a cycle ergometer to conventional physical therapy did not change the outcomes analyzed.

Key Words: intensive care, early ambulation, clinical trial

INTRODUCTION

Patients in the intensive care unit (ICU) are exposed to prolonged immobility, which leads to loss of muscle mass.[1] The reduction of contractile tissue, in turn, is strongly associated with an impaired muscle capacity to produce force.[2] It is known that bed rest induces muscle atrophy, with a loss of 3% to 11% of muscle mass in the first 3 weeks of immobility.[3,4] Muscle weakness may occur within a few hours of invasive mechanical ventilation (MV), and is apparent in 25% to 100% of patients mechanically ventilated for more than 7 days.[5,6] It is also associated with increased length of hospital stay and mortality and decreased functional status even years after hospital discharge, compromising the quality of life.[7,8]

The association between prolonged MV and deleterious effects of immobility results in significant changes in muscle fibers, leading to a reduction in respiratory and peripheral muscle strength.[9] Systemic inflammation and sepsis are often accompanied by such prolonged immobility and the use of sedatives, corticosteroids, and neuromuscular blockers. This combination may lead to multiple organ failure, which is associated with loss of muscle mass.[10] Despite the multifactorial etiology of this weakness, early mobilization of ICU patients may help reduce muscle atrophy, loss of muscle mass, and deconditioning associated with bed rest.[11]

An apparatus that has proven to be useful in the hospital setting is the cycle ergometer, a stationary device that promotes cyclic rotations in the lower and/or upper limbs and can be used to perform passive, active, or resistance exercises.[12] In the ICU, it has shown to be a safe and feasible tool for early exercise training in critically ill patients,[13] although, to date only two previous studies examined the effects of this intervention in mechanically ventilated patients.[12,13] In the first, published in 2009, patients received intervention with cycle ergometer five times a week only from the fifth day of ICU admission.[13] More recently, a brazilian group included stable patients within 72 hours of MV for a single intervention of passive cycle ergometer.[12]

On the above, this is the first randomized controlled trial to investigate whether early mobilization by passive leg cycle exercise preserves the morphology of the knee extensors in mechanically ventilated ICU patients. We hypothesized that passive mobilization would induce mechanical stress in contractile tissue and, consequently, preserve quadriceps excursion and muscle thickness. Because of great tissue fragility observed in these patients, we expected that a stress stimulus (rather than a contraction) would be able to preserve muscle morphology. The current trial was therefore set up to compare, in a group of mechanically ventilated critically ill patients, the effects of early ambulation using a bedside cycle ergometer combined with conventional physical therapy vs. conventional physical therapy alone on the thickness and architecture of the quadriceps muscle.

METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The procedures were performed in compliance with the Resolution No. 466/12 of the Brazilian National Health Council. The study was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre (IRB No. 10-0530), Brazil. The trial is registered at ClinicalTrials.gov (NCT 02300662). Written informed consent was obtained from all participants prior to enrollment.

Patients

This was a single-blind randomized controlled trial with per-protocol analysis of patients admitted to the ICU at Hospital de Clínicas de Porto Alegre between May 2013 and November 2014. Eligible participants were all ICU patients aged $\geq$ 18 years who were transferred to the ICU from the emergency department or inpatient units with no more than 1 week of hospitalization and received invasive MV for a minimum of 24 hours and a maximum of 48 hours. Exclusion criteria were use of neuromuscular blockers for 2 or more consecutive days and presence of neuromuscular disorders associated with motor deficits, such as stroke, multiple sclerosis, amyotrophic lateral sclerosis,

myasthenia gravis, and Guillain-Barré syndrome. In addition, patients were excluded retrospectively if they (*a*) were extubated within 48 hours after inclusion in the study, (*b*) had hemodynamic instability (norepinephrine > 0.5 µc/kg/min for a mean arterial pressure [MAP] > 60 mmHg), (*c*) had complications during the protocol, such as pneumothorax, deep vein thrombosis, and pulmonary embolism, (*d*) had a Shiley catheter in the femoral vein, (*e*) required reintubation, (*f*) had prolonged weaning (failed 3 spontaneous breathing trials), (*g*) had a body mass index (BMI) > 35 kg/m^2, and (*h*) developed pressure ulcers in the calcaneal region during the protocol.

For sample selection, an assessor conducted a daily search for potential trial participants using the computerized system of the hospital. Then, electronic medical records were reviewed for patient identification, medical diagnosis, and current medical condition in order to assess patients for eligibility. The next of kin to each eligible patient was approached for study enrollment. Those who agreed to participate were asked about the laterality of the patient and required to provide written consent.

Interventions

Conventional (chest and motor) physical therapy was performed by staff physical therapists, who had at least 2 years of experience in the care of critically ill patients. All patients received 30-minute physical therapy sessions twice daily (morning and afternoon). The protocol consisted of passive diagonal movements based on the proprioceptive neuromuscular facilitation (PNF) stretching technique for the upper and lower extremities (two sets of 10 repetitions per set of each diagonal movement bilaterally) and manual bronchial hygiene techniques, such as chest compression-vibrations, resuscitation maneuvers with an Ambu bag, and suction of secretions when necessary.

The intervention group, in addition to conventional physical therapy, underwent passive cycling exercise training for the lower extremities using a bedside cycle ergometer (Flexmotor; Cajumoro, São Paulo, SP, Brazil). For the cycling exercise, patients were lying supine with the head of the bed elevated to 30°.

Each patient performed passive cycling movements at 20 revolutions per minute for 20 minutes once daily, in the afternoon prior to conventional physical therapy, until extubation or day 7 of the protocol. The protocol was discontinued if hemodynamic instability occurred (norepinephrine > 0.5 µc/kg/min for an MAP > 60 mmHg), systolic blood pressure (SBP) > 200 mmHg, heart rate < 40 beats/min and persistent peripheral arterial saturation <88% or tracheostomy was performed.

Before and after each exercise session, the cycle ergometer was cleaned following the cleaning procedures adopted in the ICU and the criteria established by the hospital infection control committee. Before starting the cycling exercise, all procedures were briefly explained to the patient regardless of their level of consciousness or sedation. To minimize contact with the device, the heel region was covered with sterile gauze and secured with adhesive tape so that the ankle joint was close to a 90° angle. The passive cycling movements generated alternating extension and flexion of the knee and hip, bilaterally, for 20 consecutive minutes. All procedures were performed under the supervision of one of the investigators.

In the two groups, arterial blood gas values were recorded daily and the following parameters were monitored during all sessions in order to monitor the safety of the technique: heart rate, respiratory rate, MAP, peripheral oxygen saturation, and ventilatory parameters.

After extubation or on day 7 of the protocol (whichever occurred first), all patients underwent a second ultrasound examination (final assessment) and continued to receive conventional physical therapy until ICU discharge.

Assessment

After completing 24 to 48 hours of MV, patients were actually enrolled in the study and an ultrasound was performed to assess the morphology of the knee extensors (dominant side). The first ultrasound examination was performed on the first day of patient participation in the study (initial assessment). A second examination was performed on day 7 of the protocol or

24 hours after extubation, whichever occurred first (final assessment). Both assessments were performed by the same trained examiner, who was blinded to group assignment and data analysis.

With the patient lying supine, real-time B-mode ultrasound scanning was performed using a 7.5 MHz linear-array transducer (SonoSite, Washington, DC, USA). The probe was coated with water-soluble transmission gel to provide acoustic contact without depressing the dermal surface.[14] First, the quadriceps muscle length was identified and marked on the skin, and its midpoint was determined. To ensure that the same region of the muscle was scanned on subsequent sessions, a map of this region was recorded and traced on a clear acetate sheet using a permanent marker. Bony prominences and birthmarks were also included in the map, as well as the probe outline in order to ensure that the probe was held at the same angle relative to the frontal plane during all measurements.[14] Quadriceps muscle thickness was determined on cross-sectional images by measuring the distance from the outer edge of the femur to the inner edge of the aponeurosis in the upper part of the rectus femoris muscle.[15]

Ultrasound-based measurements of the vastus lateralis muscle architecture were made on images obtained at sites corresponding to the points on the muscle belly of highest contractile muscle volume. The muscle length was marked on the skin, its lower two-thirds were determined, and a point was then marked on the vastus lateralis muscle belly. With the patient lying supine, legs and knees extended, hip without rotation and ankle in neutral position, the ultrasound transducer was oriented along the axial plane of the vastus lateralis muscle belly. Axial-plane images of the vastus lateralis were then acquired and muscle architecture parameters, such as fascicle length, fascicle pennation angle, and muscle thickness, were measured.[16] Finally, data on fascicle length were normalized to femur length for each patient.

Outcomes

The primary endpoint with respect to the efficacy of passive leg cycle exercise in preserving muscle morphology was the difference in cross-sectional thickness of the dominant quadriceps muscle from initial to final assessment between groups. Secondary efficacy endpoints included changes in muscle architecture parameters, such as vastus lateralis fascicle length, fascicle pennation angle, and muscle thickness. We also assessed length of ICU and hospital stay, duration of MV, successful extubation, and death. In addition, septic (requiring vasoactive drugs) and non-septic patients were compared in terms of primary and secondary outcomes.

Sample Size Calculation

The sample size calculation was based on a pilot study with 10 patients. To achieve an effect size of 1.2 standard errors between groups as cross-sectional thickness of the quadriceps muscle, significance level of 5% and power of 85% and 2 repeated measures (initial and final), the sample size estimated by the WinPepi versão 11.43 statistical program was of 14 patients in each group.

Randomization

Patients were randomly assigned to receive either conventional physical therapy (conventional group) or exercise training intervention using a cycle ergometer associated with conventional physical therapy (intervention group). Randomization sequence was created using the website www.randomization.com, with a 1:1 allocation ratio using blocks of 10 participants.

To ensure the confidentiality of randomization sequence, the sequence was generated by an assessor who did not participate in data collection or study design and was contacted via telephone only after the participant had been included in the study and was ready to start the protocol.

Statistical analysis

Continuous variables were expressed as mean and standard deviation or standard error, or as median and interquartile range. Categorical variables were expressed as absolute and relative frequencies. The Shapiro-Wilk test was used to test the normality of distribution, and Levene's test was used to assess homogeneity of variance for all group comparisons. Student's *t* test for independent samples was used to compare means between groups, and the Mann-Whitney test was used to compare medians between groups. Qualitative data were analyzed using the chi-square test or Fisher's exact test when at least 25% of the cells exhibited the expected frequency <5. To evaluate the intra-group effects, the group and subgroups (septic *versus* non-septic) in changing muscle parameters, the model of Generalized Estimating Equations (GEE) was performed with Bonferroni adjustment. Analysis of covariance (ANCOVA) was used to control for confounding factors, such as BMI, duration of protocol and duration of MV. Statistical analysis was performed using SSPS, version 17.0. The level of significance was set at 5% ($p \leq 0.05$).

RESULTS

From May 2013 to November 2014, 1321 ICU patients were screened for eligibility. Of these, 1279 were excluded. Initially, 42 mechanically ventilated patients were randomized to one of the two treatment groups (21 patients in each group). Figure 1 shows the flow of participants, including losses to follow-up and exclusions after randomization.

At the end of the study, 32 patients had completed the protocol, 18 in the intervention group and 14 in the conventional group. There was no difference between groups regarding mean age or severity of illness score ($p > 0.05$). The characteristics of the study sample are shown in Table 1.

Muscle architecture and thickness of patients in both groups remained unaltered during the study, with no significant difference in the cross-sectional

thickness of the quadriceps muscle ($p = 0.100$) or in the vastus lateralis fascicle length ($p = 0.712$), pennation angle ($p = 0.603$), and muscle thickness ($p = 0.552$) (Table 2).

Likewise, there was no significant difference between groups in duration of MV ($p = 0.905$), length of ICU stay ($p = 0.619$), length of hospital stay ($p = 0.643$), rate of successful extubation ($p = 0.411$), or death rate ($p = 0.672$) (Table 3).

Vital signs and ventilatory parameters were stable throughout the interventions in both groups. There was no adverse event in either group. The analysis of group and subgroup (septic vs. non-septic) effects on changes in muscle parameters showed no significant difference between groups ($p > 0.05$). Likewise, duration of protocol and duration of MV had no effect on muscle parameters.

DISCUSSION

In this study, adding passive cycle ergometer exercise to conventional physical therapy did not result in any meaningful changes in the cross-sectional thickness and architecture of the quadriceps muscle in mechanically ventilated critically ill patients. In addition, presence of sepsis did not influence the outcomes analyzed, and no differences were observed between groups in the duration of MV, length of ICU and hospital stay, rate of successful extubation, and death.

Thomsen et al.[17] in a study of patients with respiratory failure, recommended that muscle mass should be evaluated because a two-fold decrease in ambulation was observed in these patients, which may be associated with greater loss of lean body mass in the extremities after the onset of critical illness. Immobility, even of short duration, is a catabolic state for the muscle, resulting in significant loss of muscle mass both in healthy individuals and critically ill patients.[18] Puthucheary et al.[19] assessed rectus femoris muscle loss on days 1, 3, 7, and 10 of ICU stay using three measures, histological,

biochemical and ultrasound assessment, and observed that this reduction was a consequence of muscle protein decreased synthesis and increased breakdown.

Reduction in muscle cross-sectional area due to immobility in bed is a major cause of death.[20] Thus, alternative therapies, such as bedside cycle ergometer for critically ill patients, have been widely used in the intensive care setting.[3,21] In our study, no differences were found between groups. This result may be explained in part by the fact that patients were sedated and on MV, which may lead to a state of extreme body relaxation, producing no further changes in muscle morphology than those generated by conventional physical therapy. Another possible explanation is that the intensity at which the cycle ergometer was set may have been insufficient to generate gains in muscle thickness. It is known that joint mobilization by cyclic movements using a cycle ergometer generates a stress load due to cyclic stretching. For this type of load, the higher the speed, the greater the intensity. In the present study, cycle ergometer speed was the same for all patients.

The first randomized controlled trial evaluating the safety of using a bedside cycle ergometer in critically ill patients showed that a daily standardized cycling exercise session using this device was a feasible and safe strategy, which could be performed early during ICU stay.[13] In the study by Porta et al.,[22] the addition of cycling exercise using a bedside ergometer in patients on prolonged MV also increased exercise capacity and reduced muscle fatigue and perceived dyspnea. Morris et al.[23] reported that passive mobilization for 3 consecutive hours, on a daily basis, using a cycle ergometer was able to reduce fiber atrophy and protein loss compared with passive stretching performed twice daily for 5 minutes. When comparing those results with ours, we have considered the possibility of using more than 20 minutes in the cycle ergometer in future studies, or just increasing the intensity, in an attempt to find results similar to those found by the authors using less time.

Some studies have used thigh circumference measurement to evaluate patients.[3,24] In our study, as well as in the studies conducted by Gerovasili et al.[18] and Gruther et al.,[25] ultrasound was used and appears to be a promising

tool for muscle assessment in ICU patients. This technique overcomes many of the problems associated with anthropometric and body composition measurements, such as edema,[22] which may be a source of bias when assessing muscle thickness. Reid et al.[26] showed that ultrasound was able to detect muscle wasting even in the presence of severe fluid retention. Another advantage of ultrasound is that it is noninvasive and can be used at the bedside, eliminating the need for patient transport and radiation exposure.[27,28]

Gruther et al.,[25] in a double-blind controlled trial evaluating the effect of neuromuscular electrical stimulation (NMES) in two groups of ICU patients, showed a significant decrease in muscle thickness in the group receiving early intervention, indicating that electrical stimulation did not prevent loss of muscle mass. Poulsen et al.,[29] in a study involving ICU patients with septic shock, applied NMES to the quadriceps muscle for 7 consecutive days for 60 minutes per day and found no difference in muscle mass between the stimulated and nonstimulated side as assessed by computed tomography. Likewise, Gerovasili et al.[18] evaluated by ultrasound 26 patients undergoing NMES applied to the quadriceps muscle and also found that muscle mass decreased in both groups; however, muscle mass decreased less in the NMES group, further supporting the concept that NMES may have a protective effect against muscle wasting.

In our study, the overall median duration of MV and length of ICU stay were 9 and 12 days, respectively, and the rate of successful extubation was 75%. Schweickert et al.,[30] assessing the efficacy of an early ambulation program compared with conventional physical therapy, concluded that motor activity in critically ill patients improves respiratory muscle strength and increases ventilator-free days, reducing length of ICU stay. Routsi et al.[31] applied NMES to the quadriceps and peroneus longus muscles of critically ill patients and also found shorter duration of weaning from MV in patients assigned to the intervention group. In a case report, the patient showed a sustained loss of muscle mass even 1 year after ICU discharge despite an extensive rehabilitation program.[32] An early ICU mobilization program can preserve greater physical capacity and function and reduce length of hospital

stay in critically ill patients; however, the implementation of early ambulation in hospitals remains a challenge.[33,34]

In our study, patients followed the protocol for up to 7 days. A heterogenous duration of early mobilization interventions has been reported in the literature, but some studies suggest that a longer protocol duration may yield more favorable results.[25] Future studies aiming to further explore questions like the effects of different cycle ergometer speeds on quadriceps muscle thickness, or seeking to extend the protocol throughout the ICU stay, or even hospital stay, are of utmost importance to clarify some questions that remain unanswered.

In conclusion, early mobilization using a bedside cycle ergometer did not provide additional benefits to conventional physical therapy in the outcomes of interest analyzed here. There was preservation of the thickness and architecture of the quadriceps muscle in mechanically ventilated critically ill patients during the acute phase of ICU stay.

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FIGURES AND TABLES

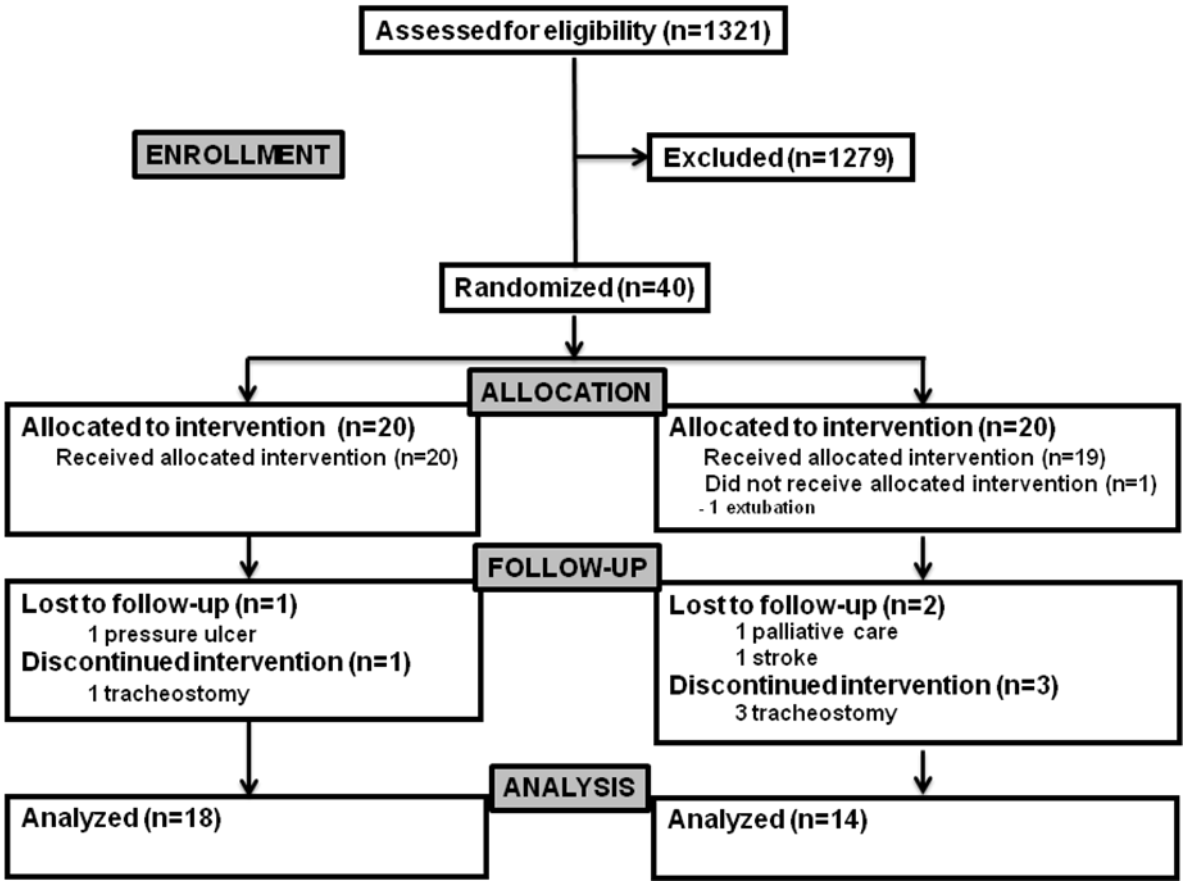

Figure 1. Study flowchart.

Table 1. Baseline characteristics.

Variable	Intervention Group (*n*=18)	Conventional Group (*n*=14)	p-value*
Age, yr, mean ($_{SD}$)	52.3 (22.7)	56.1 (23.0)	0.650
Gender, *n* (%)			0.465
Female	13 (72.2)	8 (57.1)	
Male	5 (27.8)	6 (42.9)	
BMI, kg/m^2, mean ($_{SD}$)	26.0 (5.8)	23.6 (4.4)	0.105
Laterality, *n* (%)			1.000
Right-handed	16 (88.9)	13 (92.9)	
Left-handed	2 (11.1)	1 (7.1)	
APACHE II, mean ($_{SD}$)	23.7 (7.7)	23.8 (8.7)	0.981
Reason for ICU admission, *n (%)*			1.000
Sepsis	8 (44,4)	7 (50,0)	
Respiratory	5	3	
Abdominal	1	3	
Urinary	2	1	
Outher	10 (55,6)	7 (50,0)	
Descompensated HF	3	3	
CRA	2	1	
Descompensated CRF	1	2	
Outher	4	1	
Duration of protocol, days, mean ($_{SD}$)	4.6 (2.4)	4.9 (2.5)	0.778

Values are expressed as mean and standard deviation, n and percentage; * Student's *t* test for independent samples and chi-square test or Fisher's exact test ($p \leq 0.05$); BMI: body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; HF: heart failure; CRA: cardiorespiratory arrest; CRF: chronic renal failure.

Table 2. Analysis of group effect on changes in the cross-sectional thickness of the quadriceps muscle and vastus lateralis muscle architecture.

Variable	Intervention Group (n=18)				Conventional Group (n=14)				Interaction Effect (p-value)**	
	Initial Mean (SE)	Final Mean (SE)	Difference (CI 95%)	p*	Initial Mean (SE)	Final Mean (SE)	Difference (CI 95%)	p*	p	$p_{adjusted***}$
Cross-sectional thickness of the quadriceps muscle, cm	2.01 (0.16)	1.77 (0.16)	0.24 (-0.04 to 0.54)	0.151	1.73 (0.16)	1.72 (0.16)	-0.01 (-0.64 to 0.56)	1.000	0.100	0.176
Vastus lateralis fascicle length, cm	3.49 (0.10)	3.55 (0.08)	-0.06 (-0.37 to 0.26)	1.000	3.46 (0.09)	3.45 (0.08)	0.01 (-0.35 to 0.38)	1.000	0.712	0.664
Vastus lateralis fascicle pennation angle, cm	11.5 (0.85)	10.6 (0.69)	0.92 (-1.03 to 2.87)	1.000	12.4 (1.04)	10.7 (1.12)	1.76 (-1.99 to 5.51)	1.000	0.603	0.895
Vastus lateralis muscle thickness, cm	1.36 (0.07)	1.15(0.06)	0.21 (0.01 to 0.42)	0.042	1.40 (0,11)	1.26 (0.12)	0.14 (-0.13 to 0.40)	1.000	0.552	0.426

Values are expressed as mean and standard error (SE); *intra-group effect by Bonferroni adjustment through the model of generalized estimating equations (GEE); **model of generalized estimating equations (GEE) with Bonferroni adjustment (p≤0,05); ***adjusted by BMI, duration of protocol and duration of MV; cm: centimeter.

Table 3. Data on duration of mechanical ventilation, length of ICU and hospital stay, successful extubation, and death.

Variable	Intervention Group (*n*=18)	Conventional Group (*n*=14)	p value
Duration of MV, days, median ($_{IQR}$)	9 (7-10)	8 (5-13)	0.905
Length of ICU stay, days, median ($_{IQR}$)	11 (10-19)	15 (10-25)	0.619
Length of hospital stay, days, median ($_{IQR}$)	21 (15-37)	25 (17-36)	0.643
Successful extubation, *n* (%)	12 (66.7)	12 (85.7)	0.411
Death, *n* (%)	4 (22.2)	2 (14.3)	0.672

Values are expressed as median and interquartile range (IQR) and n and percentage; * Mann Whitney test and chi-square test or Fisher's exact test ($p \leq 0.05$); MV: mechanical ventilation; ICU: intensive care unit.

CONSIDERAÇÕES FINAIS

- Houve preservação da espessura e arquitetura muscular durante a fase aguda de internação no UTI nos pacientes estudados;
- Adicionar cicloergômetro passivo à fisioterapia convencional não resultou em diferença nos desfechos analisados;
- O quadro séptico não implicou em alteração nas medidas observadas;
- Não houve diferença quanto aos tempos de ventilação mecânica, internação no UTI e no hospital, bem como na taxa de sucesso na extubação e óbito;
- O tempo de protocolo, juntamente com a duração, frequência e intensidade da intervenção devem ser alvos de futuras pesquisas.

ANEXOS E APÊNDICES

ARTIGO III

Efeito do cicloergômetro passivo na mobilidade diafragmática de pacientes críticos em ventilação mecânica invasiva na Unidade de Terapia Intensiva: ensaio clínico randomizado

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RESUMO

Objetivo: Avaliar o efeito do cicloergômetro sobre a mobilidade diafragmática de pacientes críticos em ventilação mecânica invasiva no Centro de Tratamento Intensivo (CTI). **Método:** Ensaio clínico randomizado cego realizado no CTI do Hospital de Clínicas de Porto Alegre, Brasil. Quarenta e dois pacientes estavam com 24 a 48 horas de VMI e, no máximo, 7 dias de internação, onde poderiam apresentar para a mobilização de membros inferiores. Os pacientes foram randomizados para realizar fisioterapia convencional ou fisioterapia convencional (grupo convencional) adicionando o cicloergômetro. O cicloergômetro (grupo intervenção) foi realizado de forma passiva por 20 minutos, com 20 rotações por minuto, uma vez ao dia, a partir da intubação até a extubação ou até o momento que o paciente completasse 7 dias de protocolo. **Resultados:** A mobilidade diafragmática foi avaliada através da ultrassonografia no momento da intubação e na extubação. Quatorze pacientes foram incluídos no grupo convencional (56,1±23,0 anos) e dezoito no grupo intervenção (52,3±22,7 anos). Houve preservação na mobilidade diafragmática tanto no grupo convencional (0,61±0,07 pré vs. 0,64±0,12 pós) (p=0,474) quanto no grupo intervenção (0,54±0,06 pré vs. 0,68± 0,09 pós). Houve correlação direta entre a variação da mobilidade diafragmática e o tempo de protocolo (r=0,031; p=0,915) e de ventilação mecânica (r=0,199; p=0,495) no grupo intervenção. **Conclusão:** A mobilidade diafragmática foi preservada em ambos os grupos durante a fase aguda de internação no CTI, portanto o uso do cicloergômetro não alterou os desfechos analisados. Houve associação entre a variação da mobilidade diafragmática e os tempos de protocolo e ventilação mecânica no grupo intervenção.

Palavras-chave: intensive care, early ambulation, clinical trial

INTRODUÇÃO

Pacientes na Unidade de Terapia Intensiva (UTI) apresentam diversas comorbidades e estão expostos muitas vezes a imobilização prolongada o que leva a complicações neuromusculares importantes.[1,2] Dificuldades no desmame ventilatório são encontrados em 20% a 25% dos pacientes que estão em ventilação mecânica, deixando-os suscetíveis a diversas situações clínicas relevantes como hipotensão, hipóxia e desenvolvimento da sepse.[3-5] A ventilação mecânica, por sua vez, pode induzir à disfunção diafragmática diminuindo a capacidade de produção de força do diafragma.[6] A fraqueza diafragmática é muito freqüente no paciente crítico e está associada a atrofia de fibras de contração rápida e lenta, podendo ocorrer mesmo em breves períodos de ventilação mecânica.[7] Tudo isso pode estar associado ao aumento no período de hospitalização e na mortalidade dos pacientes, comprometendo assim a qualidade de vida.[5,8]

A perda de fibras musculares resultante da ventilação mecânica e do imobilismo também pode levar a uma redução da força dos músculos respiratórios e dos membros inferiores[9], onde a mobilização precoce pode ser utilizada na preservação da massa muscular dos pacientes críticos.[2] Neste contexto, um dos recursos que vem sendo muito utilizado é o cicloergômetro para membros inferiores, o qual pode ser acoplado ao paciente promovendo rotações cíclicas de toda a musculatura dos membros inferiores.[1] Essa intervenção vem se mostrando uma ferramenta segura, podendo ser utilizada passivamente ou ativamente, sendo ajustada de acordo com a capacidade de cada indivíduo.[2,9,10]

Diversos métodos são utilizados para a avaliação da disfunção diafragmática como a fluoroscopia, a estimulação elétrica do nervo frênico entre outros, porém essas técnicas são difíceis de serem realizadas na prática clínica.[6,11] A ultrassonografia é um instrumento de fácil manuseio e pode ser realizado a beira do leito sendo uma ferramenta diagnóstica importante para pacientes que estão na UTI.[6,11,12] O estudo realizado por Kim et al (2011) demonstrou que 29% dos pacientes em ventilação mecânica apresentam disfunção diafragmática, os quais apresentam maior tempo no desmame e na ventilação mecânica.[6]

Não encontramos estudos avaliando a função diafragmática através do ultrassom após a intervenção com cicloergômetro. Portanto, o objetivo deste trabalho foi avaliar o efeito do cicloergômetro sobre a mobilidade diafragmática de pacientes críticos em ventilação mecânica invasiva no CTI, bem como verificar a associação entre a variação da mobilidade diafragmática e o tempo de protocolo e de ventilação mecânica.

MATERIAIS E MÉTODOS

Este estudo caracteriza-se como um ensaio clínico randomizado realizado no Centro de Tratamento Intensivo (CTI) do Hospital de Clínicas de Porto Alegre (HCPA), sendo financiado pela Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) e com verba do Fundo de Incentivo á Pesquisa do Hospital de Clínicas de Porto Alegre (FIPE-HCPA). Foi conduzido de acordo com os princípios da Declaração de Helsinki das Boas Práticas Clínicas, sendo aprovado pelo comitê de ética do HCPA com o número (CEP n° 10-0530) onde foi registrado no sistema de estudos randomizados ClinicalTrials.gov (NCT 02300662). O consentimento informado por escrito foi obtido de todos os responsáveis e dos pacientes que participaram do estudo.

População do estudo

Foram incluídos pacientes com idade ≥ 18 anos, de ambos os gêneros, internados no CTI do HCPA com o período de ventilação mecânica de 24 a 48 horas. Podendo ser proveniente da emergência ou da unidade de internação, possuindo no máximo 1 semana de internação. Foram excluídos os pacientes que apresentavam doenças neuromusculares ou déficit motor, tais como acidente vascular encefálico, esclerose múltipla, esclerose lateral amiotrófica, miastenia gravis e Guillain Barré. Os indivíduos extubados em menos de 48 horas após ser incluídos no estudo e que apresentaram complicações durante o protocolo, tais como: pneumotórax, trombose venosa profunda e embolia pulmonar, cateter de Shilley na veia femoral, necessidade de reintubação, desmame prolongado (falha em 3 testes de ventilação espontânea), índice de massa corpórea (IMC) > 35

kg/m^2 e surgimento de escara na região do calcâneo durante o protocolo, foram considerados como perda do desenvolvimento do estudo.

Na seleção da amostra um avaliador realizou uma busca diária de indivíduos elegíveis para o estudo através do sistema de administração de gestão hospitalar do Hospital de Clínicas de Porto Alegre (AGHWEB/HCPA). Posteriormente, por meio do prontuário eletrônico, foram coletados os dados de identificação, diagnóstico médico e condições clínicas atuais. Ao selecionar o paciente, o responsável pelo mesmo era convidado a assinar o Termo de Consentimento Livre e Esclarecido (TCLE).

Os pacientes foram distribuídos aleatoriamente para o grupo fisioterapia convencional ou para o grupo fisioterapia convencional mais o cicloergômetro. A randomização foi realizada através do site www.randomization.com em blocos de 10 pacientes. Para manter o sigilo da sequência de randomização, a mesma foi gerada pelo mesmo avaliador, que não participava da coleta, e não tinha conhecimento prévio do estudo.

Ultrassonografia

Após completar o período entre 24 a 48 horas de VM e estar efetivamente incluso no estudo, o indivíduo foi submetido a um exame ultrassonográfico, para avaliar a mobilidade diafragmática.

A ultrassonografia foi realizada ocorreu no primeiro dia de inclusão do indivíduo no estudo sendo também realizada no sétimo dia de VM ou no momento da extubação quando o período fosse inferior a 7 dias. A avaliação foi realizada por um pesquisador treinado e cegado para o estudo.

Para a avaliação da mobilidade diafragmática os sujeitos foram posicionados em decúbito dorsal e por meio de uma sonda de arranjo linear (*Ultrasound probe linear array* 7,5 MHz – em modo M; marca SONOSITE®, Whashington, USA). A sonda foi embebida em um gel de transmissão solúvel em água promovendo contato acústico sem deprimir a superfície da pele, sendo posicionada por meio da janela anatômica de análise do fígado entre posição medioclavicular e linha axilar anterior com direção cranial. Desta forma, a sonda

foi posicionada médio, cranial e dorsal, fazendo o feixe do ultrassom alcançar o terço posterior do diafragma.[12,13] A excursão inspiratória e expiratória diafragmática foi realizada em Módulo “M” no aparelho de ultrassom. A excursão inspiratória foi considerada por meio da medida da altura vertical da base do início da inspiração até o ápice da inclinação no final da inspiração. Já a excursão expiratória foi considerada pela altura vertical do ápice da inspiração até o retorno da base.[12,13]

Intervenção

Os pacientes foram divididos em dois grupos: grupo convencional (GC) e e grupo intervenção (GI). O grupo intervenção realizou, além da fisioterapia convencional, cicloergômetro para membros inferiores 1 vez ao dia por um pesquisador treinado, objetivando a padronização das condutas e seguiu até o sétimo dia de VM, extubação do paciente ou óbito.

Na realização do cicloergômetro os pacientes estavam em decúbito dorsal, com cabeceira elevada a 30º. Foram realizados exercícios de forma passiva (Flexmotor – Cajumoro, São Paulo, Brazil). O movimento passivo do cicloergômetro foi realizado bilateralmente. A flexão e a extensão de joelhos e quadril do paciente pelo tempo de 20 minutos consecutivos. O número de rotações por minuto foi estabelecido em 20 e todos os procedimentos foram realizados 1 vez por dia no turno da tarde antes da realização da fisioterapia convencional todos os sinais clínicos foram supervisionados por um dos pesquisadores do estudo.[9]

Antes e depois da aplicação do cicloergômetro, o aparelho foi limpo de acordo com as rotinas da unidade de tratamento intensivo segundo a Comissão de Controle de Infecção Hospitalar do Hospital (CCIH – HCPA). Antes de aplicar o cicloergômetro foi explicado ao paciente o que seria realizado, independente do nível de consciência ou grau de sedação. A região do tornozelo dos pacientes foi coberta por compressas esterilizadas a fim de minimizar o atrito com o aparelho, sendo acopladas faixas adesivas para que a articulação ficasse mais próxima do ângulo de 90 graus.

A fisioterapia convencional (fisioterapia respiratória e motora) foi realizada duas vezes por dia e ficou a cargo dos profissionais do serviço sendo realizada durante 30 minutos. Os exercícios consistiram de diagonais do método de facilitação neuromuscular proprioceptiva (duas séries de 10 repetições cada diagonal bilateral) para membros superiores e inferiores, exercícios manuais para higiene brônquica, como vibrocompressão, manobras com Ambú® e aspiração de secreções quando necessário.

Durante os atendimentos foram monitorados os valores de frequência cardíaca e respiratória, pressão arterial média, saturação periférica de oxigênio e parâmetros ventilatórios. A partir da extubação, o indivíduo foi novamente avaliado pelos mesmos instrumentos e permaneceu recebendo os atendimentos de fisioterapia respiratória e motora convencionais pelos profissionais do serviço de fisioterapia, até alta da UTI.

Desfechos

O desfecho primário foi a mobilidade diafragmática, utilizando como desfechos secundários o tempo de permanência em ventilação mecânica, tempo de permanecência no CTI e no hospital, bem como o sucesso na extubação e óbito dos pacientes.

Análise Estatística

O cálculo do tamanho da amostra foi baseado em um estudo piloto com 10 pacientes. Com um tamanho de efeito de 1,2 desvios padrão entre os grupos, nível de significância de 5%, poder de 85% e 2 medidas repetidas (inicial e final), o tamanho amostral estimado pelo programa estatístico WinPepi versão 11.43 foi de 14 pacientes por grupo.

As variáveis contínuas foram descritas por média e desvio padrão ou erro padrão e mediana e amplitude interquartil, e as categóricas por frequências absolutas e relativas. Foi realizado o teste de normalidade de Shapiro-Wilk e testada homocedasticidade através do teste de Levene. Para comparar médias entre os grupos, o teste t-student para amostras independentes foi aplicado e, para comparação de medianas, o de Mann-Whitney. Para análise dos dados

qualitativos, o teste Qui-Quadrado ou Exato de Fisher (quando no mínimo 25% das células apresentaram frequência esperada < 5) foi aplicado. Para avaliar os efeitos intragrupo, do grupo e dos subgrupos (sépticos *versus* não sépticos) na mudança dos parâmetros musculares, o modelo de equações de estimativas generalizadas (GEE) foi realizado com ajuste por Bonferroni. A associação entre as variáveis foi avaliada pelo coeficiente de correlação de Spearman. Para controle de fatores confundidores como IMC, tempo de protocolo e tempo de VM, a Análise de Covariância (ANCOVA) foi utilizada. O nível de significância adotado foi de 5% ($p \leq 0,05$) e as análises foram realizadas no programa SPSS versão 17.0.

RESULTADOS

Entre maio de 2013 e novembro de 2014, 1321 foram rastreados para elegibilidade no CTI. Entre eles, 1279 não preencheram os critérios de inclusão. Inicialmente foram randomizados 42 pacientes em ventilação mecânica para o estudo (21 em cada grupo) e, durante o período de estudo, houve perda de seguimento e descontinuidade da intervenção por razões expressas na Figura 1. Ao final do estudo, 32 pacientes haviam completado o protocolo de estudo, sendo 18 do GI e 14 do GC.

Desfechos

Houve preservação na mobilidade diafragmática tanto no grupo intervenção quanto no grupo convencional (Figura 2). Não foi encontrada diferença entre os grupos quanto ao tempo de ventilação mecânica ($p=0,905$), tempo internação no CTI ($p=0,619$) e tempo de internação no hospital ($p=0,643$), bem como na taxa de sucesso no extubação ($p=0,411$) e no número de óbitos ($p=0,672$) (Tabela 2).

Houve correlação direta entre a variação da mobilidade diafragmática e o tempo de ventilação no grupo intervenção ($r=0,199$; $p=0,495$) e correlação indireta no grupo convencional ($r= -0,873$; $p = 0,010$) (Figura 3). Da mesma forma, na associação entre a variação da mobilidade diafragmática e o tempo de protocolo,

foi observada correlação direta no grupo intervenção (r=0,031; p=0,915) e uma correlação indireta no grupo convencional (r= -0,797; p = 0,018) (Figura 4).

Ao analisar os sinais vitais e parâmetros ventilatórios foi observado uma estabilidade durante as intervenções, não havendo nenhum evento adverso durante o período de aplicação das técnicas.

DISCUSSÃO

O principal achado deste estudo foi a preservação da mobilidade diafragmática tanto nos pacientes que realizaram a fisioterapia convencional isolada, quanto no grupo que realizou o cicloergômetro associado. Houve correlação direta entre a variação da mobilidade diafragmática e os tempos de protocolo e ventilação mecânica no grupo intervenção, sendo que o mesmo não foi encontrado no grupo convencional. Da mesma forma, não foi observado impacto nos tempos de ventilação mecânica, taxa de sucesso de extubação, óbito e internação na UTI e no hospital.

Sabemos que pacientes na UTI estão expostos a diversas comorbidades, principalmente pacientes em ventilação mecânica. O diafragma pode sofrer disfunção contrátil diminuindo sua capacidade de força, e podendo estar associado ao aumento do tempo de desmame.[14] Por isso, a mobilização precoce pode ser eficaz na preservação da massa muscular, tanto periférica quanto dos músculos respiratórios.[14] Estudos apontam que a mobilização precoce com cicloergômetro é uma ferramenta segura e viável para ser utilizada em pacientes críticos, melhorando a capacidade funcional e a força dos pacientes,[9] porém não temos nenhum estudo que avalie o impacto desta intervenção sobre o diafragma.

Acreditamos que o paciente crítico que não recebe nenhum tipo de mobilização precoce é submetido a diversos problemas relacionados à imobilidade especificamente a disfunção diafragmática. Neste estudo analisando os dois grupos nos momentos pré e pós não tivemos diferença estatística. Indivíduos em ventilação mecânica que não realizaram intervenção de mobilização precoce perdem força muscular em torno de 25% no período entre 4 a 7 dias de internação. Estas alterações podem estar associadas a um aumento

da mortalidade e da demanda de oxigênio e impactam no desmame ventilatório dos pacientes.[9,10,15,16] Quando indivíduos saudáveis foram submetidos à imobilização no leito por dez dias apresentaram uma diminuição na força do quadríceps entre 1% a 1,5% para cada dia imobilizado, sendo mais acentuado em pacientes idosos.[17] Inúmeros fatores podem levar a fraqueza muscular, como má nutrição, imobilidade prolongada, aumento de citocinas inflamatórias e anormalidades neuromusculares. Assim, a imobilidade no leito associado ao quadro clínico levam a uma maior diminuição da massa muscular, principalmente nos membros inferiores.[2]

Neste trabalho não tivemos alterações nos sinais vitais ou nos parâmetros ventilatórios. A mobilização precoce tem sido cada vez mais utilizada na reabilitação de pacientes críticos.[17] Um estudo recente utilizou o cicloergômetro uma única vez durante vinte minutos a partir do 5° dia de internação em indivíduos sedados, sendo avaliado variáveis hemodinâmicas como débito cardíaco, resistência vascular sistêmica, venosa central, a saturação de oxigênio no sangue, frequência respiratória, volume corrente, consumo de oxigênio, dióxido de carbono e lactato sanguíneo.[18] O exercício com cicloergômetro foi considerado seguro, pois os autores não encontraram alterações significativas nos parâmetros hemodinâmicos, respiratórios ou das variáveis metabólicas.[18] Em outro estudo que teve como objetivo avaliar as respostas do exercício passivo por 20 minutos, os autores também não acharam diferença na frequência cardíaca, pressão arterial média e saturação de oxigênio em qualquer momento da aplicação do exercício.[19]

Em nosso estudo foi utilizado o ultrassom para a avaliação da mobilidade diafragmática, sendo este uma ferramenta importante na avaliação do diafragma, já que é um instrumento prático e simples de ser aplicado. Após analisar a disfunção diafragmática com método semelhante ao utilizado,estudo de Kim et al (2011) encontraram que o ultrassom pode predizer falha no tempo de extubação.[6] Além disso, pacientes com disfunção diafragmática apresentaram maior tempo de ventilação mecânica. Sendo assim, o ultrassom pode ser uma ferramenta importante para ser utilizada dentro da UTI. Em pacientes que apresentam dificuldades no desmame.[6] Grosu et al (2012) demonstrou que os pacientes

submetidos a ventilação mecânica têm redução da espessura muscular levando à disfunção diafragmática.[20] Essas medidas podem auxiliar no desmame desses pacientes e identificar o que ocorre com o músculo respiratório durante o período de ventilação mecânica. Os mesmos autores demonstraram, também, que dentro de 48 horas de ventilação mecânica já acontece a diminuição da espessura do diafragma e este pode afetar a função pulmonar.[20]

Não encontramos diferença no tempo de internação na CTI e no Hospital nos dois grupos avaliados, diferindo do estudo de Brahmbhatt et al (2010), o qual verificou que um protocolo de mobilização precoce promove diminuição no tempo de internação na CTI e diminui os custos na UTI ao comparar pacientes que receberam cuidados usuais. O grupo que realizou a intervenção também saiu do leito mais rápido, e apresentou menor tempo de internação na UTI e no hospital, realizamos intervenção com os dois grupos, por isso as diferenças podem não ter sido significativas.[21] Este fato também foi confirmado por Schweickert et al (2009) 59% dos pacientes que realizaram exercício precoce retornaram a independência funcional após alta hospitalar, neste mesmo estudo houve também diferença no período fora da ventilação mecânica, sendo maior no grupo intervenção, quando comparado ao grupo controle.[22] Estes estudos demonstram a importância da mobilização precoce no paciente crítico mesmo sem a utilização do cicloergômetro.[21,22]

Alguns estudos utilizaram o cicloergômetro e analisaram a força de quadríceps e massa muscular, sendo os resultados melhores no grupo intervenção, porém parâmetros como tempo de internação e mortalidade não mostraram diferença entre os grupos[9], isto demonstra a importância da fisioterapia convencional na melhora dos pacientes, pois as perdas musculares poderiam ser maiores.[9,23] Pacientes que receberam intervenção com mobilização precoce logo no início da internação na UTI tiveram preservação da capacidade física, funcionalidade e diminuição no tempo de internação, porém mesmo a literatura afirmando que a mobilização precoce é uma ferramenta segura e importante na saúde do paciente, a implementação diária nos hospitais ainda é um desafio.[17, 24]

Em um estudo que buscou avaliar com ultrassom em modulo M, mesma técnica utilizada neste trabalho, com indivíduos que estavam por mais de 48 horas em ventilação mecânica, durante teste de respiração espontânea foi observado que pacientes com disfunção diafragmática permaneceram maior tempo em ventilação mecânica.[6] Nosso estudo, observou-se que houve uma correlação indireta entre a variação da mobilidade diafragmática e o tempo de protocolo e ventilação mecânica no grupo convencional e direta no grupo intervenção nos mostrando, assim, que os pacientes com diminuição de mobilidade diafragmática permaneceram mais tempo em ventilação mecânica, prolongando o desmame no grupo convencional. Vários autores sugerem que a mobilização precoce é importante para pacientes críticos com ventilação mecânica prolongada, proporcionando melhora na função pulmonar, diminuindo tempo de ventilação mecânica e permanência na UTI.[1,9,25]

Observa-se também na literatura trabalhos que utilizaram o cicloergômetro de membros inferiores em pacientes na UTI, com métodos semelhantes do presente estudo, acrescentando a mobilização após a retirada da sedação e extubação. O estudo de Burtin et al. concluiu que treinamento com exercícios precoce promove um incremento na capacidade funcional, funcionalidade e força muscular no momento da alta hospitalar.[9] Por isso, acreditamos que a realização do protocolo até a alta hospitalar seria importante para resultados mais precisos.

O tempo de realização do protocolo (7 dias) e a duração e frequência da intervenção foram possíveis limitações na pesquisa realizada e podem ter influenciado nos resultados. Trabalhos que busquem estender o tempo de protocolo durante toda a internação do paciente no hospital podem ser importantes para dirimir estas dúvidas.

Sendo assim, com este estudo verificamos que a mobilidade diafragmática se manteve em ambos os grupos, porém o uso adicional do cicloergômetro não alterou os desfechos analisados. Além disso, houve associação entre a variação da mobilidade diafragmática e os tempos de protocolo e ventilação mecânica no grupo intervenção durante a fase aguda de internação no CTI.

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FIGURAS E TABELAS

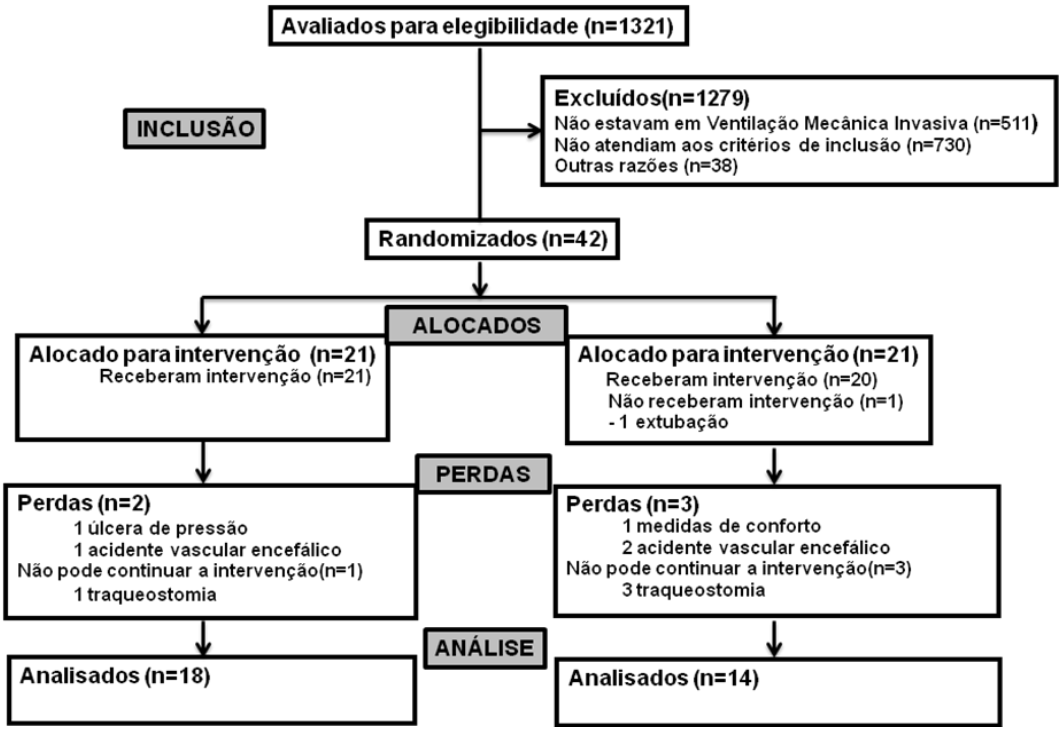

Figura 1. Representação do diagrama do estudo.

Tabela 1. Características da amostra estudada.

Variável	Grupo Intervenção (*n*=18)	Grupo Convencional (*n*=14)	Valor p*
Idade, anos, média ($_{DP}$)	52,3 (22,7)	56,1 (23,0)	0,650
Gênero, *n* (%)			0,465
Feminino	13 (72,2)	8 (57,1)	
Masculino	5 (27,8)	6 (42,9)	
IMC, kg/m^2, média ($_{DP}$)	26,0 (5,8)	23,6 (4,4)	0,105
Lateralidade, *n* (%)			1,000
Destro	16 (88,9)	13 (92,9)	
Sinistro	2 (11,1)	1 (7,1)	
APACHE II, média ($_{DP}$)	23,7 (7,7)	23.8 (8,7)	0,981
Motivo de internação no CTI, *n (%)*			1,000
Sepse	8 (44,4)	7 (50,0)	
Outros	10 (55,6)	7 (50,0)	
Tempo de protocolo, dias, média ($_{DP}$)	4,6 (2,4)	4,9 (2,5)	0,778

Valores expressos em media e desvio padrão, n e porcentagem; *teste t-student para amostras independentes e qui-quadrado ou exato de Fisher (p≤0,05); IMC: índice de massa corporal; APACHE II: *Acute Physiology and Chronic Health Evaluation II*

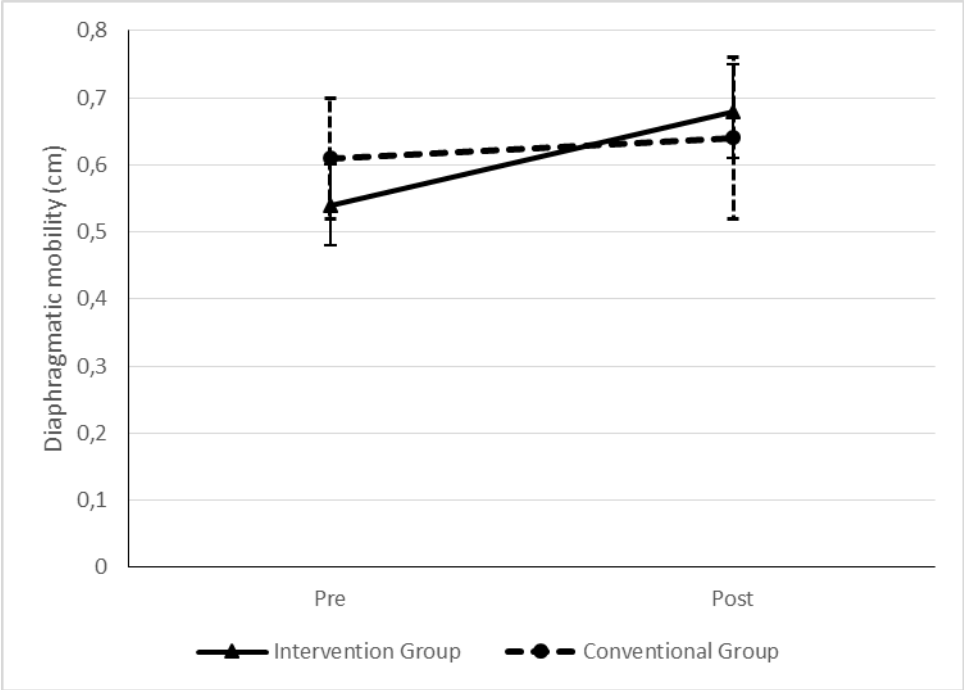

Figura 2. Avaliação do efeito do grupo sobre a mobilidade diafragmática Os círculos e triângulos representam a média e as barras de erro representam o erro padrão. Não houve nenhum efeito significativo no modelo de equações de estimativas generalizadas (GEE): grupo (p=0,853); tempo (p=0,277) e grupo x tempo (p=0,474).

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Tabela 2. Dados referentes a tempo de permanência em ventilação mecânica, internação no CTI e no hospital, sucesso na extubação e óbito.

Variável	Grupo Intervenção (*n*=18)	Grupo Convencional (*n*=14)	Valor p
Tempo de VM, dias, mediana ($_{AIQ}$)	9 (7-10)	8 (5-13)	0,905
Tempo no CTI, dias, mediana ($_{AIQ}$)	11 (10-19)	15 (10-25)	0,619
Tempo no hospital, dias, mediana ($_{AIQ}$)	21 (15-37)	25 (17-36)	0,643
Sucesso na extubação, *n* (%)	12 (66,7)	12 (85,7)	0,411
Óbito, *n* (%)	4 (22,2)	2 (14,3)	0,672

Os dados foram expressos em mediana e amplitude interquartil e n e porcentagem; *Mann Whitney e qui-quadrado ou exato de Fisher (p≤0,05); VM: ventilação mecânica; CTI: centro de tratamento intensivo.

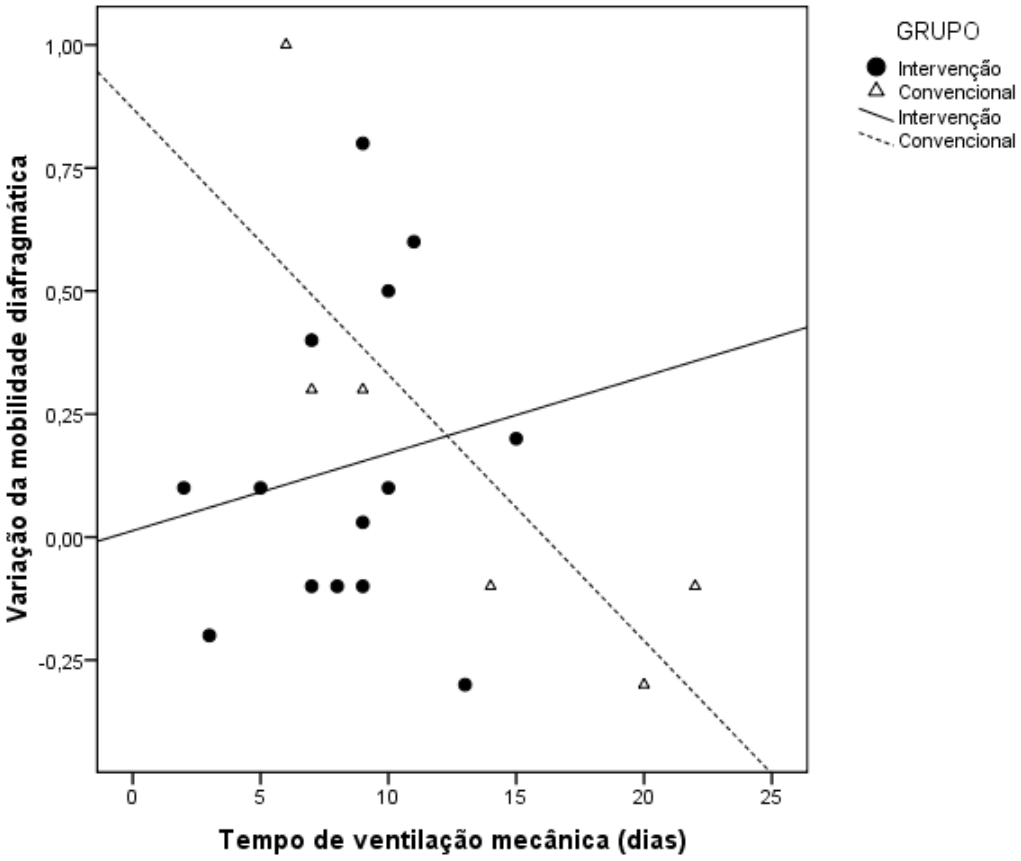

Figura 3. Associação entre a variação da mobilidade diafragmática e tempo de ventilação mecânica nos grupos intervenção (r_s=0,199; p=0,495) e convencional (r_s=-0,873; p=0,010).

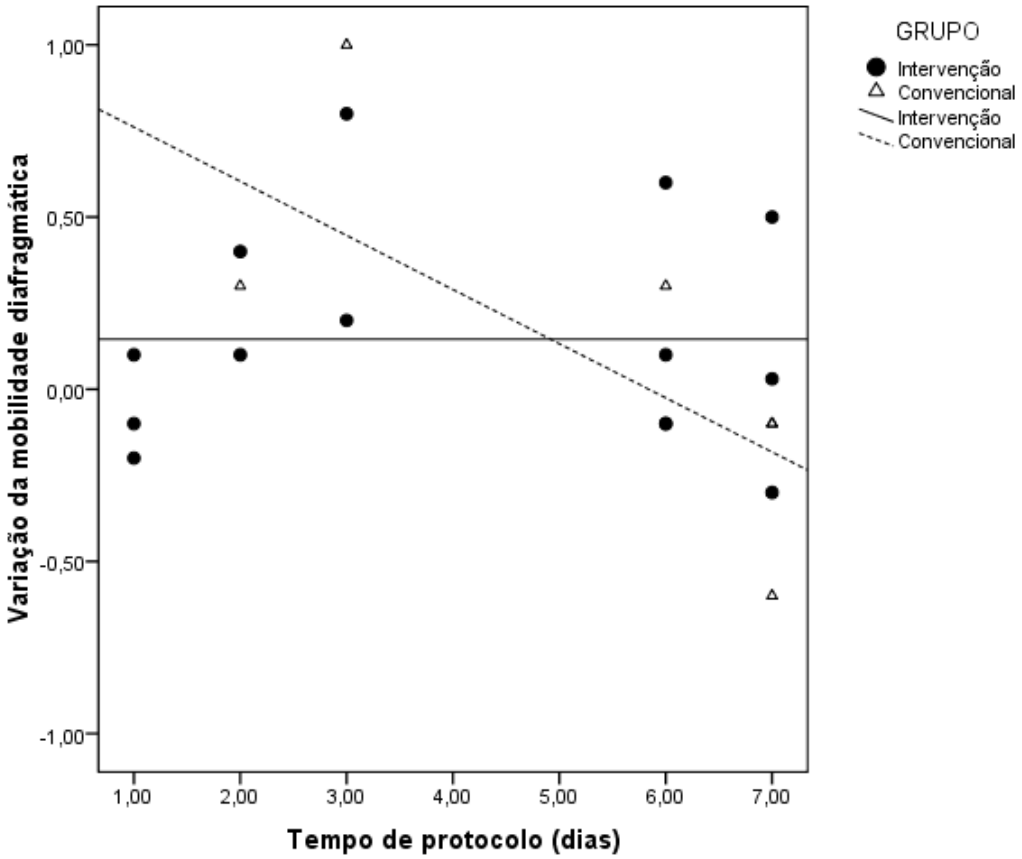

Figura 4. Associação entre a variação da mobilidade diafragmática e tempo de protocolo nos grupos intervenção (r_s=0,031; p=0,915) e convencional (r_s=-0,797; p=0,018).

ARTIGO IV

The effects of early mobilization with neuromuscular electrical stimulation in critical care patients: study protocol for a randomized controlled trial

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ABSTRACT

Background: Neuromuscular electrical stimulation (NMES) has recently began to be used as an early treatment method used to for Intensive Care Unit (ICU) patients on invasive mechanical ventilation (IMV) to compensate for or reduce muscle mass losses and muscular atrophy. To evaluate the effects of early mobilization with neuromuscular electrical stimulation in critical care patients on invasive mechanical ventilation.

Methods/Design: Randomized clinical trial and controled to be conducted in the Intensive care unit (ICU) at the Hospital de Clínicas de Porto Alegre (HCPA), RS, Brazil, composed of the intervention group (conventional physiotherapy and NMES) and placebo group (conventional physiotherapy and placebo NMES). Patients on invasive mechanical ventilation (IMV) who meet the inclusion criteria will be recruited. The intervention will be administered using a 4-channel Ibramed® Neurodyn Functional Electrical Stimulation (FES) machine, every day for thirty minutes until extubation or death. Muscle thickness of pectoral and abdominal muscles and diaphragmatic excursion are evaluated by ultrasound at the beginning of VMI in sétimodia intervention and immediately after extubation. Blood lactate and heart rate variability on the first day will be parsed (before starting the protocol, in the mid thirty minutes and soon after finalizing the application. Statistical analysis will be conducted using the Statistical Package for the Social Sciences (SPSS) 20.0 and the significance level will be $p<0.05$.

Discussion: Several studies have been reported in the literature pointing different methodologies for the utilization of electrical stimulation, and most of them did not produce consistent results to support the use. This scheme shows the different identified in literature considering that the muscles set to receive electrical stimulation have not been studied and measurements and parameters are based on these.

Trial registration: date of enrollment in clinical trials: 17/11/2014; Trial registration number: NCT: 02298114

BACKGROUND

Individuals hospitalized in intensive care units have high clinical severity, where mortality rates are between 5.4 to 33%.[1,2] While in the ICU, patients are often subjected to prolonged immobilization, which in turn plays an important part in the emergence of neuromuscular complications.[3,4] Bed rest causes skeletal muscle weakness, triggering muscular atrophy and loss of 3 to 11% of muscle mass within the first 3 weeks of immobilization.[5] In turn, muscle weakness and loss of muscle mass are caused by acquired myopathy by desuse, polyneuropathy or a combination of the two.[6] The prevalence of patients who acquire polyneuropathy while in an intensive care setting ranges from 58 to 96%.[7] Notwithstanding, recent evidence suggests that muscle weakness can be present within hours of starting invasive mechanical ventilation (IMV) and is detectable in 25 to 100% of patients ventilated for more than 7 days.[8] Among these individuals, muscle weakness is associated with increased length of hospital stay and higher mortality and with impaired functional status that can still be detected years after hospital discharge, compromising their quality of life.[9,10]

Neuromuscular electrical stimulation (NMES) is a technique that consists of generating visible muscle contractions using portable devices connected to surface electrodes[11] and shown to be effective in the treatment of impaired muscle,[12] because it has the potential to maintain synthesis of muscle protein and avert muscular atrophy during prolonged periods of immobilization.[13]

A growing number of studies have been undertaken into the subject over recent years and the majority of them have reported positive results with relation to neuromuscular electrical stimulation. Routsi (2010) [14] published results showing that patients given daily stimulation with electrical current had higher scores on the *Medical Research Council* (MRC) scale for muscle strength, shorter time to wean and shorter length of hospital stay. Rodriguez (2012)[15] found increased muscle resistance after 13 days' intervention. In 2013, Parry (2013)[16] conducted a systematic review that showed that neuromuscular electrical stimulation is a promising technique that can overcome problems caused by the inability of ICU patients to participate actively and was beneficial for attenuating muscle mass losses. Also recently, Maffunetti[17] conducted another systematic review with the

objective of evaluating neuromuscular electrical stimulation for prevention of musculoskeletal weakness in critical care patients, finding that the combination of NMES and conventional physiotherapy offered greater benefit than conventional therapy alone.

The objective of this study is to evaluate the effects of early mobilization using neuromuscular electrical stimulation on muscle mass in critical care patients on invasive mechanical ventilation. Secondary objectives are to compare the effects of neuromuscular stimulation on blood lactate levels, diaphragm thickness, diaphragm excursion and heart rate and also on duration of mechanical ventilation, extubation success and length of stay in the ICU, by comparing results for intervention and control groups.

METHODS

Study design

This study was approved by the ethics committee in research donates Hospital de Clínicas de Porto Alegre Brazil through the platform under the report number 353 996.

This will be a randomized clinical trial recruiting patients of both sexes aged $\geq$ 18 years, no more than 15 days after admission to the intensive care unit at the Hospital de Clínicas de Porto Alegre, after transfer from the emergency department or wards and put on invasive mechanical ventilation for at least 24 hours. Exclusion criteria will include neuromuscular diseases causing motor deficits, such as strokes, multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis and Guillain Barré syndrome. Patients will also be excluded in the event of extubation less than 48 hours after enrolment on the study; complications during the protocol, such as pneumothorax, reintubation or delayed weaning (3 failed spontaneous ventilation tests); body mass index (BMI) > 35 kg/m^2; pacemaker use, history of epilepsy; or if a patient has undergone an operation involving abdominal or pectoral incisions.

Outcome measures

Measured variables:

Muscle analysis

After patients are recruited, and before starting the protocol, each will undergo an ultrasound examination of the thickness of the pectoral and abdominal muscles, during which diaphragm muscle thickness and activity will also be evaluated. Ultrasound scans will be conducted three times: on the day of enrolment on the study, after 7 days on the protocol, and once more 24 hours after extubation.

Cross-sectional muscle thickness was measured with patients positioned lying down in decubitus dorsal, with the head inclined at 30º, using a 3.5mm, 7.5 MHz, linear array ultrasound probe (SONOSITE) to conduct analyses in B mode. The probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin.

The sites for image acquisition will be determined using anatomic landmarks previously determined.[18]

Criteria for probe placement in muscle:

a) Pectoral: the first step is to mark the midpoint of the sternum. The probe is then positioned obliquely from the midpoint in the direction of the mammary line, attempting to achieve alignment through the largest muscle belly.

b) Rectus abdominis muscle: the rectus abdominis muscle will be measured from a point 2 centimetres lateral of the umbilical scar.

Acquisition of images:

After landmarks have been identified, cross-sectional images showing the pectoral and rectus abdominis muscles will be captured. Muscle thickness will then be determined by measuring the distance between the internal margins of the upper and lower aponeuroses of the pectoral and rectus abdominis muscles.

Thickness of Diaphragm

Ultrasound measurement of the thickness of the diaphragm muscle will be conducted with patients lying in decubitus dorsal. The probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin.

Criteria for probe placement: The probe will be positioned perpendicular to the diaphragm in the intercostal space, over the tenth rib at the anteroaxillary line.

Acquisition of images: For image acquisition the probe will be coated in a water-soluble transmission gel to enable acoustic contact without depressing the surface of the skin. The probe will then be positioned perpendicular to the diaphragm and the image will be acquired for measurement of the thickness at the end of the inspiration.

Excursion of the Diaphragm

Criteria for probe placement:

The probe will be positioned using the anatomic window for liver analysis between the medioclavicular line and the anterior axillary line, in the cranial direction. The probe will therefore be positioned medially, cranially and dorsally in such a way that the ultrasound beam transects the posterior third of the diaphragm.[19,20]

Acquisition of images:

Inspiratory and expiratory excursion of the diaphragm will be determined with the ultrasound machine in M Mode. Inspiratory excursion will be defined as the vertical height measured from the baseline at the start of inspiration to the apex of inclination at the end of inspiration. Expiratory excursion will be defined as the vertical height from the apex of inspiration until the baseline returns.

All examinations will be conducted by the same examiner, who will be blinded to which group studied each patient belongs and to the data analysis.

Measurement of blood lactate levels

Blood lactate will be measured using an *Accutrend Plus Roche*® handheld meter on the first day the patient is put on the protocol and before starting NMES, halfway through the stimulation session and within 1 minute of switching off the machine.

Heart rate variability

Heart rate variability will be recorded using a *Polar Smart Coaching*® heart rate monitor on the first day of the protocol for 10 minutes before starting the first NMES session and for 10 minutes after the session ends. Another recording will also be evaluated 24 hours after the first electrical stimulation session, once more for 10 minutes. Finally, one more recording will be made after extubation of each patient.

Protocol

Randomization will be accomplished using the www.randomization.com website in blocks of 10 patients. In order to preserve the secrecy of the randomization sequence, this will be generated by an independent evaluator, away from the data collection setting and unaware of the study, who will be contacted by telephone after enrolment of each patient, at the point at which they are ready to start the protocol.

The patients will be divided into two groups: an intervention group (G1) and a placebo group (G2). The intervention group will undergo neuromuscular electrical stimulation (for 30 minutes) once per day, plus conventional physiotherapy (twice a day), administered by a trained researcher (in an attempt to standardize the

treatment received) which will be continued until extubation or death. The placebo group will undergo conventional physiotherapy administered by the Intensive Care team twice a day, plus placebo electrical stimulation.

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation will be applied using a 4-channel Ibramed® *Neurodyn Functional Electrical Stimulation* (FES) machine. Where necessary, regions with body hair will be shaved in advance. The negative electrodes will be placed over the motor points of the following muscles: pectoral muscles (fibres of the pectoralis major muscle) and rectus abdominis muscles (bilaterally) and a second electrode (positive) will be positioned distally of the first, at a convenient location close to the muscle that is being electrostimulated.

The first training session will have a duration of 30 minutes, which will then be extended by 1 minute for every 2 days of administration. The parameters employed will be as follows: frequency of 50 hertz (Hz), pulse duration of 300 microseconds, Rise Time of 1 second, stimulation time (ST) of 3 seconds, Decay Time of 1 second and relaxation time (OFF) of 10 seconds. The intensity will be increased until muscle contraction is visible or palpable or, for patients who are conscious, intensity will be adjusted according to their tolerance.

The control group will receive placebo electrical stimulation. In this case the procedure is the same, but intensity is set to a sensory level, i.e. not high enough to provoke either visible or palpable muscle contractions.

Conventional physiotherapy

Conventional physiotherapy will be administered by professionals from the physiotherapy department twice a day, for 30 minutes. The protocol will include upper and lower extremity functional diagonals from the proprioceptive neuromuscular facilitation method (two series of 10 repetitions for each bilateral diagonal), manual bronchial hygiene exercises, such as thoracic

vibrocompression, manoeuvres with a manual resuscitator (bag squeezing) and aspiration of secretions where necessary.

Physiotherapy protocols will be started after initial assessments, during the first 48 hours on IMV. During these treatments all groups will be monitored for heart and respiratory rates, mean arterial blood pressure, peripheral oxygen saturation and variables provided by the mechanical ventilator. Arterial blood gas analysis values will also be noted.

After extubation, the patient swill once more be assessed using the same instruments and will continue to receive conventional respiratory and motor physiotherapy until discharge from the ICU.

Statistical analysis

Sample sizes were calculated for the variables pectoral and abdominal muscle mass on the basis of the results of a pilot study with 10 patients, using *Winpepi software*. The results were adjusted for a delta calculated by subtracting the final muscle thickness measurement from the initial measurement and dividing by the number of days the patient spent on the (EF-EI)/ND. The sample size estimated for pectoral muscle thickness was larger, at eighteen patients, nine in each group.

Data will be expressed as means and standard deviations, and standard mean differences. Continuous variables will be analyzed using Student's *t* test and sociodemographic and patient identification variables will be compared with the chi-square test. Generalized Estimating Equations will be used to compare groups, times and stays (adjusted by the length of hospital stay in days). The analysis will be conducted with the aid of the Statistical Package for the Social Sciences (SPSS) 20.0 and the significance level will be $p<0.05$.

DISCUSSION

Abu-Khaber et al. (2013)[21] investigated the effectiveness of neuromuscular electrical stimulation for prevention of muscle weakness and reduction of time on

mechanical ventilation, employing similar inclusion and exclusion criteria to the ones defined for this study. The groups and electrical stimulation parameters were also similar, with the only difference being that the time the machine was left in the ON position was 15 seconds and the total duration of intervention per day was 1 hour. However, that study was unable to prove that NMES had prevented muscle weakness, but did show that it reduced patients' degree of muscle fragility and was also able to show a tendency to shorter mechanical ventilation weaning times, but these results were not statistically significant because of the small sample size.

Maffiuletti et al. (2013)[17] conducted a systematic review of eight studies and found that there were considerable differences between them in terms of the characteristics of the interventions administered. The duration of treatment varied from 7 days to 6 weeks and the majority of studies standardized a specific duration as part of their inclusion criteria, in contrast to this study which will follow patients from their second day on mechanical ventilation until extubation or death and will analyze all patients, irrespective of duration of intervention. Site of NMES application also varied: one study treated the gluteal musculature; all studies applied NMES to the quadriceps; one treated the hamstring muscles; three treated the fibularis longus muscles; and one study applied NMES to the brachial biceps muscles. The majority recruited more than one musculature at the same time. In the protocol described here, the pectoral and abdominal muscles will be recruited, in contrast with the studies reviewed by Maffiuletti et al. (2013)[17] However, in all of those studies the criterion for establishing the minimum NMES intensity was a visible or palpable contraction, in common with this protocol. Maffiuletti et al. (2013)[17] concluded that combining NMES with routine treatment was more effective than routine treatment alone for prevention of muscle weakness in critical care patients, but there is also inconclusive evidence relating to its benefits for prevention of muscle mass loss.

Parry et al. (2013)[16] conducted a systematic review of nine studies, just one of which employed the same NMES frequency (50hz) as the present protocol, and just two of which employed the same pulse duration (300µs). In common with the studies reviewed by Maffiuletti (2013),[17] and in common with the present protocol, all of the studies reviewed by Parry et al. (2013)[16] employed a visible or palpable

contraction to establish the minimum intensity for neuromuscular electrical stimulation. These authors concluded that NMES appears promising, but that the study methodologies lack the uniformity and sample sizes needed to obtain clear results with relation to the acute response to this therapy.

Rodriguez (2012)[15] conducted a study to assess the effects of NMES on muscle strength in patients with sepsis. In this case the intervention was administered twice a day to the brachial biceps and vastus medialis muscles on one side of the body only, in contrast with the present protocol, which stipulates that the intervention would be administered once a day to the pectoral and abdominal muscles on both sides of the body.

Trial status

Recruiting since August 2013.

List of abbreviations

NMES - Neuromuscular Electrical Stimulation

IMV - Invasive Mechanical Ventilation

ICU - Intensive Care Unit

FES - Functional Electrical Stimulation

SPSS - Statistical Package for the Social Sciences

MRC - Medical Research Council

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

ASD was the leader of the research team and conducted a review of the article. ANDA participated in the development of the Protocol, data collection and wrote the article. AS participated in the development of the protocol, participated in the data collection and wrote the article. FAL participated in the protocol development, data collection and wrote the article. LJS participated in the protocol development and conducted a review of the article. MPR participated in the development of the protocol and data collection. TB held data collection and assisted in revising it. WSN participated in the data collection and assisted in revising it. SRRV held the supervision of data collection and revised the article. GS participated in the protocol development and assisted in revising it.

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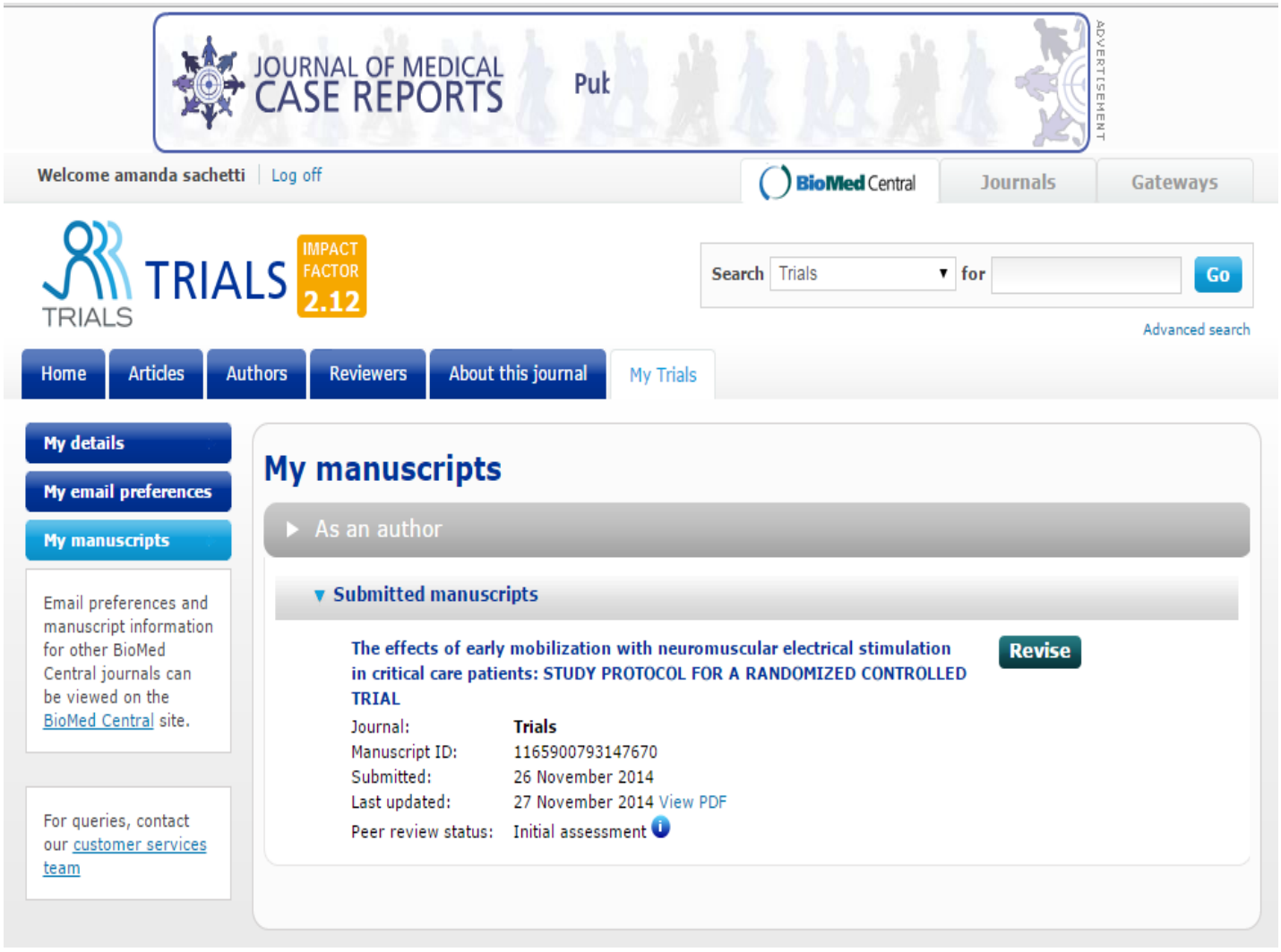
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Peer review status: Initial assessment

ARTIGO V

Use of electrical neuromuscular stimulation to preserve the morphology of abdominal and chest muscles of critical patients: randomized clinical trial

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ABSTRACT

Background: Neuromuscular electrical stimulation (NMES) has been used as an early therapeutic modality at intensive care units (ICUs) to treat patients on invasive mechanical ventilation (IMV) to compensate and/or decrease loss of muscle mass. **Objective:** To evaluate and compare the effects of NMES combined with conventional physical therapy on muscle thickness of critically ill patients on IMV. **Methods:** Double blind randomized controlled trial conducted at the ICU of the Hospital de Clínicas de Porto Alegre, Brazil. Twenty-five patients who had been in hospital for at most 15 days and were receiving IMV for 24 to 48 hours were included in the study. Patients were randomized to the intervention group (NMES + conventional physical therapy) or conventional group (conventional therapy + placebo NMES). Interventions were conducted daily for 30 minutes until the seventh day or upon extubation. **Results:** The primary outcome was thickness of the transverse rectus abdominis and chest muscles of the dominant side assessed by ultrasound before and after the intervention. Eleven patients were included in the intervention group (56±13 years) and fourteen in the conventional group (61±15 years). After NMES administration, rectus abdominis muscle thickness (0.47±0.08 before vs. 0.51±0.08 after, p=0.505) and chest muscle thickness (0.44±0.08 before vs. 0.49±0.08 after, p=0.083) were preserved in the intervention group, whereas there was significant reduction of thickness in the conventional group (rectus abdominis: 0.43±0.05 before vs. 0.36±0.04 after, p=0.001; chest: 0.42±0.05 before vs. 0.35±0.04 after, p=0.001), with a significant difference between the groups. There was statistically significant difference between the groups in terms of length of ICU stay, with shorter length of stay in the intervention group (10±4, p=0.045). We found no significant difference related to the other secondary outcomes between the groups. **Conclusion:** There was no change in the rectus abdominis and chest muscle thickness in the intervention group; however, we found a significant decrease in the measures in the conventional group.

Keywords: electrical stimulation, muscular atrophy, intensive care unit

Trial registration: NCT02298114

INTRODUCTION

Intensive care units (ICUs) are focused on treating critically ill patients. The mortality rates at these units is between 5.4% and 33%.[1,2] According to the 2nd Brazilian Census of ICUs, the mean length of ICU stay ranges from 1 to 6 days[3] and, according to Williams et al,[4] the worldwide mean length of ICU stay is 5.3 days.

Seriously ill patients are often exposed to prolonged immobilization, which contributes to the development of neuromuscular complications.[5,6] Patients who stay in bed for long periods of time are prone to develop skeletal muscle weakness, leading to muscle atrophy and a loss of muscle mass between 3% and 11% in the first 3 weeks of immobilization.[7] Such loss of muscle mass and muscle weakness are caused by acquired myopathy, polyneuropathy, or a combination of both.[8] The development of polyneuropathy worsens the functional status of ICU patients, affecting 25% to 100% of patients ventilated for more than 7 days,[9] with a prevalence of 58% to 96%[10] of ICU patients. In these patients, muscle weakness is associated with increased length of hospital stay, mortality, and decline in functional status even years after hospital discharge, compromising their quality of life.[11,12]

Neuromuscular electrical stimulation (NMES), a technique consisting of generating visible muscle contractions using portable devices connected to surface electrodes,[13] has been shown to be effective in the treatment of deficient muscles.[14] NMES is able to preserve muscle protein synthesis and prevent muscle atrophy during prolonged immobilization.[15] Recently, NMES has started to be used to treat polyneuropathy at ICUs. This technique does not require active cooperation of the patient, and it provides beneficial acute systemic effect on skeletal muscle microcirculation,[16] offering structural and functional advantages to critically ill patients. Studies conducted in critically ill patients with chronic conditions, such as patients with congestive heart failure and chronic respiratory failure, particularly those with chronic obstructive pulmonary disease (COPD), have suggested that NMES has been used in a safe and effective manner, improving these patients' peripheral and respiratory muscle strength.[17-19] Some

studies aimed at improving the ventilation process based on muscle strengthening using this method achieved effective results.[20-22]

Transverse muscle section and/or muscle thickness is strongly associated with force generation capacity. However, few studies have been conducted at ICUs, especially involving trunk muscles, such as abdominal and chest muscles. Studies on NMES have suggested that this technique is useful in medical practice with the purpose of preventing or decreasing loss of muscle mass and peripheral muscle atrophy in this population.[23,24] We could not find reports of its benefits in core muscle groups. Therefore, the main objective of the present study was to evaluate the effects of NMES combined with conventional physical therapy on the rectus abdominis and chest muscle thickness compared with placebo NMES combined with conventional physical therapy in patients undergoing invasive mechanical ventilation (IMV). We also analyzed diaphragm muscle thickness and inhaling and exhaling diaphragmatic motion as secondary objective.

METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The procedures were performed in compliance with the Resolution No. 466/12 of the Brazilian National Health Council. The Ethics Research Committee of the Hospital de Clínicas de Porto Alegre (HCPA) approved the study (CEP HCPA no. 353.996), which was registered in ClinicalTrials.gov (NCT 02298114). All patients' legal guardians signed an informed consent form.

Study Design and Patients

We conducted a double blind study (for outcome assessors and patients), with per-protocol analysis, from August 2013 to August 2014 at the ICU of the HCPA. Female and male participants were aged≥18 years. They had been hospitalized for at most 15 days and had received at least 24 hours of IMV. Exclusion criteria were patients with neuromuscular diseases, such as stroke, multiple sclerosis,

amyotrophic lateral sclerosis, myasthenia gravis, and Guillain Barré, presenting with motor deficit. We also excluded patients who were extubated within 48 hours after being included in the study and those showing complications during the protocol, such as: pneumothorax, prolonged weaning (3 failed spontaneous breathing trials), body mass index (BMI) > 35 kg/m^2, patients with pacemakers, hemodynamic instability (noradrenaline > 0.5 mc/kg/min for a mean arterial pressure > 60 mmHg) with a history of epilepsy or postoperative with abdominal or chest incision, and use of neuromuscular blockers for longer than 2 consecutive days.

Sample selection

A researcher searched the computerized system of the HCPA for sample selection and selected the eligible individuals. Later, using the patients' electronic medical records, we collected identification data, medical diagnosis, and current medical conditions to assess the possibility of including the patients in the study. When a specific patient was selected, his/her legal guardian was asked to sign the informed consent form.

Randomization

Randomization was carried out using the website www.randomization.com in blocks of 10 patients. To ensure the confidentiality of the randomization sequence, the sequence was generated by a blinded assessor who was contacted on the phone after the individual had been included in the study and was ready to start the protocol.

Patients were divided into two groups: intervention group (NMES + conventional physical therapy) and conventional group (placebo NMES + conventional physical therapy). The NMES group received NMES for 30 minutes once a day + conventional physical therapy, whereas the conventional group received placebo NMES for 30 minutes once a day + conventional physical therapy. The protocol was interrupted after the 7th day, when the patient was extubated, or if the patient died, whatever occurred first. The administration of NMES in both groups was performed by professionals trained in procedure standardization. Conventional

physical therapy of both groups was administered by ICU professionals twice a day.

Outcomes

The primary outcome was rectus abdominis and chest muscle thickness of the dominant side. We also analyzed diaphragm muscle thickness and inhaling and exhaling diaphragmatic motion as secondary outcomes. We assessed the ICU and hospital length of stay, time on mechanical ventilation, successful extubation, and death.

Evaluation of outcomes

After inclusion in the trial and before starting the protocol, all participants underwent ultrasound of the chest and abdominal muscles. Muscle thickness and diaphragmatic motion were assessed. Ultrasound was performed at two different times: on the first day of participation in the study (24 to 48 hours of MV) and on the seventh day of IMV or 24 hours after extubation.

Evaluation of muscle thickness

In order to measure the participants' transverse muscle thickness, patients were placed in supine position, the head of bed was elevated at 30°, and a 3.5-mm probe arranged linearly (7.5 MHz linear-array probe - B mode; SONOSITE, Washington, USA) as used to perform the analyses. The probe was coated with water-soluble transmission gel to provide acoustic contact without depressing the dermal layer. The sites for image acquisition were determined using anatomical parameters as described below.[25] In order to assess the chest muscle, the location of the midpoint of the sternum was determined. Starting at this point, the probe was positioned obliquely toward the nipple line, seeking to reach an area of larger muscle belly. In order to assess the rectus abdominis muscle, we obtained the measure at a lateral distance of 2 cm from the umbilicus.

After the sites were marked, a transverse image was acquired. Using this image, we could view the chest and rectus abdominis muscles. Therefore, muscle

thickness was determined based on the measurements performed between the inner edge of the upper and lower aponeuroses of the chest and rectus abdominis muscles.

For assessment of diaphragmatic muscle thickness by ultrasound, the patients were placed in supine position. The probe was positioned perpendicularly to the diaphragm in the intercostal space over the tenth rib on the anterior axillary line. For image acquisition, the probe was positioned perpendicularly to the diaphragm and thickness was measured at the end of inspiration.

For assessment of diaphragmatic motion, the probe was positioned through the anatomical window provided by the liver between midclavicular position and the anterior axillary line towards the skull. Thus, the probe was placed in a medial, cranial, and dorsal position, making it possible for the ultrasound beam to reach the posterior third of the diaphragm.[26,27]

The inhalation and exhalation diaphragmatic excursion was performed in "M" module. The inhalation excursion was considered according to the measurement of the vertical height of the base of the beginning of inhalation up to the peak slope at the end of inhalation. Conversely, the exhalation excursion was considered according to the vertical height of the inhalation peak until return to the base.

All ultrasound exams were performed by the same professional, who was blinded to the group to which patients belonged. The measurements taken by ultrasound exams were expressed in centimeters.

Intervention

NMES was performed using a 4-channel Neurodyn II (Ibramed®, São Paulo, BR). First, hairy body areas were shaved as necessary. However, only the dominant side of each patient was considered for analysis. The electrodes were placed in the motor points of the following muscles: chest muscles (pectoralis major muscle fibers) and rectus abdominis muscles bilaterally. A second electrode was positioned distally to the first, in a convenient location close to the muscle that was being electrically stimulated.

The training session lasted for 30 minutes. One minute was added every two days of administration. The parameters used were as follows: 50 hertz (Hz) of frequency, pulse duration of 300 microseconds, rise time of 1 second, stimulus time (ON) of 3 seconds, decay time of 1 second, and relaxation time (OFF) of 10 seconds. Intensity was increased until muscle contraction was visible or could be identified through palpation. In conscious patients, we adjusted the intensity according to their tolerance.

The control group received placebo NMES. The procedure was blinded; however, the intensity was adjusted at a sensory level, i.e., without visible or palpable muscle contractions.

Chest physical therapy and conventional physical therapy

Conventional physical therapy was administered by ICU professionals twice a day for 30 minutes. The protocol consisted of functional-diagonal movement patterns of the proprioceptive neuromuscular facilitation technique (two series of 10 repetitions of bilateral diagonal movement) using the upper and lower limbs. At first, physical therapy was administered in a passive manner if the patient was sedated. The exercises evolved to assisted movements and active resisted movements according to the patient's cooperation. Manual bronchial hygiene exercises were performed, such as: vibration with chest compression, maneuvers with an Ambu bag (bag-squeezing), and aspiration of secretions when necessary.

Conventional group

This group underwent the same protocol as the intervention group, except for the placebo NMES, that is, the intensity was adjusted up to the sensorial level, without causing visible and palpable muscle contractions.

The protocols were initiated after the baseline evaluation within the first 48 hours of IMV. During protocol administration, the following parameters were monitored in both groups: heart rate and respiratory rate, mean blood pressure, peripheral oxygen saturation, and ventilatory parameters.

After the seventh day or upon extubation (whatever occurred first), patients were assessed again using the same tools and kept receiving only chest physical

therapy and conventional physical therapy provided by the ICU professionals until ICU discharge.

Sample size calculation

Sample size calculation was performed based on a pilot study of ten patients for the variable transverse abdominal and chest muscle thickness using the statistical program Winpepi. These measures were adjusted using a delta value considering the measures of final muscle thickness subtracted from the baseline measures divided by the number of days the participant remained in the protocol. With an effect size of 0.7 standard deviations between the groups, a significance level of 5%, and power of 80%, the largest sample size was found for chest muscle thickness, including 18 patients, 9 for each group.

Statistical analysis

Data storage, arrangement, and maintenance were performed using a MS Excel 2007 spreadsheet. For data analysis, we used the Statistical Package for the Social Sciences (SPSS) 20.0. Data were expressed as mean, standard deviation, or standard error. Student's t test for independent samples, the chi-square test, or Fisher's exact (when more than 25% of the cells had the expected frequency < 5) were used to compare means between the groups for qualitative data. We carried out the Shapiro-Wilk test and tested homoscedasticity using Levene's test. The model of generalized estimating equations (GEE) was performed with Bonferroni's adjustment to assess intra- and intergroup interaction in terms of primary and secondary outcomes. In the model of GEE, we also controlled for possible confounding factors, adjusting for septic and non-septic patients and APACHE II score >25 and <25. Significance level was set at 5% ($p \leq 0.05$).

RESULTS

During the data collection period, 1,321 patients were analyzed considering the eligibility criteria. Of these, 1,283 were not eligible for the study. Thirty-eight patients were randomized to the intervention group (19) and to the conventional

group (19). There were 11 patients in the intervention group and 14 in the conventional group for the final analysis.

Table 1 shows the characteristics of the sample, including a mean overall age of 59±14 years and 64% of male patients. The most prevalent medical diagnosis was sepsis (60%). We only found statistically significant differences when comparing the variable days of ICU stay. ICU stay was shorter in the NMES group (p=0.045). During the administration of NMES, there were not complications or significant changes in the vital signs. None of the patients used neuromuscular blockers for over two consecutive days.

Primary Outcomes

We found a statistically significant difference in the interaction between the intervention and control groups in terms of abdominal and chest muscle thickness (p>0.001). Considering the comparison between the initial and final evaluation within each group, there was no change in the muscle mass of the NMES group, whereas there was a statistically significant decrease in the measures of the conventional group (p>0.001). Even after adjusting for the potential confounders (sepsis and APACHE II), the results were significant (p<0.001) (Table 2).

Secondary Outcomes

We found that there was a significant difference in terms of days of ICU stay, with a shorter length of stay in the intervention group when compared to the conventional group (p=0,045). There was no statistically significant difference in terms of diaphragm muscle thickness and inhaling and exhaling diaphragmatic motion in the interaction between the groups, as well as in the comparison between baseline and end evaluation within each group. Even after adjusting for APACHE II and sepsis, the values remained non-significant (p<0.005) (Table 3).

DISCUSSION

Our study demonstrated that the intervention with NMES combined with conventional physical therapy preserved the chest and rectus abdominis muscle thickness in critically ill patients on IMV. The findings of Gerovasili et al[28] are in agreement with those of our study. These authors evaluated 26 individuals, divided into control and intervention groups. They found that patients who had NMES administered to the quadriceps muscle as well as the control group showed decreased muscle mass. However, this decrease was significantly lower in the NMES group, suggesting that NMES may have a protective effect on loss of muscle mass. Nevertheless, Poulsen et al[29] administered NMES in the quadriceps muscle using the contralateral limb as control. The authors did not find any differences in the muscle mass between the stimulated and non-stimulated side assessed by computed tomography. Gruther et al[30] used ultrasound to investigate the effects of NMES on the thickness of quadriceps muscle during the acute phase (less than 7 days of hospitalization) and in the long term (more than 14 days after admission) in critically ill patients. The authors found increased thickness only for long-term patients who started NMES after 2 weeks of ICU admission. However, there was no increased thickness in acute patients. This is in agreement with the findings of our study, demonstrating no change in muscle mass even when starting the NMES protocol early (up to 48 hours of ICU admission).

As for the secondary outcomes, we found no statistically significant difference regarding the interaction between the groups in terms of diaphragm thickness and inhaling and exhaling diaphragmatic motion. There was a significant difference in the number of days of ICU stay, with a shorter stay in the NMES group when compared with the conventional group. The implementation of early mobilization programs, which is the type of intervention proposed in our study, may lead to reduction of ICU length of stay.[31] The use of MV may also induce diaphragmatic dysfunction, reducing the patients' force generation capacity and mobility.[32,33] Martin et al[34] used physical therapy to assess the improvement in the peripheral and respiratory muscle strength as well as the functional status of mechanically ventilated patients. They also found a positive correlation between upper limb strength and ventilation weaning time. However, in our study, there was no statistically significant difference regarding days of IMV and reintubation rate. In a

study by Dall'Acqua et al,[19] the authors found increased inspiratory and expiratory muscle strength by administering NMES using Russian current in the rectus abdominis and abdominal oblique muscle in inpatients with COPD when compared with the control group.

The most prevalent ICU admission diagnosis in our study was sepsis (60%). Studies involving the use of NMES conducted at ICUs demonstrated that the most common diagnoses at admission are sepsis, COPD, and trauma.[28,30,35] Sepsis is known for generating a reaction of protein hypercatabolism in the muscles, contributing to the loss of muscle mass. Loss of muscle mass is partially attributed to sepsis, multiple organ dysfunction syndrome, and use of drugs, such as neuromuscular blockers, as well as immobilization.[36] Therefore, we adjusted the outcomes by dividing the patients into septic and non-septic, and the results were statistically significant even after the adjustment. The reintubation rate in the NMES group was 25%, whereas there was a 38% rate in the convention group. Routsi et al[37] used NMES in quadriceps and peroneus longus muscles and found reduced weaning time in the intervention group. However, in agreement with our findings, there was no significant difference in the reintubation rate between the groups. Conversely, another study conducted by Abu-Khaber,[38] evaluating the prevention of muscle weakness and facilitation of weaning from mechanical ventilation in critically ill patients using NMES in the quadriceps muscle starting the protocol in the first two days of mechanical ventilation, reported unclear conclusions about the role of NMES in facilitating the weaning process. In addition, the number of days on mechanical ventilation was lower in the NMES group when compared with placebo, but the statistical significance level was very low ($p=0.048$).

In our study, APACHE II score was similar in both groups. In a systematic review on the use of NMES in intensive care, Parry et al[39] concluded that patients with APACHE II score greater than 20 did not benefit from NMES to preserve muscle mass. Conversely, those individuals with an APACHE II score lower than 16 showed better muscle response to NMES. Such negative results may be linked to the correlation between NMES intensity and disease severity, because the excitability of muscle tissue in this condition may induce dysfunctions of the

muscle membrane compromising its contraction and increasing catabolism, thus enhancing loss of muscle mass.[29,40] Letter et al[41] evaluated the risk factors for developing polyneuromyopathy in critically ill patients. APACHE II score seemed to be relevant in the analysis of these risk factors and was found to be an important indicator for the development of muscle weakness. However, our findings demonstrated positive effects in terms of preservation of muscle mass, even after adjusting the values for patients with APACHE II score >25 and <25, suggesting that NMES may prevent muscle mass loss even in patients with high APACHE II score.

The mean NMES time in our study was 5 days in the intervention group. In comparison with our study, the duration of treatment was significantly longer in days in other studies using NMES in the peripheral muscles of critically ill patients; therefore, these studies showed positive results regarding muscle mass gain.[28,29] The studies by Gruther et al[42] and Routsi et al[37] used, respectively, 60 and 55 minutes a day of NMES, demonstrating positive results in terms of muscle mass and development of polyneuropathy. In our study, we initially used 30 minutes of NMES in the rectus abdominis and chest muscles, adding 1 minute every 2 days, and we found positive results in terms of muscle thickness. Such findings suggest that the initial daily use of 30 minutes of NMES bring benefits to critically ill patients.

We decided to use ultrasound to evaluate muscle and diaphragmatic behavior in the administration of NMES because it is a valuable tool in the management of ICU patients.[43] Ultrasound exams make it possible to quantify diaphragmatic motion and accurately assess muscle atrophy. Some studies used perimetry to assess patients.[7,44] In a systematic review on the use of NMES in critically ill patients,[46] only three out of the eight studies published used ultrasound as a tool for evaluation.[23] The choice of this tool seems to be more accurate in muscle evaluation in ICU patients[28] and overcomes many of the problems associated with anthropometric and body composition measures, such as edema, which may be a bias when analyzing muscle thickness.[30] Currently, ultrasound is the most reliable method and it established validity in intensive care.[39]

Our findings are limited by a relatively small number of patients who underwent NMES sessions. Furthermore, sedation and the use of vasopressor drugs might have affected the microcirculation in these patients.

Further studies with larger samples might provide subgroup analysis to identify the potential beneficial effects of NMES when administered to the muscles involved in respiratory mechanics of different populations, since the initial results of this approach are shown to be positive in the prevention of loss of muscle mass in these muscle groups.

CONCLUSION

The results of the present study indicated that there was preservation of the muscle mass of the rectus abdominis and chest muscle in the intervention group, whereas there was a significant reduction in these measures in the conventional group. In addition, the length of ICU stay was significantly shorter in the NMES group.

Abbreviations

NMES, Neuromuscular Electrical Stimulation; ICU, Intensive Care Unit; IMV, Invasive Mechanical Ventilation; APACHE II, Acute Physiology and Chronic Health Evaluation; US, ultrasound; HCPA, Hospital de Clínicas de Porto Alegre

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AMDA and AS made substantial contribution to conception and design of the review. All authors made substantial contribution to data acquisition, analysis, and interpretation. All authors were involved in drafting and critically revising.

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FIGURES

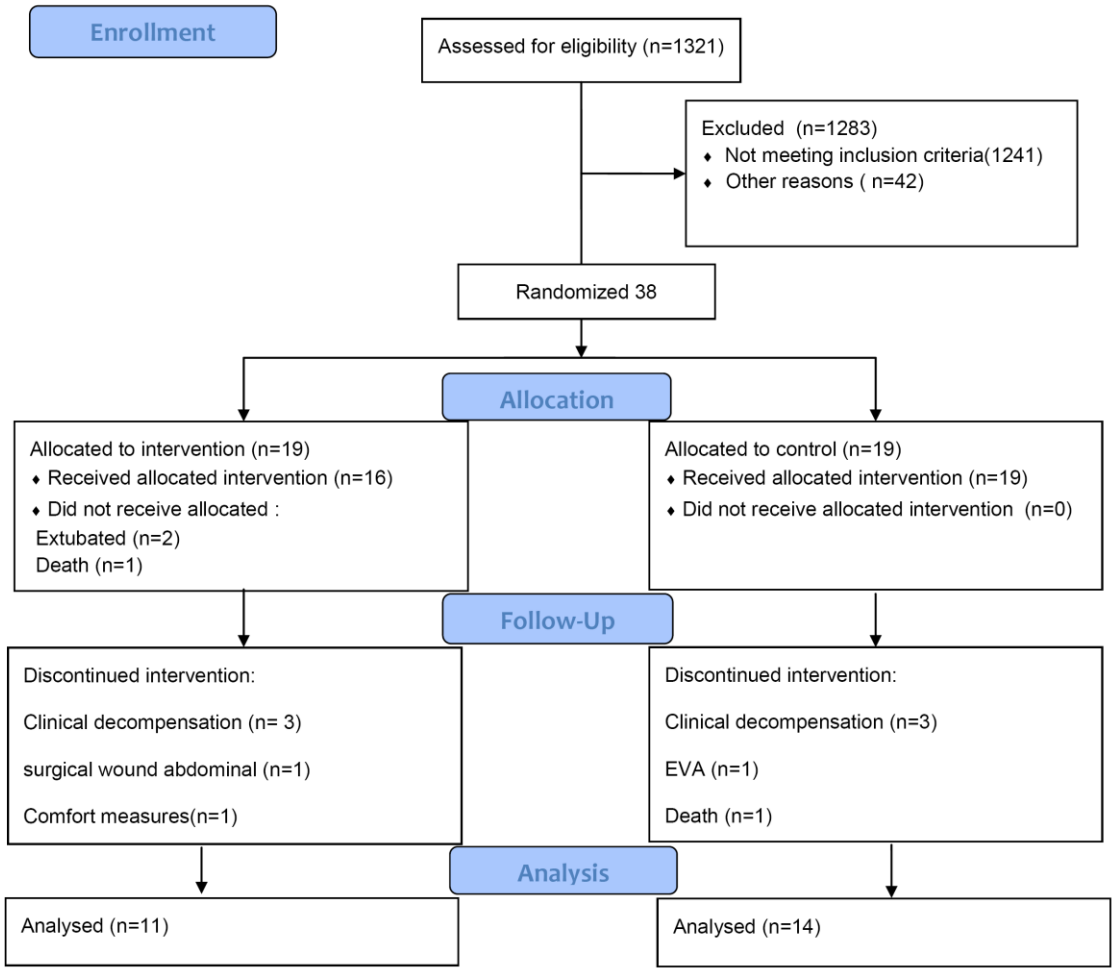

Figure 1. Study flowchart.

TABLES

Table 1. Characteristics of the sample.

Variables	Intervention group (n=11)	Conventional group (n=14)	P-value
Age (years)	56±13	61±15	0.436
Sex n (%)			1.000
Female	4 (36.3)	5 (35.7)	
Male	7 (63.7)	9 (64.3)	
BMI (kg/m^2)	25 ± 4	24±5	0.687
Laterality n (%)			0.604
Right-handed	10 (90.9)	11 (78.5)	
Left-handed	1 (9.1)	3 (21.5)	
APACHE II	26±5	29±7	0.206
Continued sedation (days)	2±1	3±2	0.845
Hemodialysis n (%)	8 (73)	5 (43)	0.227
NMES time (days)	5±2	5±2	0.889
ICU stay (days)	10±4	16±9	0.045
MV time (days)	7±2	8±3	0.607
Reintubation rate n (%)	3 (25)	5 (38)	1.000
Deaths n (%)	3 (27)	3 (21)	1.000
Reason for ICU admission (n)			
Sepsis	7	8	
ALE	1	2	
Other	3	4	

Data were expressed as n (%), mean ± standard deviation, median (interquartile range). Body Mass Index (BMI) in kilograms per square meter (kg/m²); P-value was calculated using Student's t test for quantitative data and the chi-square test or Fisher's exact test for qualitative data ($p>0.05$). Intensive Care Unit (ICU), Mechanical Ventilation (MV), Neuromuscular Electrical Stimulation (NMES), Acute Physiology and Chronic Health Disease Classification System II (APACHE II), Acute Lung Edema (ALE).

Table 2 – Comparison of the muscle thickness between the groups

Variables	Intervention Group (n=11)				Conventional Group (n=14)				Interaction effect (group vs. time)	
	Baseline	End	Difference (95%CI)	P*	Baseline	End	Difference (95%CI)	P*	p**	Adjusted P***
	Mean ± SE	Mean ± SE			Mean ± SE	Mean ± SE				
CT	0.44 ± 0.08	0.49 ± 0.08	0.05 (-0.00 to 0.10)	0.083	0.42 ± 0.05	0.35 ± 0.04	-0.06 (-0.10 to -0.02)	<0.001	<0.001	<0.001
AT	0.47 ± 0.08	0.51 ± 0.08	0.04 (-0.02 to 0.10)	0.505	0.43 ± 0.05	0.36 ± 0.04	-0.07 (-0.10 to -0.04)	<0.001	<0.001	<0.001

Data were expressed as mean±standard error. *intra-group effect using Bonferroni's adjustment method through the generalized estimating equation model (GEE); ** intergroup effect using Bonferroni's adjustment method through the generalized estimating equation model (GEE); *** adjusted for APACHE II and sepsis. Chest thickness (CT), Adbominal thickness (AT).

Table 3 – Comparison of diaphragmatic motion and thickness between the groups.

Variables	Intervention Group (n=11)				Conventional Group (n=14)				Interaction effect (group vs. time)	
	Baseline	End	Difference (95%CI)	P*	Baseline	End	Difference (95%CI)	P*	P**	Adjusted P***
	Mean ± SE	Mean ± SE			Mean ± SE	Mean ± SE				
IDM	0.36 ± 0.05	0.47 ± 0.05	0.11 (-0.05 to 0.26)	0.397	0.46 ± 0.07	0.51 ± 0.10	0.05 (-0.23 to 0.33)	1.000	0.638	0.554
EDM	0.23 ± 0.04	0.31 ± 0.04	0.08 (-0.06 to 0.22)	0.818	0.35 ± 0.07	0.31 ± 0.08	-0.04 (-0.28 to 0.20)	1.000	0.255	0.205
DT	0.28 ± 0.05	0.27 ± 0.05	-0.01 (-0.11 to 0.08)	1.000	0.20 ± 0.01	0.18 ± 0.01	-0.02 (-0.05 to 0.03)	1.000	0.960	0.996

Data were expressed as mean±standard error. *intra-group effect using Bonferroni's adjustment method through the generalized estimating equation model (GEE); ** intergroup effect using Bonferroni's adjustment method through the generalized estimating equation model (GEE); *** adjusted for APACHE II and sepsis. Inhaling Diaphragmatic Motion (IDM), Exhaling Diaphragmatic Motion (EDM), Diaphragm Thickness (DT).