DISSERTAÇÃO DE MESTRADO

EFEITOS DA ESTIMULAÇÃO ELÉTRICA NEUROMUSCULAR NA MORFOLOGIA DA MUSCULATURA ABDOMINAL E PEITORAL DE PACIENTES CRÍTICOS EM VENTILAÇÃO MECÂNICA

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

ESTIMULAÇÃO ELÉTRICA NEUROMUSCULAR PRESERVA MORFOLOGIA DA MUSCULATURA ABDOMINAL E PEITORAL DE PACIENTES CRÍTICOS EM VENTILAÇÃO MECÂNICA

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Dedico todo o esforço deste trabalho

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‘’ Não sou obrigado a vencer mas tenho o dever de ser verdadeiro. Não sou obrigado a ter sucesso mas tenho o dever de corresponde à luz que tenho’’

Abraham Lincoln

SUMÁRIO

LISTA DE ABREVIATURAS

EENM: Estimulação Elétrica Neuromuscular

VMI: Ventilação Mecânica Invasiva

UTI: Unidade de Terapia Intensiva

ATP: Adenosina trifosfato

SIRS: Síndrome da Resposta Inflamatória Sistêmica

US: Ultrassonografia

DPOC: Doença Pulmonar Obstrutiva Crônica

FES: *Functional Eletrical Stimulation*

APACHE II: *Acute Physiology and Chronic Health Evaluation*

MRC: *Medical Research Council*

RESUMO

Objetivo: Avaliar os efeitos da estimulação elétrica neuromuscular (EENM) na espessura muscular abdominal e peitoral de pacientes críticos em ventilação mecânica invasiva (VMI). **Metodos:** Estudo randomizado duplo cego. Foram incluídos 25 pacientes com idade média de 59±14 anos com no máximo 15 dias de internação hospitalar que estavam com 24 a 48 horas de VMI. Os pacientes foram randomizados para o grupo intervenção (EENM associado a fisioterapia convencional) ou para o grupo convencional (EENM placebo associada a fisioterapia convencional). As intervenções foram realizadas diariamente, tendo duração inicial de 30 minutos, até o sétimo dia ou extubação dos pacientes. **Medições e Principais Resultados:** O desfecho primário foi espessura muscular transversal do reto do abdomem e peitoral do lado dominante avaliados através da ultrassonografia antes e após o protocolo. Na comparação da interação entre os grupos encontramos diferença significativa (p>0,001), onde as medidas do peitoral e abdominal foram preservadas no grupo intervenção, havendo uma diminuição significativa no grupo controle. **Conclusão**: Houve preservação da massa muscular no grupo intervenção e uma diminuição significativa das medidas no grupo convencional.

INTRODUÇÃO

Pacientes na Unidade de Terapia Intensiva (UTI) estão expostos frequentemente à imobilização prolongada que desempenha um papel importante nas complicações neuromusculares.[1,2] O repouso no leito reflete em fraqueza músculo esquelética, induzindo a atrofia muscular com uma perda de 3% a 11% de massa muscular nas primeiras 3 semanas de imobilização.[3] Atualmente é reconhecido que pacientes com longa permanência em terapia intensiva adquirem a polineuropatia do doente crítico, atingindo uma prevalência de 58% a 96%.[4]

Por sua vez, a fraqueza muscular dos pacientes críticos está associada com o aumento do tempo de hospitalização, mortalidade e declínio do estado funcional até mesmo anos após alta hospitalar, comprometendo a qualidade de vida destes indivíduos.[5,6] Pacientes submetidos a períodos prolongados de ventilação mecânica sofrem fraqueza muscular esquelética global, que limita a capacidade de desmame bem como de executar as atividades de vida diária.[7] Portanto, a associação de ventilação mecânica prolongada com efeitos do imobilismo resulta em perda de fibras musculares acarretando significativa redução da força muscular respiratória e periférica.[8]

Outros fatores de risco incluem os níveis glicêmicos, hiperosmolaridade, uso de nutrição parenteral e medicamentos como corticosteróides e bloqueadores neuromusculares.[7] Embora a etiologia dessa fraqueza muscular seja multifatorial, a mobilização precoce de pacientes internados na UTI pode ajudar a reduzir a atrofia, perda de massa muscular e descondicionamento associado ao repouso no leito. [2]

A estimulação elétrica neuromuscular (EENM) vem surgindo como uma modalidade terapêutica precoce, utilizada em UTI em pacientes sob ventilação mecânica invasiva a fim de compensar e/ou diminuir a perda de massa e atrofia muscular. É um método não- invasivo, que independe dos esforços do paciente e não afeta as variáveis cárdio-respiratória.[3]

Em pacientes incapazes de realizar contração muscular voluntária como nos pacientes críticos, a estimulação elétrica neuromuscular é um recurso

frequentemente utilizado por fisioterapeutas para melhora da função muscular, proporcionando contração muscular involuntária e aumento da capacidade oxidativa, podendo representar uma alternativa de treinamento físico mais suave. 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.[9]

Sabe-se que a área de secção tranversal e/ou a espessura muscular tem forte associação com a da capacidade de produção de força. Contudo, poucos estudos ainda foram feitos utilizando EENM no ambiente de UTI, sendo que até o presente momento não identificamos nenhum estudo abordando seus efeitos sobre as musculaturas do tronco como o peitoral e os abdominais. Os trabalhos existentes sobre EENM destacam-a como um recurso favorável a ser utilizado na prática clínica e que impede ou diminui a perda de massa e atrofia muscular periférica nesta população[10-12], porém não temos relato dos benefícios de sua aplicação em grupos musculares centrais que participam da mecânica respiratória, sendo essa a justificativa para elaboração deste estudo. Portanto objetivo principal deste estudo foi avaliar 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 (VMI). Como objetivo secundário foi analisada a espessura do diafragma e medidas de mobilidade diafragmática inspiratória e expiratória.

REVISÃO DA LITERATURA

2.1 Perda de Massa Muscular e Fraqueza Adquirida na Unidade de Terapia Intensiva

A Unidade de Terapia Intensiva (UTI) desempenha um papel crucial na sobrevida de pacientes gravemente enfermos, tendo o objetivo centrado na recuperação ou manutenção de suas funções fisiológicas.[13] No entanto, pacientes criticamente doentes tratados em UTI frequentemente desenvolvem fraqueza muscular que é associada com a imobilidade devido ao repouso no leito, aumento da duração da ventilação mecânica invasiva (VMI), tempo de internação na UTI e mortalidade, podendo prejudicar o estado funcional até anos após a alta hospitalar.[14-16] Evidências apontam para uma diminuição de força muscular em 1% a 1,5% por dia de repouso absoluto e 4% a 5% para cada semana, o que acarreta uma redução de 10% após uma semana de imobilização completa.[16,17]

Repouso no leito resulta em alterações nas fibras musculares, marcadores inflamatórios e parâmetros metabólicos. A atrofia muscular ocorre por desuso e isso se explica devido à ocorrência de um desequilíbrio entre a síntese de proteína muscular, que causa perda líquida de massa muscular, levando a atrofia.[18,19] Há associação de perda de peso corporal com um aumento na porcentagem de gordura.[20] O imobilismo também reduz o glicogênio e adenosina trifosfato (ATP), a resistência muscular, que pode comprometer a irrigação sanguínea com consequente diminuição da capacidade oxidativa, redução da força muscular e torque, que resulta em falta de coordenação devido à fraqueza, com atrofia das fibras musculares do tipo I e II, gerando movimento de má qualidade.[13]

Sabemos dos avanços que ocorreram na terapia intensiva nas duas últimas décadas, principalmente na VMI, que aumentou a sobrevida dos pacientes críticos. No entanto, alguns pacientes desenvolvem a necessidade de VMI prolongada mostrando-se descondicionados devido à insuficiência respiratória.[21] Essa necessidade prolongada pode levar ao desenvolvimento de atrofia diafragmática, ou seja, o ventilador mecânico assume uma proporção

maior de trabalho respiratório, reduzindo o trabalho exercido pela ventilação espontânea. Isso resulta na ausência completa ou parcial da ativação neural e da mecânica muscular reduzindo assim a capacidade que o diafragma tem de gerar força.[20,21] Além deste, existem outros efeitos deletérios advindos do uso da VMI, como a disfunção dos mecanismos de higiene traqueobrônquica, diminuição da expansibilidade torácica, alteração na ventilação/perfusão (V/Q), lesão mecânica nas vias aéreas e aumento no risco de infecções respiratórias.[22]

Nos dias atuais, a sedação profunda e o repouso no leito ainda são uma prática comum na rotina médica de cuidados de pacientes ventilados mecanicamente, entretanto na literatura atual há uma nova tendência no manejo do paciente em VMI incluindo redução da sedação profunda e ampliação da abordagem de mobilização e do treinamento físico funcional, o mais precoce possível nestes pacientes.[8]

A fraqueza na UTI é geralmente relatada em pacientes que foram ventilados por mais que 7 dias, entretanto há provas de que a lesão no músculo e nervo pode começar no início do curso da hospitalização, principalmente em pacientes de alto risco.[23] A etiologia e patogênese dessa fraqueza são multifatoriais. Polineuropatia da doença crítica ou miopatia são causas bem conhecidas, associadas com a Síndrome da Resposta Inflamatória Sistêmica (SIRS), sepse, falência de múltiplos órgãos, além de níveis séricos de glicose, hiperosmolaridade, uso de nutrição parenteral e fármacos como corticosteróides e bloqueadores neuromusculares.[2,18]

Na última década estudos identificaram uma série de fatores de risco para fraqueza muscular adquirida na unidade de terapia intensiva, mas na sua maioria são estudos observacionais pequenos com limitações metodológicas importantes.[24,25] Há dados limitados e conflitantes em relação à associação entre a gravidade da doença e fraqueza adquirida na UTI, sendo a neuromiopatia uma importante causa da mesma, podendo ser caracterizada como uma forma de falência de órgãos neuromusculares.[24]

A hiperglicemia pode ser um importante fator de risco para o desenvolvimento de fraqueza e perda de massa muscular. Dois grandes

estudos controlados, realizados em UTI cirúrgica e médica, observaram uma redução significativa da fraqueza muscular com o rígido controle glicêmico.[26,27] Podemos destacar a associação de desenvolvimento de fraqueza muscular na UTI com outros dois fatores de risco comumente citados: corticosteróides e agentes bloqueadores neuromusculares. Apesar de três estudos observacionais prospectivos mostraram um maior risco de fraqueza muscular adquirida na UTI com a exposição de corticosteroides,[28-30] outros falharam em demonstrar uma associação significativa.[25,31] Da mesma forma, há evidências que sugerem fraqueza persistente após infusão prolongada de bloqueadores neuromusculares, no entanto estudos subsequentes não encontraram qualquer associação significativa com a fraqueza muscular.[32] Um estudo recente com doentes com síndrome da desconforto respiratório agudo, onde os pacientes foram randomizados para tratamento com cisatracúrio ou placebo, demonstrou uma redução significativa na mortalidade em 28 dias, sem qualquer diferença significativa entre os grupo em relação a fraqueza adquirida na UTI.[33]

2.2 Avaliação da Perda Muscular na UTI

Alguns dos indivíduos internados nas UTIs desenvolvem claramente polineuropatia, enquanto outros miopatia, mas com a evolução do conhecimento sobre estas condições, agora é aceito que a maioria dos pacientes desenvolvem uma mistura complexa envolvendo patologias de nervos e músculos. O diagnóstico de fraqueza muscular na UTI é dado com base na história consistente e exame físico dos pacientes, e às vezes é apoiada por estudos da condução nervosa (eletromiografia), e raramente por biopsia dos músculos ou nervos.[34] No entanto estas abordagens de diagnóstico podem ser um desafio, porque aspectos tanto do exame físico e do teste eletromagnético exigem cooperação do paciente, além disso, estudos eletrodiagnósticos são desconfortáveis quando os pacientes não estão totalmente sedados. Alguns são invasivos, de difícil realização e interpretação em um ambiente de terapia intensiva por causa da interferência elétrica.[35]

Novas técnicas para auxiliar no diagnóstico vem sendo utilizadas, servindo como potenciais biomarcadores da progressão de doença, sendo exploradas atualmente para avaliação/diagnóstico de pacientes com risco de

desenvolvimento de fraqueza muscular na UTI. A ultrassonografia (US) é um sistema emergente de diagnóstico em que os transdutores de alta resolução são utilizados para aferir imagem dos nervos e músculos dos pacientes com condições que afetam o sistema nervoso periférico.[10] Ela é frequentemente usada em combinação com estudos eletrodiagnósticos, e está ganhando popularidade porque é indolor, não-invasiva, sem radiação, e fornece informações anatômicas em tempo real sobre nervos e músculos. Além disso o ultrassom é uma tecnologia de fácil acesso, particularmente na UTI.[36,37]

Dois estudos publicados detectaram, através da US, desenvolvimento de atrofia muscular em pacientes internados na UTI.[38,39] Já um terceiro estudo não detectou a instalação da atrofia muscular, avaliada com o mesmo instrumento, sugerindo que este fato pode ser atribuído aos dias de segmento dos pacientes (14 dias), relatando que um período mais longo de observação, como observado em outros estudos, pode ter implicado na detecção da atrofia.[40]

2.3 Alterações Diafragmáticas em Pacientes em Ventilação Mecânica Invasiva

Os distúrbios neuromusculares adquiridos na UTI podem apresentar-se como fraqueza flácida e difusa.[41] O quadro clínico consiste em dificuldades no desmame da ventilação mecânica, tetraparesia e perda de massa muscular.[42] Dificuldades no desmame são atribuídas ao comprometimento do nervo frênico, diafragma, músculos respiratórios intercostais e outros acessórios também afetados.[43]

O diafragma é o principal músculo respiratório dos seres humanos, sendo suscetível a diversas agressões comuns na UTI, tais como hipotensão, hipóxia e sépse.[44,45] Além disso, a VMI propriamente dita pode induzir disfunção diafragmática, diminuindo a força geradora de capacidade do mesmo, uma condição referida como disfunção diafragmática induzida pelo ventilador.[46,47] Desta forma a função do diafragma em pacientes críticos pode ser facilmente comprometida. No entanto, a prevalência de disfunção diafragmática em pacientes internados na UTI ainda não são claras[48,49].

Estudos experimentais em modelos animais indicam que a infecção pode induzir significativa fraqueza do diafragma.[50,51] Além disso, os dados sugerem que hiperglicemia e baixos níveis de albumina sistémicas são fatores de risco para a ventilação mecânica prolongada e poderiam, teoricamente, ser associado com o desenvolvimento de fraqueza muscular respiratória. No entanto a importância da infecção, uremia, hiperglicemia e níveis reduzidos de albumina, como fatores de risco para o desenvolvimento de fraqueza diafragmática em pacientes sob VMI, ainda são desconhecidos.[52-54]

A fraqueza do diafragma pode predispor os doentes a insuficiência respiratória prolongada, prolongando significativamente o tempo necessário para o desmame da ventilação mecânica e piora os resultados clínicos.[55]

As ferramentas tradicionalmente usadas para estudar as disfunção do diafragma são a fluoroscopia, estudo da condução do nervo frênico e medição de pressão transdiafragmática. No entanto, as mesmas apresentam algumas limitações e desvantagens, incluindo o uso de radiação ionizante, baixa disponibilidade, invasivas, bem como a necessidade de transporte de pacientes e profissionais qualificados ou especificamente treinados.[56]

Recentemente, o ultrassom tem sido utilizado para avaliar a função diafragmática. Vantagens do ultrassom incluem segurança, prevenção de riscos de radiação e disponibilidade na beira do leito.[57] A ultrassonografia (US) pode ser usada para medir a mobilidade diafragmática, espessura e velocidade de contração do mesmo.[57-59] Entre os pacientes com necessidade de VMI, a detecção de disfunção diafragmática realizada por US durante o teste de respiração espontânea, está associada com maior tempo de VMI e desmame.[51]

2.4 Mobilização Precoce com Estimulação Elétrica Neuromuscular na Unidade de Terapia Intensiva

Em termos gerais, mobilização precoce de pacientes na UTI inclui a aplicação dos métodos tradicionais de fisioterapia e/ou o uso de novas técnicas de mobilização precoce, por exemplo bicicleta ergométrica e estimulação elétrica neuromuscular (EENM). A mobilização precoce é indicada para pacientes que de alguma forma permanecem quase imóvel, podendo ser uma

alternativa segura e viável na recuperação funcional de pacientes críticos, reduzindo o tempo de internação na UTI, diminuindo readmissões na mesma e até mesmo melhorar sobrevivida destes pacientes.[61--65]

Neste contexto, destacamos a EENM como uma forma de mobilização precoce na UTI, consistindo em aplicação da eletricidade com finalidade terapêutica, promovendo reações biológicas e fisiológicas, as quais são aproveitadas para melhorar os distintos tecidos, quando se encontram acometidos de enfermidades ou alterações metabólicas das células que o compõem. A eletroestimulação aplicada na superfície da pele sobre uma parte do sistema neuromuscular intacto pode provocar um potencial de ação no músculo ou fibra nervosa que é idêntico aos potenciais de ação gerados fisiologicamente. Portanto, sabemos que o potencial evocado no axônio motor periférico alfa resulta em contração muscular, que também parece ser idêntica à contração voluntária fisiológica.[8]

Os pacientes criticamente enfermos, que são submetidos a períodos prolongados de imobilização, estão sujeitos a diversas complicações decorrentes da doença. Alguns exemplos destas complicações são inflamações sistêmicas, atelectasia, disfunção vascular e metabólica, contraturas articulares, úlceras de pressão e perda de massa muscular.[40,66,67] A redução da massa muscular é uma das complicações mais debilitantes em pacientes críticos dificultando a sua recuperação após a alta da UTI devido a perda de funcionalidade.[68,69]

Em pacientes incapazes de realizar contração muscular voluntária como acontece nos pacientes críticos em fase aguda, a EENM é um recurso frequentemente utilizado por fisioterapeutas para melhora a 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.[70]

A EENM tem sido utilizada em pacientes com Doença Pulmonar Obstrutiva Crônica (DPOC) grave sob ventilação mecânica. O treinamento físico é capaz de melhorar sua força muscular, mesmo quando acamados com um grau severo de comprometimento funcional e fazendo uso de VMI. A adição da

EENM pode aumentar ainda mais os efeitos sobre a reabilitação destes pacientes, quando adicionada aos tratamentos clássicos.[71]

A EENM tornou-se um método para induzir o crescimento do músculo esquelético, bem como para aumentar a força e a capacidade de resistência para pacientes que não são capazes de realizar exercícios ativos, assim ela poderia ser um caminho promissor para evitar a perda de massa muscular.[72] Um estudo recente revelou resultados promissores para a EENM de curto prazo sobre o metabolismo do músculo esquelético e espessura das camadas muscular em pacientes criticamente enfermos.[73]

A EENM é bem tolerada na doença crônica, com poucos efeitos adversos. A maioria dos estudos não tem encontrado mudança significativa na frequência cardíaca e na pressão sanguínea, embora um estudo tenha encontrado um pequeno aumento estatisticamente significativo, mas não importante clinicamente, na frequência cardíaca (4±3 batimentos/minuto). Baseada nas provas existentes, as diretrizes da Sociedade Americana Torácica, Sociedade Europeia Respiratória e Sociedade Europeia de Medicina em Cuidados Intensivos declararam que a terapia com eletroestimulação pode ser considerada com uma terapia adjuvante em pacientes criticamente doentes que estão acamados e com alto risco de desenvolver fraqueza da musculatura esquelética[74].

Segundo Zhonguo et al.[75] o desuso muscular provoca alterações histológicas, fisiológicas e anatômicas, fatos que geram perda instantânea da atividade voluntária muscular o que predispõe ao desenvolvimento de atrofia muscular progressiva. Fernandes et al.[76] obtiveram resultados significativos com correntes de baixa frequência, quando aplicado no músculo sóleo, demonstrando que há plasticidade das fibras musculares, sendo o músculo capaz de sofrer adaptações, essas observadas por aumento na densidade das fibras, minimizando sua atrofia. Em outro estudo realizado por Arias et al.[77], onde foi avaliado o efeito do *Functional Eletrical Stimulation* (FES) em pacientes com paralisia cerebral, houve um aumento significativo da força muscular dos extensores do punho, sendo uma evidência científica do uso de correntes de baixa frequência para ganho de trofismo muscular. Vale resaltar que frequências acima de 15 Hz produzem contrações tetânicas. Neste tipo de

contração o músculo não apresenta período refratário, dessa maneira o músculo não relaxa entre os potenciais de ação porque a segunda contração é somada à primeira, ocorrendo somação entre entre elas. O efeito tetânico permite que a força total de contração aumente progressivamente à medida que se aumenta a frequência. Próximo aos 50 Hz esse aumento progressivo atinge um platô, dessa maneira o aumento adicional da frequência acima desse valor não provoca aumento adicional na força de contração muscular[78].

Um dos primeiros ensaios clínicos randomizados foi realizado por Zanotti et al.[71] com pacientes DPOC dependentes da VMI por mais 30 dias. Os pacientes que receberam corticosteróides sistêmicos ou bloqueador neuromuscular por mais de 5 dias foram excluídos do estudo devido a fraqueza neuromuscular provocada pelos medicamentos. A eletroestimulação foi realizada nos pacientes acamados, usando eletrodos superficiais no quadríceps bilateral, na região do reto femoral e vasto lateral. Cada sessão de eletroestimulação compreendia-se de 5 minutos de frequência (F) de 8 Hz e tempo de pulso (TP) de 250μs e em seguida 25 minutos com F: 35Hz com TP: 350μs. Observou-se melhora do escore de força muscular e decréscimo do número de dias necessários para transferência da cama para a cadeira nos pacientes que associavam EENM com a mobilização convencional quando comparados aos que só eram mobilizados.

Estudos mais recentes, como o de Gerovasili et al.[79] analisaram 26 pacientes com um escore de admissão *Acute Physiology and Chronic Health Evaluation* (APACHE II) ≥13, sendo randomizados para grupo EENM e grupo controle, onde foram estimulados os músculos reto femoral e vasto intermédio, sendo avaliada a espessura tranversal dos mesmos através do US. Foi observando uma diminuição significativa da espessura muscular em ambos os grupos, porém essa diminuição foi significativamente menor no grupo que recebeu a intervenção, concluindo que a EENM é bem tolerada e parece preservar a massa muscular de pacientes criticamente enfermos. Em uma análise secundária realizado por Karatzanos et al.[80] deste mesmo estudo, onde vários grupos musculares foram avaliados através da escala de força muscular *Medical Research Council* (MRC) e da força de preensão manual. Nesta anáise foram incluidos 24 pacientes no grupo de EENM e no grupo controle,

observando que pacientes que receberam EENM alcançaram maior pontuação na MRC do que os controles ($p \leq 0,05$) para flexão do punho, flexão do quadril, extensão do joelho e dorsiflexão do tornozelo. A força de preensão manual foi maior no grupo intervenção ($p \leq 0,01$), sendo correlacionada com o aumento da força muscular dos membros superiores e inferiores no geral. Em conclusão, relatam que a EENM tem efeitos benéficos sobre a força de pacientes críticos, principalmente sobregrupos musculares analisados, apresentando-se como um meio de mobilização precoce eficaz na preservação de força muscular nesta população de pacientes.

Poulsen et al. [9] em um estudo piloto com 8 pacientes adultos do gênero masculino internados na UTI com choque séptico incluídos no prazo de 72 horas após o diagnóstico, realizaram EENM no músculo quadríceps utilizando o membro contralateral como controle durante 7 dias consecutivos e durante 60 minutos por dia. Todos os pacientes foram submetidos à tomografia computadorizada de ambas as coxas, imediatamente antes e após o período de tratamento de 7 dias, não havendo diferença significativa no volume muscular entre o lado estimulado e o não estimulado. Gruther et al.[73] em um estudo randomizado controlado duplo-cego piloto com 33 pacientes com idade média de 55 anos, tendo como principais diagnósticos o politraumatismo, doenças cardiovasculares, transplante, pneumonia, investigando através da US os efeitos da EENM na espessura do músculo quadríceps na fase aguda (menos de 7 dias de hospitalização) e a longo prazo (superior a 14 dias de internação) em pacientes críticos. Os autores observaram que a espessura aumentou apenas para pacientes de longa duração que iniciaram a EENM após 2 semanas de internação na UTI, mas não para pacientes agudos.

Um estudo realizado por Rodriguez et al.[74] avaliaram o efeito da EENM sobre a força muscular em pacientes sépticos que necessitaram de VMI, onde 14 pacientes sépticos foram analisados e incluídos dentro de 48 horas de internação na unidade de cuidados intensivos. A EENM foi administrada duas vezes por dia no bíceps braquial e vasto medial (quadríceps), em um hemicorpo, utilizando o membro contralateral como controle, até a saída da VMI. Foi avaliada a espessura bíceps por US e da força muscular após o

despertar com MRC. A EENM foi aplicada durante 13 dias, sendo a força do bíceps e quadríceps significativamente maiores no lado estimulado na avaliação final. A melhora foi observada principalmente em pacientes mais graves e mais fracos. A circunferência do braço não estimulado apresentou diminuição significativa em relação ao estimulado (p = 0,015), no entanto não foi observado diferença significativa quanto a circunferência e espessura da perna ou bíceps. Em conclusão, relatam que a EENM foi associado com um aumento na resistência do músculo estimulado em pacientes sépticos submetidos a VMI, sugerindo que a mesma pode ser útil para prevenir fraqueza muscular nessa população

Uma revisão sistemática realizada em 2013 investigando os efeitos da EENM na prevenção de fraqueza muscular na UTI, incluindo 8 estudos publicados entre 2003 a 2012, fornece evidências de que a adição de terapia com EENM ao tratamento convencional é mais eficaz do que se ambos forem realizados independentemente. No entanto, ressaltam que há provas inconclusivas sobre a eficácia da EENM para a preservação da massa muscular em pacientes de UTI.[12] Em uma segunda revisão publicada no mesmo ano, 9 estudos foram incluídos, sendo 8 ensaios clínicos randomizados, observando que a EENM parece preservar a massa muscular e força nos participantes de longa permanência na UTI e naqueles com menos acuidade. No entanto, nenhum desses benefícios foram observados quando a eletroestimulação começou antes de 7 dias de internação ou em pacientes com alta 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.[11] Uma terceira revisão sistemática publicada em 2014 incluindo 9 estudos investigou os efeitos da EENM em pacientes críticos, concluindo que a mesma pode gerar bons resultados quando usada para preservar a massa muscular e força de pacientes críticos na UTI, sendo reforçada por uma pequena meta-análise apresentada.[10]

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ORIGINAL ARTICLE

USE OF NEUROMUSCULAR ELECTRICAL STIMULATION TO PRESERVE THE THICKNESS OF ABDOMINAL AND CHEST MUSCLES OF CRITICALLY ILL PATIENTS: A RANDOMIZED CLINICAL TRIAL.

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ABSTRACT

Background: Neuromuscular electrical stimulation (NMES) has been used as an early therapeutic modality in intensive care units (ICUs) to treat patients on invasive mechanical ventilation (IMV) to compensate and/or reduce the 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:** A double blind randomized controlled trial was conducted in the ICU at Hospital de Clínicas de Porto Alegre, Brazil. Twenty-five patients who had been hospitalized for no longer than 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 (sham NMES + conventional physical therapy). Interventions were performed once daily for 30 minutes until day 7 or extubation. The primary outcome was thickness of the rectus abdominis and chest muscles of the dominant side determined on cross-sectional ultrasound images before and after the intervention. **Results:** Eleven patients were included in the intervention group (age, 56±13 years) and 14 in the conventional group (age, 61±15 years). After NMES, 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 a significant reduction in 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 groups. There was a statistically significant difference between groups in length of ICU stay, with shorter length of stay in the intervention group (10±4 days, p=0.045). There were no significant differences between groups in other outcomes. **Conclusion:** There was no change in 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 rate in these units ranges from 5.4% to 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 3% to 11% of muscle mass 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% of ICU patients.[10] Two large studies evaluated survivors of acute respiratory distress syndrome at 3, 6, and 12 months and at 2, 3, 4, and 5 years after discharge from the ICU and concluded that these patients have persistent functional disability one year after discharge from the ICU and that most patients have extrapulmonary conditions, with muscle weakness and loss of muscle mass being most prominent. Also, after 5 years, patients show exercise limitation, physical and psychological sequelae, and decreased 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 in ICUs. This technique does not require active cooperation of the patient and has a beneficial acute systemic effect on skeletal muscle microcirculation,[16] offering structural and functional advantages to critically ill patients. Studies involving 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 peripheral and respiratory muscle strength in these patients.[17-19] Some studies using this method for muscle strengthening in order to improve the ventilation process have achieved effective results.[20-22]

Muscle cross-sectional area and/or thickness is strongly associated with force generation capacity. However, few studies have been conducted in 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 rectus abdominis and chest muscle thickness compared with sham NMES combined with conventional physical therapy in patients receiving invasive mechanical ventilation (IMV).

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 Research Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA No. 353.996). The trial is registered at 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 a per protocol analysis, from August 2013 to August 2014 at the HCPA ICU. Eligible participants were all female and male patients aged $\geq$ 18 years who had been hospitalized for no longer than 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 syndrome, associated with motor deficits. In addition, patients were excluded if they (*a*) were extubated within 48 hours after inclusion in the study, (*b*) had complications during the protocol, such as pneumothorax, (*c*) had prolonged weaning (failed 3 spontaneous breathing trials), (*d*) had a body mass index (BMI) > 35 kg/m^2, (*e*) had a pacemaker, (*f*) had hemodynamic instability (norepinephrine > 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 (*g*) used neuromuscular blockers for 2 or more consecutive days.

Sample selection

An assessor conducted a search using the computerized system of the HCPA for potential trial participants. Then, the patients' electronic medical records were reviewed for identification data, medical diagnosis, and current medical conditions to assess patients for eligibility. The legal guardian of each eligible patient was approached for study enrollment, and those who agreed to participate were asked to sign the informed consent form.

Randomization

Randomization sequence was created using the website www.randomization.com, with a 1:1 allocation ratio using blocks of 10 patients. To ensure the confidentiality of randomization sequence, the sequence was generated by a blinded assessor who was contacted via telephone only after the participant had been included in the study and was ready to start the protocol.

Patients were randomly assigned to receive either NMES + conventional physical therapy (intervention group) or sham NMES + conventional physical therapy (conventional group). The NMES group received NMES for 30 minutes once a day + conventional physical therapy, whereas the conventional group received sham NMES for 30 minutes once a day + conventional physical therapy. The protocol was interrupted on day 7, when the patient was extubated, or if the patient died (whichever occurred first). NMES was

administered in both groups by previously trained professionals for procedure standardization. Conventional physical therapy in both groups was performed by ICU professionals twice a day.

Outcomes

The primary outcome was the difference in rectus abdominis and chest muscle thickness of the dominant side from initial to final assessment between groups. Secondary outcomes included changes in diaphragm muscle thickness and inhaling and exhaling diaphragmatic motion. We also assessed ICU and hospital length of stay, duration of IMV, 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 for assessment of muscle thickness and diaphragmatic motion. Ultrasound examination was performed at two different occasions: on the first day of participation in the study (24 to 48 hours of IMV) and on day 7 of IMV or 24 hours after extubation.

Evaluation of muscle thickness

Muscle thickness was determined on cross-sectional ultrasound images. With the patient lying supine and the head of the bed elevated at 30°, real-time B-mode scanning was performed using a 3.5-mm, 7.5 MHz linear-array transducer (Sonosite®, Washington, DC, USA). The scanning head was coated with water-soluble transmission gel to provide acoustic contact without depressing the dermal surface. The sites for image acquisition were determined using anatomical parameters reported in the literature.[25] To assess the chest muscle, the midpoint of the sternum was determined. Starting at this point, the transducer was positioned obliquely toward the nipple line, seeking to reach an area of larger muscle belly. 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 on the skin, a cross-sectional image was acquired, which included the chest and rectus abdominis muscles. Muscle thickness was determined based on measurements performed between the inner edge of the upper and lower aponeuroses of the chest and rectus abdominis muscles.

For ultrasound-based measurement of diaphragmatic muscle thickness, the patient was placed in the supine position. The transducer was positioned perpendicularly to the diaphragm in the intercostal space over the tenth rib on the anterior axillary line, image was acquired, and thickness was measured at the end of inspiration.

For assessment of diaphragmatic motion, the ultrasound transducer was positioned through the anatomical window provided by the liver between the midclavicular position and the anterior axillary line towards the skull. Thus, the transducer 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 measured on M-mode ultrasound images. The inhalation excursion was determined by measuring the vertical height of the base of the beginning of inhalation up to the peak slope at the end of inhalation, and the exhalation excursion by measuring the vertical height of the inhalation peak until return to the base.

All ultrasound examinations were performed by the same professional, who was blinded to group assignment. All ultrasound measurements were expressed in centimeters.

Interventions

In the intervention group, NMES was performed using a 4-channel Neurodyn II (Ibramed®, São Paulo, SP, Brazil). Only the dominant side of each patient was considered for analysis, and hairy body areas were shaved as necessary. The negative electrodes were placed in the motor points of the following muscles: chest muscles (pectoralis major muscle fibers) and rectus abdominis muscles

bilaterally. A second (positive) electrode was positioned distally to the first, at a site close to the muscle that was being electrically stimulated.

Each NMES session lasted 30 minutes. One minute was added every two days of administration. The following parameters were used: 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, the intensity was adjusted according to their tolerance.

The conventional group received sham NMES following the same protocol applied to the intervention group. The procedure was blinded; however, the intensity was adjusted at a sensory level, i.e., without visible or palpable muscle contractions.

Conventional (chest and motor) physical therapy was administered in both groups by ICU professionals twice daily for 30 minutes. The protocol consisted of functional-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). 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 techniques were performed, such as chest compression-vibrations, maneuvers with an Ambu bag (bag-squeezing), and suction of secretions when necessary.

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, respiratory rate, mean blood pressure, peripheral oxygen saturation, and ventilatory frequency.

On day 7 of the protocol or upon extubation (whichever occurred first), all patients were assessed again by ultrasound and continued to receive only conventional (chest and motor) physical therapy provided by the ICU professionals until ICU discharge.

Sample size calculation

Sample size calculation was based on a pilot study of 10 patients for the variable cross-sectional area of abdominal and chest muscle thickness using the statistical program Winpepi. These measures were adjusted using a delta value, defined as the measures of final muscle thickness subtracted from the baseline measures divided by the number of days the participant remained in the protocol. For an effect size of 0.7 standard deviations between the two groups, with a 5% significance level and power of 80%, a sample size of 18 patients (9 patients per group) was required.

Statistical analysis

Data storage, arrangement, and maintenance were performed using a MS Excel 2007 spreadsheet. Data were expressed as mean and 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 groups for qualitative data. The Shapiro-Wilk test was used to test the normality of distribution, and the Levene's test was used to assess homogeneity of variance for all group comparisons. A generalized estimating equations (GEE) model with Bonferroni's correction was used to assess intra- and intergroup interaction for primary and secondary outcomes. In the GEE model, possible confounding factors were controlled by adjusting for septic and non-septic patients and APACHE II score >25 and <25. Statistical analysis was performed using SPSS, version 20.0. The level of significance level was set at 5% ($p \leq 0.05$).

RESULTS

From August 2013 to August 2014, 1321 patients were screened for eligibility. Of these, 1283 were not eligible for the study. Thirty-eight patients were randomized to the intervention group (n=19) and to the conventional group (n=19). Eleven patients in the intervention group and 14 in the conventional group completed the protocol and were included in the final analysis. Figure 1

shows the flow of participants, including losses to follow-up and exclusions after randomization.

Figure 1. Study flowchart

Table 1 shows the characteristics of the study sample. Mean overall age was 59±14 years, and 64% of patients were male. The most prevalent medical diagnosis was sepsis (60%). During administration of NMES, there were no complications or significant changes in vital signs.

Primary Outcomes

There was a statistically significant difference between the intervention and conventional groups in abdominal and chest muscle thickness ($p>0.001$). Considering the comparison between the initial and final assessment within each group, there was no change in muscle mass in the intervention group, whereas there was a statistically significant decrease in these measures in the conventional group ($p>0.001$). Even after adjusting for potential confounders (sepsis and APACHE II), the results remained significant ($p<0.001$) (Table 2).

Secondary Outcomes

There was a significant difference in length of ICU stay, which was shorter in the intervention group than in the conventional group ($p=0.045$). There was no statistically significant difference in diaphragm muscle thickness or inhaling and exhaling diaphragmatic motion between the two groups. Likewise, the comparison between baseline and end evaluation within each group showed no significant differences. Even after adjusting for APACHE II and sepsis, the values remained non-significant ($p<0.005$) (Table 3).

DISCUSSION

Our study demonstrated that intervention using NMES combined with conventional physical therapy preserved the chest and rectus abdominis muscle thickness in critically ill patients on IMV. This finding is consistent with those reported by Gerovasili et al,[28] who evaluated 26 individuals, divided into control and intervention groups, and found that patients undergoing NMES applied 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 against muscle wasting. Nevertheless, Poulsen et al[29] applied NMES to the quadriceps muscle, using the contralateral limb as a control, and found no difference in muscle mass between the stimulated and non-stimulated side as assessed by computed tomography. Gruther et al[30] used ultrasound to investigate the effects of NMES on the thickness of the 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 present findings, which demonstrated no change in muscle mass even when the NMES protocol was started early (up to 48 hours of ICU admission).

As for our secondary outcomes, there was no statistically significant difference between groups in diaphragm thickness or inhaling and exhaling diaphragmatic motion. There was only a significant difference in the number of days of ICU stay, with a shorter stay in the intervention 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 a reduction in length of ICU stay.[31] The use of IMV 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 peripheral and respiratory muscle strength and functional status of mechanically ventilated patients and 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 previous study conducted by our research group, we 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.[19]

The most prevalent ICU admission diagnosis in our study was sepsis (60%). Studies conducted in ICUs involving the use of NMES have demonstrated that the most common diagnoses on admission are sepsis, COPD, and trauma.[28,30,35] Sepsis is known to generate a reaction of protein hypercatabolism in the muscles, contributing to the loss of muscle mass. Loss of muscle mass is partially attributed to sepsis and also to multiple organ dysfunction syndrome, use of drugs, such as neuromuscular blockers, and immobilization.[36] Therefore, we adjusted the outcomes by dividing our patients into septic and non-septic, and the results were statistically significant even after the adjustment. The reintubation rate in the intervention group was 25% against 38% in the conventional group. Routsi et al[37] applied NMES to the quadriceps and peroneus longus muscles of critically ill patients 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 groups. Conversely, a study conducted by Abu-Khaber et al,[38] evaluating the prevention of muscle weakness and facilitation of weaning from mechanical ventilation in critically ill patients using NMES in the quadriceps muscle and starting the protocol within 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 sham stimulation, 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, 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, and APACHE II score seemed to be relevant in the analysis of these risk factors and was found to be an important indicator of 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, which suggests that NMES may prevent loss of muscle mass even in patients with high APACHE II score.

The mean NMES duration in the current study was 5 days in the intervention group. In comparison with our study, the duration of treatment was significantly longer (in days) in previous 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 per 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 found positive results in terms of muscle thickness. Such findings suggest that the initial daily use of 30 minutes of NMES brings 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. Ultrasound examination makes it possible to quantify diaphragmatic motion and accurately assess muscle atrophy[43]. Some studies have used perimetry to assess patients.[7] In a systematic review of the use of NMES in critically ill patients, only three (out of eight) studies used ultrasound as a tool for muscle assessment.[23] The choice of this tool appears to be more accurate for muscle assessment in ICU patients[28] and overcomes many of the problems associated with anthropometric and body composition measures, such as edema, which may be a source of bias when assessing muscle

thickness.[30] Currently, ultrasound is the most reliable method and its validity is well established in intensive care.[39]

The NMES protocol used in the current study was developed by our research group, and the frequency of 50 Hz was chosen because it is known, based on electromyographic studies measuring the frequency of voluntary muscle activation, that fast- and slow-twitch skeletal muscles have firing frequencies of approximately 10 and 30 Hz, respectively, during maximum voluntary contractions.[44] For this reason, clinicians often use frequencies of 50 Hz or more to ensure tetanic contractions, which allow total contraction force to progressively increase as the frequency is increased,[45] thus providing positive results regarding increased peripheral muscle strength and possible benefits in preserving muscle mass in critically ill patients.[23,24,39] This is what we expected to occur when choosing the present parameters, that the chest and abdominal muscles, as well as the peripheral muscles, would respond positively to NMES due to activation of both fast- and slow-twitch muscle fibers.

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 applied to the muscles involved in respiratory mechanics in different populations, since the initial results of this approach are positive in the prevention of loss of muscle mass in these muscle groups.

CONCLUSION

There was no change in rectus abdominis and chest muscle thickness in the intervention group; however, we found a significant decrease in the measures in the conventional group. In addition, the length of ICU stay was significantly shorter in the group receiving active NMES.

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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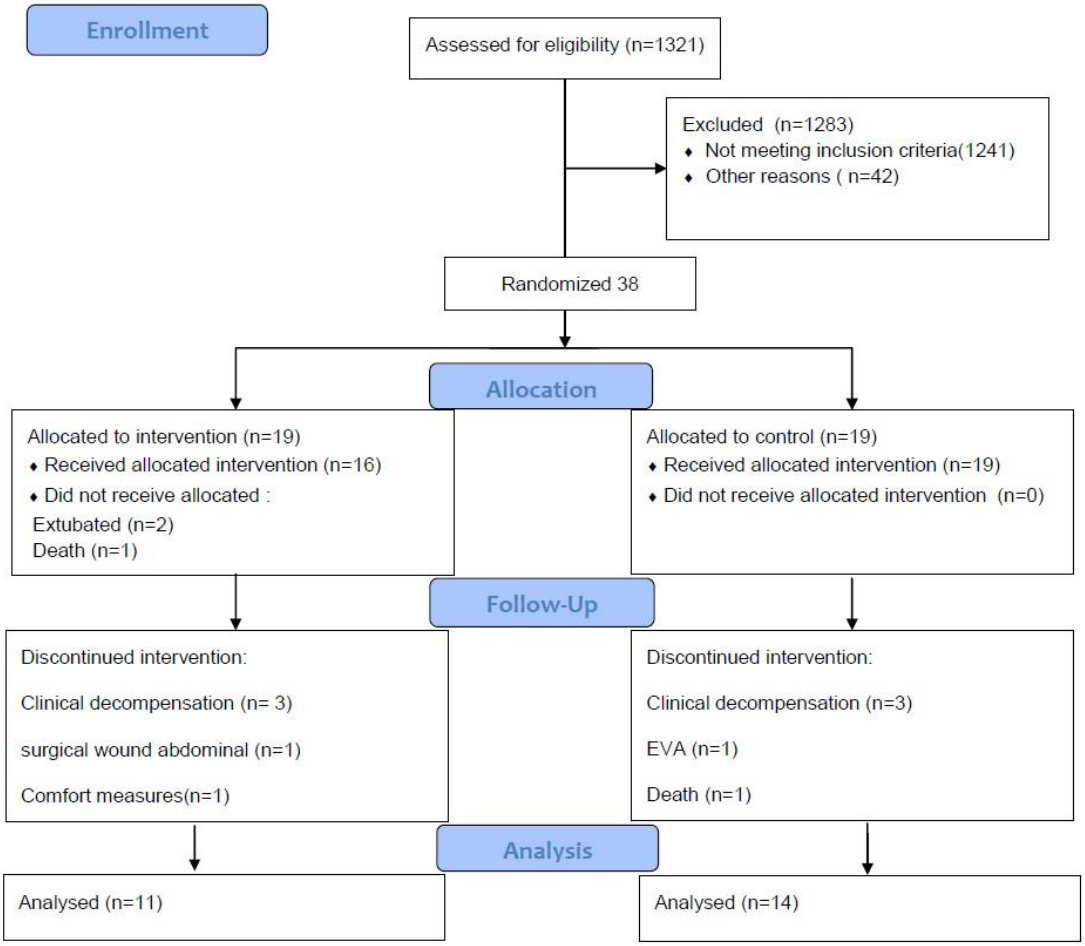
FIGURES

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).

CONCLUSÕES E CONSIDERAÇÕES FINAIS

Como principais achados deste estudo, observamos uma preservação da espessura muscular do reto do abdomem e peitoral no grupo que recebeu EENM associada a fisioterapia convencional, já no grupo que recebeu o protocolo placebo associado a fisioterapia convencional houve uma diminuição significativa das medidas, achado este que reforça a hipótese do efeito protetor da EENM sobre a perda de massa muscular em pacientes críticos.

Secundariamente, encontramos uma diferença significativa em relação ao tempo de permanência na UTI entre os grupos, sendo que a permanência na UTI foi menor no grupo EENM comparado com o grupo convencional, sugerindo que a EENM pode contribuir para diminuição da permanência dos pacientes na UTI. Cabe ressaltar que essa diferença foi limítrofe, demostrando a necessidade de novos estudos abordando esses grupos musculares, com um número maior de pacientes, objetivando conclusões mais precisas sobre este desfecho. No entanto, não encontramos diferença estatisticamente significativa quanto a espessura e mobilidade diafragmática inspiratória e expiratória entre os grupos, sugerindo que a preservação da massa muscular abdominal e peitoral, que fazem parte da mecânica respiratória, não leva a alterações na função diafragmática desses pacientes.

Durante a aplicação do protocolo não foi identificado nenhuma intercorrência na aplicação da EENM, não sendo observadas alterações importantes nos sinais vitais monitorados, reforçando que o uso de EENM em pacientes críticos é uma intervenção segura, não somente quando aplicada em grupos musculares periféricos, mas também em centrais. Novos estudos se fazem necessários, com um número maior de pacientes, para reforçar e complementar os achados deste, uma vez que foram encontrados resultados favoráveis a aplicação da EENM nos grupos musculares centrais.

ANEXOS

Artigo II Submetido para publicação.

From: **Trials-Editorial** <editorial@trialsjournal.com>
Date: 2014-11-26 12:25 GMT-02:00
Subject: Thank you for submitting your study protocol to Trials (MS: 1165900793147670)
To:"amandasachetti@gmail.com"<amandasachetti@gmail.com>
MS:1165900793147670
Study protocol
The effects of early mobilization with neuromuscular electrical stimulation in critical care patients Alexandre ASD Simões Dias, Ana Maria AMDA Dall Acqua, Amanda AS Sachetti, Fernando FAL de Aguiar Lemos, Laura Jurema LJS dos Santos, Mariana MPR Porto da Rosa, Tanara TB Bianchi, Wagner WSN da Silva Naue, Silvia Regina SRRV Rios Vieira and Graciele GS Sbruzzi Trials.

THE EFFECTS OF EARLY MOBILIZATION WITH NEUROMUSCULAR ELECTRICAL STIMULATION IN CRITICAL CARE PATIENTS

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ABSTRACT

Introduction: 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.

Objective: To evaluate the effects of early mobilization with neuromuscular electrical stimulation in critical care patients on invasive mechanical ventilation.

Methods: 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 $p<0.05$.

Trial registration: Trial registration number: NCT

Keywords: electrical stimulation, muscular atrophy, intensive care unit

INTRODUCTION

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 will be a randomized clinical trial recruiting patients of both sexes aged □ 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/m2; 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.

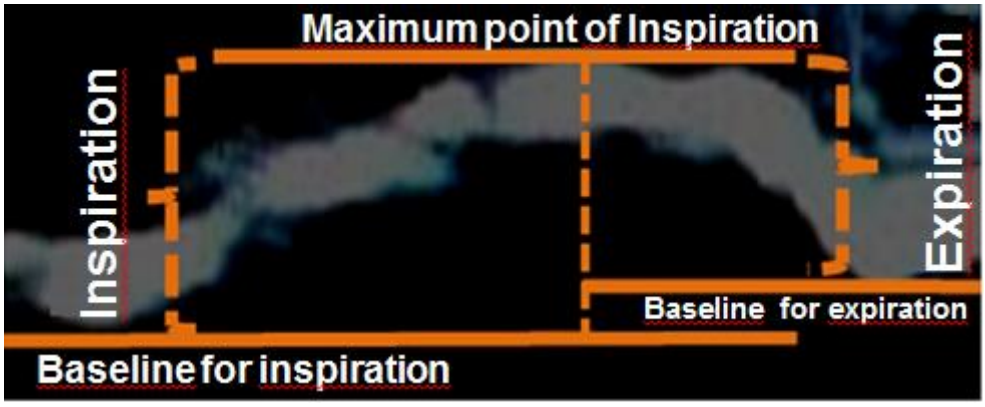

Figure 2. Example of diaphragm excursion seen on mode M ultrasound.

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

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

1. Research team leader and revising article.
2. Data collection and writing article
3. Data collection and writing article
4. Writing article and revising article
5. Data collection
6. Data collection
7. Data collection
8. Supervision and revision of article.

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