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Efeitos da Estimulação Elétrica Neuromuscular e da Fotobiomodulação em Pacientes com Insuficiência Renal Crônica em Hemodiálise

Porto Alegre
2019

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Orientador: Dr. Rodrigo Della Méa Plentz

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“Opte pelo que faz o seu coração vibrar.
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RESUMO

A doença renal crônica (DRC) na sua fase terminal é denominada insuficiência renal crônica (IRC) e os pacientes necessitam de terapia renal substitutiva que pode ser realizada através de hemodiálise (HD). Ao longo do tempo os pacientes apresentam detrimento da capacidade física e importante sarcopenia. A estimulação elétrica neuromuscular (EENM) e a fotobiomodulação (FBM) são recursos terapêuticos que podem melhorar estes aspectos. O primeiro estudo desta tese verificou o efeito crônico da EENM em pacientes com IRC em HD. Para isso, uma revisão sistemática com metanálise foi conduzida. Cinco bases de dados foram pesquisadas e 10 ensaios clínicos (totalizando 242 pacientes) incluídos. A força muscular de membros inferiores e superiores, a capacidade funcional e qualidade de vida foram os desfechos avaliados. Os resultados indicaram que a EENM quando aplicada nos músculos quadríceps e gastrocnêmio e por longo período aumenta a força muscular de membros inferiores e a capacidade funcional comparada ao grupo controle (GC). A EENM também parece melhorar a força muscular de membros superiores e alguns aspectos da qualidade de vida. O segundo estudo avaliou o efeito de oito semanas de FBM na mesma população. Para isso, um ensaio clínico randomizado foi conduzido com 28 pacientes. O grupo tratado recebeu 24 aplicações de laser de baixa intensidade nos músculos quadríceps e gastrocnêmio, de ambas as pernas e concomitante à HD. O GC recebeu apenas cuidados de rotina de enfermagem. Avaliou-se a capacidade funcional, a força muscular de membros inferiores, a percepção de dor e fadiga, a arquitetura e a qualidade muscular do quadríceps, e a qualidade de vida previamente à intervenção e após 8 semanas. Os resultados demonstraram incremento para a capacidade funcional e força muscular de membros inferiores para o grupo tratado quando comparado ao GC. O grupo tratado apresentou ainda melhora de alguns aspectos da qualidade de vida. Houve piora dos níveis de dor para o GC após o seguimento. Não foram observadas alterações na percepção de fadiga, arquitetura e na qualidade muscular para nenhum dos grupos. Conclui-se que a EENM e FBM melhoram a capacidade funcional e a força muscular de membros inferiores de pacientes com IRC em HD. Ainda, a EENM parece melhorar a força muscular de membros superiores enquanto a FBM parece modular a percepção de dor em membros inferiores. As duas terapias melhoram alguns aspectos da qualidade de vida desta população, entretanto, a qualidade da evidência é limitada para este desfecho.

Palavras-Chave: Insuficiência Renal Crônica. Estimulação Elétrica. Terapia com Luz de Baixa Intensidade.

ABSTRACT

In the terminal phase chronic kidney disease (CKD) is called chronic kidney failure (CKF) and patients require replacement renal therapy that can be performed by hemodialysis (HD). Over time, the patients present impairment of physical capacity and important sarcopenia. Neuromuscular electrical stimulation (NMES) and photobiomodulation (PBM) are therapeutic resources that can improve these aspects. The first study of this thesis verified the chronic effect of NMES in patients with CKF on HD. For this, a systematic review with meta-analysis was conducted. Five databases were researched and 10 clinical trials (totaling 242 patients) included. The muscle strength of lower and upper limbs, functional capacity and quality of life were the evaluated outcomes. The results indicated that when NMES is applied to quadriceps and gastrocnemius muscles and for a long period it increases the muscle strength of the lower limbs and the functional capacity compared to the control group (CG). NMES also appears to improve upper limbs strength and some aspects of quality of life. The second study evaluated the effect of eight weeks of PBM in the same population. For this, a randomized clinical trial was conducted with 28 patients. The treated group received 24 applications of low level laser on the quadriceps and gastrocnemius muscles of both legs and concomitant to HD. The CG received only routine nursing care. Functional capacity, muscle strength of the lower limbs, pain and fatigue perception, quadriceps muscle quality and architecture, and quality of life were evaluated before and after 8 weeks. The results demonstrated an increase on functional capacity and lower limbs muscle strength for the treated group when compared to the CG. The treated group also showed improvement in some aspects of quality of life. There was worsening of pain levels for CG after follow-up. No changes in the perception of fatigue, muscle quality and architecture were observed for any of the groups. In conclusion, NMES and PBM improve the functional capacity and lower limbs muscle strength of patients with CKF on HD. Furthermore, NMES appears to improve upper limbs strength while PBM seems to modulate the perception of lower limbs pain. Both therapies improve some aspects of the quality of life of this population, however, the quality of the evidence is limited for this outcome.

Keywords: Renal Insufficiency, Chronic. Electric Stimulation. Low-Level Light Therapy.

LISTA DE ABREVIATURAS E SIGLAS

AIDS – *Acquired Immunodeficiency Syndrome*

ATP – *Adenosine Triphosphate*

CVF – Capacidade Vital Forçada

CVM – Contração Voluntária Máxima

DRC – Doença Renal Crônica

ECR- Ensaio Clínico Randomizado

ECRs – Ensaios Clínicos Randomizados

EENM – Estimulação Elétrica Neuromuscular

FBM – Fotobiomodulação

HD – Hemodiálise

HIV- *Human Immunodeficiency Virus*

IRC – Insuficiência Renal Crônica

LBI – Laser de Baixa Intensidade

LEDs – Diodos Emissores de Luz

PEmáx – Pressão Expiratória Máxima

PImáx – Pressão Inspiratória Máxima

SF-36 – *Medical Outcomes Study 36 – Item Short – Form Health Survey*

TC6M – Teste de Caminhada de Seis Minutos

TFGe – Taxa de Filtração Glomerular Estimada

TRS – Terapia Renal Substitutiva

URR – *Urea Reduction Rate*

VEF_1 – Volume Expiratório Forçado no Primeiro Segundo

VO_2 – Volume Máximo de Oxigênio

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1 INTRODUÇÃO

A doença renal crônica (DRC) é definida como a presença de dano renal ou taxa de filtração glomerular estimada (TFGe) menor que 60 ml/min/1.73 m^2, por um período igual ou maior que três meses, independente da causa (1). Na sua fase terminal, a DRC é denominada insuficiência renal crônica (IRC) e os pacientes encontram-se intensamente sintomáticos, necessitando de terapia renal substitutiva (TRS) (2).

A hemodiálise (HD) convencional é a modalidade predominante de TRS no Brasil (3) e, embora seja indispensável para a sobrevivência desta população não é capaz de depurar as toxinas urêmicas completamente. O acúmulo de metabólitos aliado à perda da função endócrina renal ao longo do tempo leva a alterações negativas em todos os sistemas corporais do indivíduo (4). Destacam-se as alterações deletérias que ocorrem no sistema cardiovascular (5-7), respiratório (8) e musculoesquelético (9-11), uma vez que estes sistemas refletem diretamente sobre a capacidade funcional e esta é considerada um preditor independente de mortalidade (12).

Além da capacidade funcional apresentar-se reduzida em pacientes com IRC, a sarcopenia em maior ou menor grau é frequente, e esta possui associação inversa com a taxa de sobrevida (13). Assim, estratégias não farmacológicas são necessárias para atenuar este processo que é inerente à DRC e que interfere sobre a qualidade de vida desta população.

Os benefícios do exercício convencional para melhorar o condicionamento físico de doentes renais crônicos são bem documentados (14), entretanto, nem todos os pacientes possuem condições clínicas ou sentem-se suficientemente motivados para realizá-lo, implicando em baixa adesão terapêutica. Assim, outros recursos como a estimulação elétrica neuromuscular (EENM) e a fotobiomodulação (FBM) podem ser alternativas atraentes.

A EENM envolve a aplicação de uma série de estímulos intermitentes aos músculos esqueléticos, com o objetivo de gerar contração muscular visível devido à ativação de ramos nervosos intramusculares (15) e tem sido amplamente utilizada em diferentes populações com doenças crônicas e que apresentam importante fraqueza muscular (16). Alguns estudos realizados em pacientes com IRC em HD apontam para efeitos positivos da EENM sobre desfechos como força muscular de membros inferiores (17-19), arquitetura muscular (18), capacidade funcional, qualidade de vida e também sobre a eficiência da diálise (19), entretanto, a qualidade metodológica dos estudos é limitada.

A terapia de FBM refere-se ao uso de fótons como radiação não térmica para alterar a atividade biológica, podendo ser realizada através de laser de baixa intensidade (LBI), diodos

emissores de luz (LEDs) ou ambos (20, 21). O LBI e os LEDs são historicamente conhecidos pelos seus efeitos analgésico, anti-inflamatório e regenerativo (20, 21), entretanto, nos últimos dez anos, têm sido amplamente estudados como recursos terapêuticos para melhorar a *performance* durante o exercício e para reduzir a fadiga muscular em indivíduos saudáveis e atletas (22).

Já existem estudos que avaliaram o efeito agudo da FBM sobre o desempenho físico de pacientes com doença cardíaca (23) e pulmonar (24) e, um estudo que avaliou o efeito crônico desta terapia em pacientes com osteoartrose de joelho (25). Os resultados destes ensaios apontam para melhora de desfechos como força muscular de membros inferiores, capacidade funcional e redução da fadiga muscular.

Em relação a pacientes com IRC, um estudo cruzado realizado recentemente pelo nosso grupo (26) avaliou o efeito agudo de diferentes doses de LBI infravermelho sobre a força de preensão palmar e observou incremento deste desfecho quando os pacientes receberam doses de radiação de 60 e 90 J (dose total) sobre o membro superior. Até o momento da elaboração desta tese não havia evidência a respeito do efeito crônico desta terapia quando utilizada em membros inferiores de pacientes com IRC em HD sobre desfechos físicos e funcionais.

Considerando as informações supracitadas, nota-se a carência de evidências de alta qualidade metodológica no que diz respeito aos efeitos crônicos da EENM e da terapia de FBM em pacientes com IRC em HD, assim como a necessidade de se implementar estratégias terapêuticas alternativas ao exercício convencional para estes pacientes. Isto, por sua vez, justifica maior investigação científica sobre o assunto.

Esta tese encontra-se estruturada da seguinte forma: inicialmente através de um referencial teórico contextualiza-se a DRC juntamente com as suas implicações clínicas, e, na sequência são abordadas estratégias terapêuticas no âmbito da fisioterapia como o exercício físico, a EENM e terapia de FBM, visando a reabilitação desta população. Após o referencial teórico são apresentados os objetivos do trabalho e por fim dois artigos científicos. O primeiro consiste em uma revisão sistemática com metanálise abordando os efeitos da EENM em doentes renais crônicos em HD. O segundo, trata-se de um ensaio clínico randomizado a respeito dos efeitos da terapia de FBM na mesma população.

2 FUNDAMENTAÇÃO TEÓRICA

2.1 DOENÇA RENAL CRÔNICA E SUAS IMPLICAÇÕES CLÍNICAS

A DRC é definida como a presença de dano renal ou TFGe menor que 60 ml/min/1.73 m^2, por um período igual ou maior que três meses, independente da causa (1). Sua classificação é dividida em 6 categorias baseado na TFGe, onde: Estágio 1: TFG 90 ml/min/1,73m^2; Estágio 2: TFG 60 a 89 ml/min/1,73m^2; Estágio 3A: TFG 45 a 59 ml/min/1,73m^2; Estágio 3B: TFG 30 a 44 ml/min/1,73m^2; Estágio 4: TFG 15 a 29 ml/min/1,73m^2; Estágio 5: TFG < 15 ml/min/ 1,73m^2 (1).

Em relação à prevalência, a DRC atinge cerca de 12 a 13% da população mundial (27). No Brasil, conforme o Inquérito Brasileiro de Diálise Crônica publicado em 2019 por Thomé et al. (3), as taxas de incidência e prevalência de pacientes em diálise vem aumentando progressivamente. Em julho de 2017, 126.583 pacientes estavam em tratamento dialítico, sendo a HD a modalidade predominante de TRS e a região sudeste a responsável pelo maior número de pacientes. A maioria destes era do sexo masculino e teve o tratamento custeado pelo sistema único de saúde.

A etiologia da DRC é variável, entretanto, as doenças de base mais comuns responsáveis pela lesão renal são: Diabetes Mellitus tipo 2 e Hipertensão Arterial Sistêmica. Outras possíveis causas são: glomerulonefrites, doenças císticas, vasculites, hereditariedade e neoplasias (28).

A DRC quando em estágio 5 é denominada IRC e nesta fase o paciente encontra-se intensamente sintomático, necessitando de TRS (2). A TRS pode ser realizada através de diálise peritoneal, HD ou transplante renal, sendo este último a melhor opção quando considerado a taxa de sobrevida (29).

A HD *convencional* ou também chamada *intermitente* é realizada de 3 a 4 vezes por semana, através de um circuito extracorpóreo onde o sangue flui através de um acesso vascular (cateter venoso ou fístula arteriovenosa) e é impulsionado por uma bomba para o dialisador, que consiste em uma membrana semipermeável onde ocorrem as trocas entre o sangue e o banho de diálise (dialisato). A difusão de solutos entre o sangue e a solução de diálise resulta na remoção de escórias metabólicas e na reposição de solutos como bicarbonato (30).

A efetividade da diálise pode ser verificada através de índices específicos, sendo o Kt/V e o URR (*urea reduction ratio*) os mais utilizados na prática clínica. O URR, índice utilizado pelo hospital onde realizamos as coletas de dados, é calculado através da fórmula *ureia pré – ureia pós x 100/ureia pré* e indica o quão eficaz foi o tratamento dialítico em remover os

resíduos corporais, é expresso em porcentagem e deve ser maior ou igual a 65% (30). Estudos observacionais associam melhores índices a maior sobrevida em doentes renais crônicos (31, 32).

Embora a HD seja indispensável para a garantir a sobrevivência de pacientes com IRC acredita-se que ela não seja inteiramente capaz de depurar todas as toxinas que deveriam ser eliminadas e/ou metabolizadas pelo rim. Assim, a uremia crônica e a acidose metabólica permanentes, juntamente com a perda da função endócrina renal (a qual a TRS não substitui) ocasionam ao longo do tempo alterações deletérias em todos os sistemas corporais (4).

Entre as alterações no sistema cardiovascular, podemos citar a hipertrofia do ventrículo esquerdo como um dos achados clínicos mais comuns, decorrente da hipertensão arterial e hipervolemia apresentada por este paciente (5, 6). Ainda, arritmias ventriculares complexas, insuficiência cardíaca, doença coronariana, doença cérebro-vascular e doença vascular periférica são frequentes em doentes renais crônicos (6, 7) e a disfunção endotelial parece ser o mecanismo central na gênese da disfunção cardiovascular (33). Portanto, as doenças cardiovasculares podem ser consideradas a principal causa de óbito em pacientes com IRC (7, 34).

Doentes renais crônicos também apresentam importante fraqueza dos músculos ventilatórios. Schardong et al. (8) avaliaram através de um estudo transversal a função pulmonar, a força muscular respiratória e a qualidade de vida de pacientes com DRC em HD e encontraram valores reduzidos para capacidade vital forçada (CVF), volume expiratório forçado no primeiro segundo (VEF_1) assim como valores abaixo do predito para a pressão inspiratória máxima (PImáx) e para a pressão expiratória máxima (PEmáx), evidenciando prejuízo da força e da função pulmonar. Além disso, os pacientes apresentaram escores baixos para as dimensões do questionário de qualidade de vida *Medical Outcomes Study 36- Item short- Form Health Survey (SF-36).*

Em relação ao sistema musculoesquelético, a miopatia ocorre frequentemente em pacientes urêmicos como uma consequência do alto nível sérico de cálcio, ureia, ácido úrico e creatinina, da acidemia, do baixo nível de carnitina, do hiperparatireoidismo secundário e também como consequência do desuso (9, 10, 35).

Além da miopatia, pacientes em diálise apresentam fraqueza muscular importante e em maior grau quando comparado a indivíduos saudáveis (11, 36). Em geral, as causas da fraqueza muscular podem incluir a perda de massa muscular, redução na capacidade do sistema nervoso central em ativar unidades motoras normais ou a combinação desses mecanismos (37). Johansen *et al.* (38), avaliaram os efeitos da HD sobre a força, qualidade muscular e sobre a

capacidade funcional, e verificaram que a atrofia é o mecanismo primário para a fraqueza muscular.

O termo sarcopenia, portanto, se refere a perda da massa e da força ou função muscular (39) e é considerada um importante preditor de morbidade e mortalidade em pacientes em diálise (40). Pereira et al., (13) através de um estudo observacional demonstraram uma associação significativa entre sobrevivência e sarcopenia em doentes renais crônicos. Segundo os autores, quanto maior o grau de sarcopenia, menor a sobrevida de pacientes com DRC, mesmo em estágios mais iniciais da doença e em tratamento conservador.

Considerando as alterações que ocorrem nos sistemas cardiovascular, respiratório e musculoesquelético de pacientes com DRC, torna-se evidente o prejuízo importante sobre a capacidade funcional, uma vez que esta depende diretamente do bom funcionamento destes sistemas. Segundo Johansen et al. (38) pacientes com DRC apresentam redução de 40-50% da capacidade física quando comparado a indivíduos saudáveis. Nesse sentido, a fisioterapia dispõe de recursos terapêuticos capazes de atenuar o detrimento da capacidade física e de melhorar a qualidade de vida desta população.

Conforme a Diretriz de Reabilitação Cardiopulmonar e Metabólica de 2006 (41) a reabilitação na nefropatia crônica possui grau de recomendação B. Em pacientes submetidos ao tratamento dialítico, o exercício proporciona melhora da função cardiovascular, da capacidade física e da qualidade de vida, assim como da eficiência da diálise (42), reduzindo portanto a mortalidade (43).

O exercício combinado é considerado a melhor modalidade para melhora da capacidade aeróbica (VO_2 – volume máximo de oxigênio) e para o controle da pressão arterial em pacientes com IRC. Uma revisão sistemática com metanálise (14) publicada recentemente, incluindo 33 ensaios clínicos randomizados (ECRs), demonstrou que protocolos que combinam exercício aeróbico e resistido e são realizados durante HD aumentam o VO_2 em 5 ml/kg/min, reduzem a pressão arterial sistólica em 9 mmHg e a pressão arterial diastólica em 5 mmHg.

Outros recursos como a EENM e a terapia de FBM podem ser alternativas para os programas de reabilitação convencional (baseados no exercício físico), em situações em que o paciente não possui condições clínicas de realizar o exercício devido às comorbidades que acompanham a DRC ou no caso de não se sentir motivado para tal. Além de uma alternativa ao exercício físico, estes recursos podem ser também adjuvantes no processo de reabilitação, uma vez que, estudos demonstram resultados positivos para desfechos como força e arquitetura muscular (18, 26), capacidade funcional (17) e qualidade de vida (19) quando a EENM e FBM

são utilizadas. Estas modalidades terapêuticas serão abordadas em maiores detalhes na sequência deste referencial teórico.

2.2 ESTIMULAÇÃO ELÉTRICA NEUROMUSCULAR

A EENM envolve a aplicação de uma série de estímulos intermitentes aos músculos esqueléticos, com o objetivo de gerar contração muscular visível devido à ativação de ramos nervosos intramusculares (15).

De forma geral, a EENM pode ser utilizada em três situações: 1) Visando *preservar* a massa e a função muscular durante o desuso/imobilização e, neste contexto pode ser considerada superior ao exercício voluntário; 2) Objetivando *recuperar* a massa e a função muscular após o desuso/imobilização sendo considerada tão efetiva quanto o exercício voluntário; ou 3) Para *melhorar* a função muscular de um músculo saudável e, nessa situação se equipara ao exercício voluntário, podendo este último ser até mais eficaz (44). Nesse sentido, a EENM torna-se uma alternativa interessante para aqueles pacientes mais debilitados e que não conseguem desempenhar ou sustentar o exercício convencional devido a sua condição de saúde ou comorbidades associadas.

Diferentemente do exercício voluntário, a EENM possui características como contração sincrônica, superficial (próximo aos eletrodos) e espacialmente fixa. Além disso, o recrutamento das unidades motoras é desordenado/não seletivo (fibras lentas e rápidas são ativadas sem uma sequência óbvia) e o potencial de fadiga é alto (pela atividade contrátil repetida das mesmas fibras musculares) (45-48). Assim, para maximizar o recrutamento espacial sugere-se aumentar a intensidade sempre que possível (para atingir fibras mais profundas), modificar o posicionamento dos eletrodos na mesma sessão ou entre as sessões (visando ativar diferentes populações de fibras musculares superficiais) e alterar a angulação da articulação (para variar a posição das fibras musculares em relação ao eletrodo) (45, 49).

Torna-se importante mencionar que protocolos relativamente curtos de EENM (até 4 semanas) geram adaptações neurais em músculos saudáveis e comprometidos, e estas adaptações incluem o aumento significativo da contração voluntária máxima (CVM) (50, 51). Portanto, apesar do aumento da força muscular, não há alterações na síntese de proteína e logo não ocorre hipertrofia (52). Para isso, protocolos mais longos (em torno de 8 semanas) são necessários conforme demonstrado por Gondin et al. (53).

Os parâmetros para a aplicação de EENM são bastante variáveis entre os estudos, entretanto, Lloyd et al. (54) afirma que a efetividade dos programas de reabilitação não depende

na maior parte deles. Existe uma considerável variação interindividual e a otimização da EENM pode estar mais relacionada às características dos indivíduos que aos parâmetros de estimulação (45, 54).

Apesar destas colocações, há concordância sobre algumas características da EENM (55). A tensão muscular, que consiste no nível de força evocada para gerar força voluntária máxima (56) deve ser maximizada através da manipulação de dois fatores: frequência e intensidade. Assim, para otimizar a tensão muscular é fortemente recomendado usar pulsos retangulares bifásicos de 100-400 μs liberados a uma frequência de 50-75 Hz (55, 57) e a intensidade deve ser a mais alta tolerada pelo indivíduo (57, 58). Além disso, a EENM deve ser realizada em uma condição estática (isometria). Por outro lado, devido ao desconforto gerado pela corrente elétrica e objetivando a familiarização do indivíduo com a técnica, intensidades mais baixas são recomendadas nas primeiras sessões para melhorar a tolerância à EENM (45). A contração muscular voluntária realizada concomitante ao estímulo elétrico também pode melhorar o desconforto para alguns indivíduos e portanto deve ser considerada (57).

Uma revisão sistemática de ensaios clínicos realizada recentemente por Jones et al. (16) e publicada pela colaboração Cochrane, reuniu 18 estudos (933 indivíduos) realizados com pacientes adultos com doença avançada e que apresentavam fraqueza muscular (pacientes com insuficiência cardíaca crônica, doença pulmonar obstrutiva crônica, câncer e HIV/AIDS). Esta revisão sistemática com metanálise demonstrou que a EENM quando aplicada no músculo quadríceps isoladamente ou associado a outros músculos como isquiotibiais, gastrocnêmios e glúteos aumenta a força muscular de quadríceps, a distância percorrida no teste de caminhada de seis minutos (TC6M) e a massa muscular comparado ao controle. Os parâmetros de EENM utilizados foram: frequência média de estimulação 50 Hz (variando de 15 a 75 Hz); duração de pulso de 400 μs (variando de 200-700 μs), ciclo de trabalho de 33% (variando de 13 a 75%), tempo de sessão de 30 minutos (variando de 18 a 240 minutos), frequência semanal de 5 vezes/semana (variando de 2-7 vezes/semana) e duração do programa de reabilitação de 6 semanas (variando de 4 a 11 semanas). A intensidade em todos os estudos foi ajustada de modo que a contração muscular fosse visível ou palpável, de acordo com a tolerância do paciente e aumentada no decorrer do programa.

No que diz respeito ao posicionamento dos eletrodos, Bergquist *et al.* (59) sugere que estimular o tronco do nervo femoral (ponto motor) além dos ventres musculares quando a EENM é utilizada sobre o quadríceps pode otimizar o tratamento, já que assim a fadiga é reduzida. Corroborando com os achados de Bergquist et al. (59), em estudo posterior, Gobbo

et al. (60) reiteram que a identificação do ponto motor é essencial para otimizar o uso da EENM, uma vez que há grande variabilidade interindividual na localização anatômica destes.

Ainda, Sbruzzi et al. (61) realizaram um estudo para verificar qual o tamanho ideal de eletrodo para EENM, considerando o maior torque gerado e o menor desconforto ao indivíduo. Os autores concluíram que eletrodos de tamanho 7,5x13 cm tiveram melhor resposta quando comparado a eletrodos de tamanho 5x5 cm e 5x9 cm para estes desfechos. Do mesmo modo, Maffiuletti et al. (57) recomendam a utilização de eletrodos grandes para a estimulação elétrica do quadríceps objetivando minimizar a densidade da corrente e maximizar o conforto do paciente e o recrutamento muscular.

Inicialmente, a EENM foi estudada como uma ferramenta para tratamento de pacientes com doenças neurológicas (62, 63), no pós-operatório e em casos de imobilização prolongada (64, 65). Atualmente, a EENM é utilizada em pacientes com diversas condições de saúde, como insuficiência cardíaca (66), doença pulmonar obstrutiva crônica (67), disfunções ortopédicas (68), pacientes criticamente enfermos (69), transplantados (70), e, também em pacientes com IRC (18).

Estudos realizados com doentes renais crônicos em HD sugerem efeitos positivos quando esta terapia é utilizada por longo período (efeito crônico) sobre a força muscular de membros inferiores (17-19), arquitetura muscular (18), capacidade funcional (17, 19), qualidade de vida e também sobre a eficiência da diálise (19).

Dobsak et al. (19) em um ECR com 32 pacientes, utilizaram um protocolo de EENM para o músculo quadríceps e músculos da panturrilha, 3 vezes/semana, durante 20 semanas com os seguintes parâmetros: frequência 10 Hz, duração de pulso 200 μs, tempo de contração 20 s, tempo de repouso 20 s, intensidade máxima 60 mA e tempo de sessão de 60 minutos. Os autores verificaram incremento na força muscular do quadríceps, na distância percorrida no TC6M, em alguns aspectos da qualidade de vida e nos índices de efetividade da diálise (Kt/V e URR) quando comparado ao grupo controle. Dobsak et al. (19) ainda sugerem que a EENM pode ser uma alternativa ao exercício aeróbico, uma vez que, os grupos que receberam EENM ou realizaram o exercício em cicloergômetro apresentaram benefícios semelhantes.

McGregor et al. (17), da mesma forma que Dobsak et al. (19), em estudo realizado recentemente, reforçam que a EENM quando aplicada sobre o quadríceps e gastrocnêmios pode ser uma alternativa ao exercício aeróbico para pacientes com IRC em HD. Os autores realizaram um ECR com 51 pacientes alocados em três grupos (grupo exercício, grupo EENM e controle) e observaram incremento da capacidade funcional (pela melhora do VO_2 pico) e da força muscular de quadríceps para os grupos EENM e exercício. Entretanto, diferente do estudo de

Dobsak et al. (19) o treinamento foi realizado apenas por 10 semanas (3 vezes/semana) e com os seguintes parâmetros: frequência de 5 Hz; duração de pulso de 760 – 857 μs; 60 minutos/sessão e intensidade máxima tolerada pelo paciente.

Por outro lado, Schardong et al. (18) em estudo realizado com 21 pacientes, avaliaram o efeito da EENM quando aplicada sobre o músculo quadríceps de doentes renais crônicos em HD e verificaram que oito semanas de treinamento (3 vezes/semana, totalizando 24 sessões) não foram suficientes para melhorar a capacidade funcional avaliada pelo TC6M. Em contrapartida, utilizando como parâmetros de estimulação 80 Hz de frequência, 400 μs de duração de pulso, 10 s de contração, 50 a 20 s de relaxamento (tempo OFF reduzido progressivamente), intensidade máxima tolerada pelo paciente e tempo de sessão de 20-34 minutos (aumentou progressivamente) observou incremento significativo para a força muscular e um efeito protetor sobre a arquitetura muscular do quadríceps quando comparado ao grupo controle.

Apesar da EENM ter sido amplamente estudada em diferentes populações, existem poucas evidências de alto rigor metodológico a respeito dos efeitos desta terapia em pacientes com IRC em HD e estas são divergentes sobre alguns desfechos. Por fim, no melhor do nosso conhecimento, até o momento nenhuma revisão sistemática sobre o assunto foi publicada.

2.3 FOTOBIOMODULAÇÃO

A terapia de FBM refere-se ao uso de fótons como radiação não térmica para alterar a atividade biológica e pode ser realizada através de LBI, LEDs ou ambos. A propriedade física que difere estas duas fontes luminosas é a coerência. O LBI possui um feixe luminoso coerente ao contrário de LEDs (fontes luminosas não coerentes) (20, 21).

Lasers (*light amplification by stimulated emission of radiation*) são equipamentos que geram radiação eletromagnética e são relativamente uniformes em comprimento de onda, fase e polarização (71). O LBI é considerado um tipo especial de laser que possui efeitos sobre sistemas biológicos através de mecanismo não ablativo ou térmico, mas por meio de efeito fotoquímico, ou seja, a luz é absorvida e causa uma mudança química na célula (72, 73).

Existem diferentes tipos de LBI, sendo os mais comuns: Laser Rubi (694 nm); He-Ne (632.8 nm); Ga-Al-As (805 ou 650 nm) e Ga-As (904 nm) (72). Lasers com comprimentos de onda entre 390-600 nm são utilizados para tratamento de condições superficiais e lasers com comprimentos de onda entre 600-1.100 nm são utilizados para tratar tecidos mais profundos, uma vez que, a penetração do feixe luminoso é maior (74).

Em relação aos parâmetros de aplicação, podemos encontrar LBI com potências entre 0,001-0,2 Watts; comprimento de onda entre 300-10.600 nm; pulsos entre 0 (emissão contínua) a 5.000 Hz; densidade de potência entre 0,01-10 W/cm^2 e doses de 0,01 a 100 J/cm^2 (22, 75). Vale ressaltar que doses muito baixas podem ser pouco eficazes, em contrapartida, doses muito elevadas podem levar ao dano tecidual, por isso o termo FOTOBIOMODULAÇÃO (20). A lei Arnoldt-Schultz prediz a existência de um efeito dose-dependente representado por uma curva fluência *versus* resposta biológica. Assim, a quantidade de energia absorvida pela célula determina o efeito de estimulação ou inibição de processos intracelulares (76).

LBI e LEDs são amplamente conhecidos pelos efeitos analgésico, anti-inflamatório e regenerativo, uma vez que, promovem aumento do tecido de reparo (20, 21).

O mecanismo biológico básico e mais aceito para justificar os efeitos terapêuticos do LBI é a absorção de luz pelos cromóforos mitocondriais, especificamente pela enzima *citocromo c oxidase* que está localizada na cadeia respiratória mitocondrial (77). É hipotetizado que a absorção da energia luminosa pode causar foto dissociação do óxido nítrico (um inibidor) da *citocromo c oxidase* (78), levando ao aumento da atividade enzimática (79), transporte de elétrons (80), respiração mitocondrial e produção de adenosina trifosfato (ATP) (81, 82). Consequentemente, o LBI altera o estado redox celular que induz a ativação de numerosas vias de sinalização intracelular como a síntese de ácido nucleico, síntese de proteína, ativação de enzimas e progressão do ciclo celular (83). A figura 1 ilustra o mecanismo descrito acima.

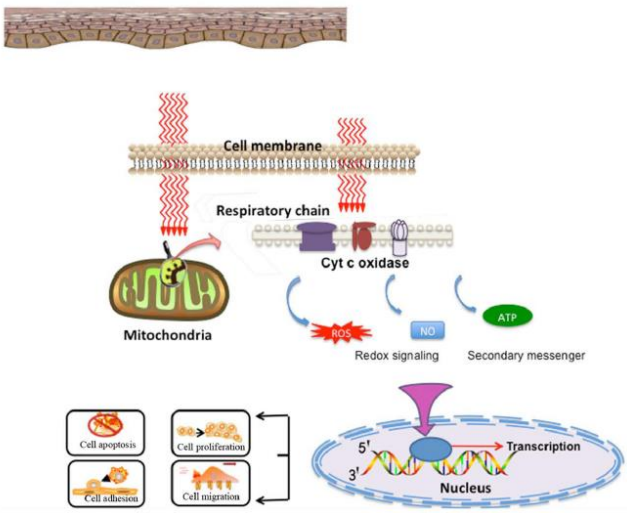

Figura 1 - Mecanismo de ação do LBP

Fonte: Avci et al., 2013 (84)

A terapia de FBM é utilizada para tratamento de inúmeras doenças e condições clínicas no âmbito da fisioterapia. Entretanto, nos últimos dez anos o uso do LBI e LEDs para melhora da *performance* de exercício e para redução da fadiga muscular em indivíduos saudáveis e atletas tem sido amplamente estudado.

Recentemente Vanin et al. (22) publicaram uma revisão sistemática com metanálise reunindo 39 ECRs (totalizando 861 participantes) que utilizaram LBI ou LEDs em indivíduos saudáveis, em algum momento do protocolo de exercícios realizado. Os autores encontraram resultados satisfatórios sobre desfechos como tempo de exaustão, número de repetições, pico de torque isométrico e níveis de creatina-quinase nos grupos que receberam FBM em comparação a grupos placebos. Ainda, observou-se que os melhores resultados foram atingidos usando tanto LBI quanto LEDs ou até mesmo quando as duas fontes luminosas foram combinadas.

Potência de 200 mW por diodo, comprimentos de onda entre 655-950 nm, doses entre 20-60 J para grupos musculares pequenos (ex.: bíceps e tríceps sural) e doses entre 60-300 J para grandes grupos musculares (ex. quadríceps) foram considerados os parâmetros relacionados aos melhores efeitos (22). A maioria dos estudos contemplados por esta revisão aplicou a terapia de FBM antes do exercício, utilizaram LBI do tipo cluster como fonte luminosa e a aplicação foi realizada em contato direto (90°) com a pele (22).

Além dos parâmetros acima, conforme as recomendações para uso de terapia de FBM publicadas recentemente por Leal-Junior et al. (85), a irradiação deve cobrir a maior área possível dos grupos musculares envolvidos no exercício a ser realizado, o tempo mínimo de aplicação por sítio deve ser de 30 s e a emissão do feixe luminoso pode ser realizada de forma contínua ou pulsada.

Em relação ao momento para aplicar a terapia de FBM, Leal-Junior et al. (85) recomendam: para efeitos agudos (um único evento) a aplicação deve ser realizada 5 minutos a 6 horas antes da atividade. Para efeitos crônicos associados ao treinamento de força a irradiação deve ser realizada imediatamente 5 a 10 minutos antes de cada sessão de exercício. Para efeitos crônicos associados ao treinamento de *endurance* a terapia de FBM deve ser realizada imediatamente antes e após cada sessão de exercício (5-10 minutos) (85).

No que diz respeito ao uso desta terapia em outras populações, já existem estudos que avaliaram o efeito da FBM sobre a *performance* muscular em pacientes com insuficiência cardíaca (23, 86), doença pulmonar obstrutiva (24, 87) e também na DRC (26), entretanto, todos estes estudos observaram o efeito agudo da terapia.

Bublitz et al. (23) conduziram um ECR com 20 pacientes com insuficiência cardíaca que estavam hospitalizados. Foi avaliado a capacidade funcional e a fadiga muscular após uma sessão de LBI (808 nm, 4J/sítio de aplicação, 7 sítios) realizada no quadríceps femoral, antes do TC6M. Não foi observado melhora no desempenho do teste para o grupo tratado em comparação ao grupo controle, entretanto, houve redução da fadiga muscular avaliada através da escala de percepção de esforço de Borg. Ainda, o grupo controle apresentou aumento dos níveis de lactato sanguíneo após, 3, 6 e 30 minutos de repouso.

Miranda et al. (24) avaliaram o efeito de uma aplicação de LBI (905 nm) e LEDs (640 e 875 nm) combinados em 13 pacientes com doença pulmonar obstrutiva crônica através de um ensaio clínico randomizado cruzado. A aplicação da terapia de FBM foi realizada em 6 sítios do músculo quadríceps femoral antes de um protocolo de exercício realizado em dinamômetro isocinético. Utilizando uma dose de 30 J por sítio de aplicação os autores observaram incremento no pico de torque, no trabalho total, na contração isométrica voluntária máxima e melhora da sensação de dispneia e fadiga em membros inferiores quando comparado ao grupo placebo.

Macagnan et al. (26), através de um ECR cruzado, avaliaram o efeito de diferentes doses (60 J, 90 J, 120 J e placebo) de LBI (850 nm) sobre a força de preensão palmar de 15 pacientes com IRC em HD. Respeitando um período de *washout* de uma semana entre cada dose, os autores observaram que os melhores resultados foram obtidos com as doses 60 e 90 J (por braço), sendo a dose de 60 J considerada a melhor dose-resposta para aumentar a força muscular do membro superior.

Em relação ao efeito crônico da FBM sobre a *performance* muscular, podemos citar os estudos de Ferraresi et al. (88) e Melo et al. (25).

Ferraresi et al. (88) verificaram que a FBM quando associada ao treinamento de força é superior ao treinamento isolado para melhora da *performance* muscular do quadríceps. Através de um ensaio clínico randomizado, 36 homens saudáveis foram alocados em três grupos (grupo controle, grupo treinamento ou grupo treinamento mais LBI). O grupo tratado com FBM após o treinamento de força em leg press, recebeu 24 aplicações de LBI (808 nm; dose de 3,6 J/sítio de aplicação) em 7 sítios do músculo quadríceps femoral e apresentou melhores resultados no teste de uma repetição máxima (1RM) comparado ao grupo que não recebeu FBM e ao grupo controle.

Melo et al. (25), através de um ensaio clínico randomizado, avaliaram o efeito da FBM sobre a capacidade funcional, arquitetura muscular e dor de 45 idosas com osteoartrite de joelho. Os pesquisadores verificaram que após 8 semanas de tratamento e 16 aplicações de LBI

(810 nm, 4-6 J/ponto de aplicação) sobre 6 pontos circunjacentes a articulação do joelho houve aumento na distância percorrida no TC6M e redução dos níveis de dor. Em contrapartida, não foram observadas alterações na arquitetura muscular.

Até o presente momento e no melhor do nosso conhecimento, não existem estudos que avaliaram o efeito da FBM por longo período (efeito crônico) como monoterapia em pacientes com IRC.

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3 OBJETIVOS

3.1 OBJETIVO GERAL

Verificar o efeito crônico da EENM e da terapia de FBM em pacientes com IRC em HD sobre a capacidade funcional e a força muscular de membros inferiores.

3.2 OBJETIVOS ESPECÍFICOS

- Revisar sistematicamente os efeitos da EENM em pacientes com IRC em HD sobre os desfechos força muscular de membros superiores e inferiores, capacidade funcional e qualidade de vida;

- Avaliar os efeitos da terapia de FBM sobre a capacidade funcional, força e arquitetura muscular de membros inferiores, percepção de dor e fadiga, e qualidade de vida de doentes renais crônicos em HD.

4 ARTIGO I

RUNNING HEAD: NEUROMUSCULAR STIMULATION IN DIALYTIC PATIENTS

TITLE: NEUROMUSCULAR ELECTRICAL STIMULATION IN CHRONIC KIDNEY FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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NEUROMUSCULAR ELECTRICAL STIMULATION IN CHRONIC KIDNEY FAILURE PATIENTS ON HEMODIALYSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Objective: To systematically review the effects of neuromuscular electrical stimulation (NMES) in chronic kidney failure (CKF) patients on hemodialysis (HD) on lower and upper limb muscle strength, functional capacity and quality of life outcomes.

Data Sources: Data were obtained from MEDLINE (via PubMed), Embase, Scielo, Cochrane Central Register of Controlled Trials and Physiotherapy Evidence Database (PEDro) databases. There were no mandatory language or publication date restrictions.

Study Selection: Clinical trials that assessed the chronic effect of NMES (alone or associated with other physical therapy) on lower limb muscle strength and/or functional capacity of CKF patients on HD compared to control, placebo or another intervention were selected by two independent reviewers.

Data Extraction: Two independent reviewers extracted data using a pre-designed data extraction form. Risk of bias was assessed with RoB 2.0 and ROBINS-I, and quality of evidence with Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Data Synthesis: Ten studies were included, totaling 242 patients. Randomized clinical trials showed some concerns/high risk of bias and the non-randomized ones moderate/critical risk of bias. Random-effects meta-analysis showed that NMES increases quadriceps muscle strength [SMD = 1.46 (95%CI: 0.86 to 2.07), p< 0.0001 - moderate quality of evidence], upper limb strength [MD = 10.02KgF (95%CI: 0,78 to 19.27), p=0.03 - low quality of evidence] and functional capacity [MD = 30.11m (95% CI: 15.57 to 44.65), p< 0.0001 - moderate quality of evidence]. When sensitivity analysis was performed for quadriceps isometric muscle strength the results were also positive for the NMES group [SMD = 1.19 (95%CI: 0.85 to 1.53), p< 0.0001 - moderate quality of evidence]. It was impossible to quantitatively analyze quality of life data, however, NMES associated or not with exercise appears to have positive effects on them.

Conclusions: NMES improves quadriceps muscle strength as well as the functional capacity of CKF patients on HD. The effects on upper limb muscle strength and quality of life seem to be positive, however, the quality of evidence is very limited.

KEYWORDS: Electric stimulation; Kidney failure, chronic; Renal Dialysis.

ABBREVIATIONS

CKD: Chronic Kidney Disease

CKF: Chronic Kidney Failure

EQ-5D: EuroQol

HD: Hemodialysis

KDQOL-SF ™: Kidney Disease Quality of Life Short Form

NMES: Neuromuscular Electrical Stimulation

RCT: Randomized Clinical Trial

RCTs: Randomized Clinical Trials

6MWT: Six Minutes Walk Test

SST: Sit-and-Stand Test

SST10: Sit to Stand to Sit 10 Test

VO_2 peak: Peak Oxygen Uptake

Chronic kidney disease (CKD) consists of renal damage and progressive and irreversible loss of kidney function (glomerular, tubular and endocrine)[1]. This is a worldwide problem, with an estimated prevalence of 8-16%, which incurs high costs for the health system[2,3]. It is believed that these numbers will increase disproportionately in the coming years, especially in developing countries[3].

Renal replacement therapy is indispensable in the more advanced stages of the disease as in chronic kidney failure (CKF), but even on dialysis, this patient presents high levels of uremic toxins[4]. This, over time and associated with loss of renal endocrine function causes systemic damage in different organs and tissues[5,6].

There is a significant reduction of physical activities among patients with CKF, and this is associated with high morbidity and mortality, impairment of quality of life, depression, reduction of physical capacity and muscle strength[7]. To the detriment of physical capacity, therapeutic resources such as conventional exercise[7,8], inspiratory muscle training[9] and neuromuscular electrical stimulation (NMES)[10] can mitigate the losses and improve the functionality of these patients.

The NMES involves the application of a series of intermittent and superficial stimuli to skeletal muscles to generate visible contractions by activating nerve branches[11] and, it has positive effects mainly on the muscle architecture and strength and on the functional capacity of patients with weaknesses and incapacities[12]. Therefore, NMES may be an alternative for patients who do not fit into conventional exercise-based rehabilitation programs. There is extensive evidence of the benefits of NMES in different populations[13-15], however, few studies have used this therapy in CKF patients[10,16] and, these trials differ in some points.

Dobsak et al.[16] evaluated the effect of NMES in CKF patients and showed an improvement in functional capacity. On the other hand, Schardong et al.[10] after the application of this therapy in the same population observed an increase in the muscle strength of the lower limbs but no gains for the functional capacity. Thus, the efficacy of NMES has not been clearly for these patients.

Considering that there is uncertainty regarding NMES efficacy in some outcomes and in the best intervention parameters and protocols, our objective was to systematically review the effects of this therapy in CKF patients on hemodialysis (HD). A systematic review of current evidence may provide additional information and increase the accuracy of effect estimates to help health care professionals customize the treatment of CFK patients. Therefore, the research question for this systematic review was: 1. Does NMES improve muscle strength, functional capacity and quality of life of CKF patients?

METHODS

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[17] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[18]. It was registered in the Prospective Register of Systematic Reviews (PROSPERO) under number number CRD42017076958.

Study Selection

We included randomized clinical trials (RCTs), non-randomized controlled clinical trials and before-and-after studies that assessed the effects of NMES (alone or in combination with another therapy) on lower limb muscle strength and/or functional capacity of CKF patients on HD (for at least three months). Secondary outcomes were upper limb muscle strength and quality of life. The strength of lower limb muscles should have been assessed by dynamometry, maximal repetition test, or sit-and-stand test (SST). Functional capacity could have been assessed by the six-minute walk test (6MWT) or ergospirometry. Muscle strength of upper limb should have been by manual dynamometry and quality of life using the Kidney Disease Quality of Life Short Form (KDQOL-SF ™) or EuroQol (EQ-5D) questionnaires. Regarding the comparator group for the case of randomized and non-randomized clinical trials, this could be the control group, placebo group, or another physical therapy when there was no control group.

We excluded studies performed with children or animals, trials in which the muscles stimulated did not belong to the lower limb, those who used another electrical current than NMES or those in which the treatment time was less than one month.

All identified citations were entered into a software for reference management (EndNote X8), and duplicates were excluded. The titles and abstracts of all articles identified by the search strategy were evaluated by two researchers (JS and CS) separately and independently. Studies that did not meet eligibility criteria according to titles or abstracts were excluded. All abstracts that did not provide sufficient information concerning the inclusion and exclusion criteria were selected for evaluation of the full text. Disagreements regarding

study eligibility were discussed between the two reviewers and if there was no consensus a third reviewer was requested (RP).

Data Sources and Searches

We searched MEDLINE (via PubMed), Embase, Scielo, Cochrane Central Register of Controlled Trials and Physiotherapy Evidence Database (PEDro) databases to retrieve potentially relevant articles from inception to January 27, 2019. In addition, the references included in the published articles identified were used as an additional source to identify other studies. Search terms included “Renal Insufficiency, Chronic”, “Kidney Failure, Chronic”, “Electric Stimulation”, and “Electric Stimulation Therapy”. Keywords related to outcomes of interest and type of publication were not included to enhance the sensitivity of the search. No language or publication date restrictions were imposed. The tailored search terms and the complete search strategies are available in supplementary material (Chart 1, 2, 3, 4 and 5).

Data Extraction and Quality Assessment

After reading and selecting the full texts, the same reviewers (JS and CS), independently, extracted data from included studies using a pre-designed data extraction form. Data extracted included study characteristics and outcomes of interest.

Regarding methodological quality, two reviewers (JS and CS) independently assessed the risk of bias of the included studies. The tool of Cochrane Group RoB 2.0[19] for RCTs and the ROBINS-I tool[20] to evaluate non-randomized clinical trials were used. If there were

disagreements a third reviewer (RP) was requested. The overall quality of evidence was assessed using the GRADE system [21,22].

Data Synthesis and Analysis

Wherever possible, data were pooled using a meta-analytic approach. After data extraction, pooled-effect estimates were obtained by comparing the change from baseline to study end for each group. A random-effects model, with DerSimonian and Laird's variance estimator was used, and the results were presented as mean difference and standard mean difference, with 95% confidence intervals (95%CI). A p value ≤ 0.05 was considered significant. Statistical heterogeneity among studies was assessed using I^2 statistic. To reduce the statistical heterogeneity, a sensitivity analysis was performed considering the type of evaluation. All meta-analyses were performed using the R statistical software version 3.5, with meta package version 4.8-1. Studies not included in the meta-analysis were described.

RESULTS

Description of studies

The electronic search strategy identified a total of 967 studies. Four additional studies were found through other sources. A total of ten studies met the inclusion criteria for this systematic review, gathering data from 242 patients. Eight studies were included at meta-analysis since two studies did not have a comparator group (before-and-after studies). Unlike the muscle strength of lower limbs and upper limbs and functional capacity, it was not possible to perform meta-analysis for quality of life outcome, because the four studies that

evaluate this variable used different questionnaires and one study was the before and after type. Figure 1 shows a flow diagram of study selection.

INSERT FIGURE 1

In 7 studies[10,16,23-27], the stimulation frequencies with NMES ranged from 5 to 80 Hz. Two studies[28,29] used fixed protocols in which the frequency varied from 2-90 Hz. One study [30] did not describe the stimulation characteristics. The pulse duration ranged from 200 to 400 µs, and only one study[24] used a higher pulse width (760-875 µs). The intensity of stimulation was adjusted according to patient tolerance. The time of session ranged from 20-60 min, with a weekly frequency of 2-3 times/week and total intervention time of 5-20 weeks. Two studies (before-and-after studies) associated physical exercise with NMES[23,30]. All the protocols occurred in an outpatient environment (during HD). Table 1 summarizes characteristics of included studies and table 2 demonstrates the variability of the parameters and protocols of electrical stimulation adopted by the studies included in this review based on the training volume.

INSERT TABLE 1 AND TABLE 2

Risk of bias and quality of evidence

The six RCTs included in this review were evaluated by the RoB 2.0 tool and all showed low risk of bias for categories “deviations from intended intervention” and “missing outcome data”. Regarding the randomization process, four of the studies[16,24,25,27] have some concerns for this topic. Regarding the bias of selective reporting, only two studies[10,24] present

low risk of bias for this item and four[16,25-27] show some concerns. The most problematic item was the "measurement of outcome", since three studies present a high risk of bias to the blinding of the outcome assessors, and these are highly influential. The overall score of RCTs ranged from “some concerns” (three studies)[24,25,31] to “high risk of bias” (three studies)[10,16,26].

The four non-randomized clinical trials were evaluated by Robins-I tool and also have major limitations. All studies present confounders to a greater or lesser extent, but, low risk of bias for item “To departure from intended intervention”. Three studies[23,28,30] present a serious risk of bias in “selection of participants”, and one[29] a moderate risk of bias. In the category “Measurement of intervention” three articles[23,28,29] presented a low risk of bias and one[30] a serious risk. As for loss of data, three studies[23,28,30] presented a low risk of bias and one a moderate risk[29] for this item. Regarding the measurement of the outcomes, none of the studies reported whether the evaluators were blinded, so it was not possible to assess the risk of bias for this category. Likewise, it is not possible to identify a selective reporting bias, since none of the studies presented a registration of the research protocol in electronic platforms, and it was not possible to evaluate publication bias. Thus, the overall score of non-randomized clinical trials ranged from “moderate” to “critical” risk of bias, one study being considered as moderate risk of bias[29], another as serious risk of bias[28] and two studies considered as critical risk[23,30]. The evaluation of methodological quality for all studies and their outcomes is available in detail in supplementary material (table 3 and table 4).

The quality of evidence, assessed through the GRADE System, suggests moderate confidence in the functional capacity and quadriceps muscle strength outcomes and low confidence in lower limb muscle strength (assessed by SST) and upper limb muscle strength,

as well as in quality of life. The evidence profile is available in supplementary material (table 5).

Effects of intervention

Lower limbs muscle strength

Quadriceps muscle strength was assessed by all studies included in the review. Eight studies evaluated muscle strength through dynamometry[10,16,24,25,27-30], one study evaluated it by a maximal repetition test [26] and another by the Daniels scale [23]. Eight studies[10,16,24-29] totalizing 221 patients were included in the meta-analysis for this outcome. NMES increased the quadriceps muscle strength by 1.46 standard deviation when compared to the control group [SMD = 1.46 (95%CI: 0.86 to 2.07, I^2:73%), p< 0.0001], and according to Cohen's classification, this is considered a very large effect [32] (figure 2). Despite the large effect size for this outcome, the heterogeneity was high. Therefore, a sensitivity analysis was performed. The article by Roxo et al. (2016)[26] was excluded from the analysis since this study was the only RCT that did not evaluate muscle strength by dynamometry (evaluated dynamic strength, not isometric strenght). Therefore, the meta-analysis with seven studies[10,16,24,25,27-29] and 181 patients showed that NMES increased the isometric quadriceps muscle strength by 1.19 standard deviation when compared to the control group presenting low heterogeneity [SMD = 1.19 (95%CI: 0.85 to 1.53, I^2:8%), p< 0.0001] (figure 3).

Two others studies (before-and-after studies) [23,30] were not included in the meta-analysis since they did not have a comparator group and combined NMES to exercise. However, these studies also demonstrate that the patients presented improvement for such an

outcome (Jiménez et al: 13.7±8.1 KgF vs 16.2±10.9 KgF, p=0.043; Martos et al: Right leg 4.1±0.5 KgF vs 4.7±0.3 KgF, p=0.014; Left leg: 4.2±0.6 KgF vs 4.9±0.3 KgF, p=0.014).

INSERT FIGURES 2 AND 3

The lower limb muscle strength assessed by the sit-and-stand test was measured by five studies [10,23,28-30]. However, four of them used SST10[23,28-30] and one conventional SST[10]. Of the studies that used SST10, two were before-and-after studies[23,30], therefore only studies by Esteve et al.[28] and Simó et al.[29] were included in the meta-analysis. The quantitative analysis totaled 61 patients and it did not show significant improvement for the NMES group in relation to the control group for this outcome [MD = −3.41 s (95%CI: −11.96 to 5.14, I^2:0%), p=0.43] (figure 4).

INSERT FIGURE 4

Among the studies that were not included in the meta-analysis for the measurement of the muscle strength of lower limbs evaluated by SST, the study by Jiménez et al.[30] did not show significant improvement to reduce the time needed to perform the 10 repetitions of the SST10 (24.6±13.4 s vs 20.1±10.1 s, p=0.054). On the other hand, Martos et al.[23] found positive results for the same outcome after combined use of NMES and physical exercise (35.3±20.3 s vs 26.4±6.43 s, p=0.005). Similarly, Schardong et al.[10] found an increase in the number of repetitions performed in the conventional SST, thus evidencing, improvement of the muscle strength of lower limb after the use of NMES compared to the control group (GI: 16.10±6.51 repetitions vs GC: 12.50 ± 4.72 repetitions, p=0.029).

Upper limb muscle strength

Upper limb muscle strength evaluated by manual dynamometer was verified by four studies[25,28-30]. The meta-analysis conducted with three studies[25,28,29], totaling 81 patients, identified an increase of this outcome after NMES compared to CG [MD = 10.02 KgF (95%CI: 0.78 to 19.27, I^2:97%), p=0.03] (figure 5). Jiménez et al.[30] also observed a significant improvement in the hand grip strength of CKF patients after an NMES-associated exercise program (23.8±15.9 KgF vs 25.1±15.9 KgF, p=0.007).

INSERT FIGURE 5

Functional capacity

Seven studies included in this review evaluated functional capacity through the 6MWT. The meta-analysis of five studies[10,16,26,28,29] and 143 patients showed an increase in the distance covered in the 6MWT after NMES compared to CG [MD = 30.11 m (95%CI: 15.57 to 44.65, I^2:0%), p< 0.0001] (figure 6). Likewise, Jiménez et al.[30] and Martos et al.[23] combined NMES with physical exercise and they also found significant improvement for this outcome (Jiménez et al.: 332.6 vs 402.7 m, p=0.014; Martos et al.: 428±106m vs 492±100 m, p=0.005).

INSERT FIGURE 6

One RCT[24] assessed functional capacity through ergospirometry and it demonstrated that the group that received NMES had peak oxygen uptake ($VO_{2\ peak}$) higher than the control

group at the end of treatment (CG: 16.3±2.53 vs 15.9±5.56 $ml.kg^{-1}.min^{-1}$ and GI: 19.6±7.1 vs 21±7.57 $ml.kg^{-1}.min^{-1}$; p=0.02), indicating the improvement of this outcome.

Quality of life

Four studies (n=95 patients)[16,23,27,29] evaluated the effect of NMES associated or not with exercise on the quality of life of CKF patients. Dobsak et al.[16] used the SF-36 questionnaire and found positive effects on aspects of mental health (vitality: 48.5±12.6 vs 54.3±7.9, p= 0.019; emotional aspects: 54±10.7 vs 63.1±9.1, p= 0.002; mental health: 62.4±12.4 vs 71.3±8.4, p=0.009; and mental component: 57.3±6.4 vs 64.5±5.3, p < 0.001) but not on physical aspects. As opposed to the intervention group, no effect was observed in the control group for this outcome.

Martos et al.[23], on the other hand, through the KDQOL-SF™ questionnaire observed only significant effects on the physical aspects (38.4±12.9 vs 45.3±13.1, p= 0.022) of quality of life after the combined use of NMES and exercise.

Simó et al.[29] used the EuroQol-5D questionnaire to assess the quality of life and found a significant improvement in the "usual activities performance" dimension in the NMES group (1.7±0.9 vs 1.2±0.5, p= 0.010) and in the "general health" evaluation (52.7± 16.3 vs. 65.5±13.4, p=0.001). The same results were not observed for the control group.

Suzuki et al.[27] used the SF-8 questionnaire to evaluate the quality of life and found no changes for this outcome for either group in any dimension.

DISCUSSION

This is the first systematic review with meta-analysis to demonstrate that when NMES is applied chronically in CKF patients during HD it improves functional capacity and muscle strength of lower and upper limb. Some aspects of quality of life also presented positive results, however due to the heterogeneity of the scales used to evaluate this outcome and diversity of study designs, the results were presented qualitatively.

Muscle strength of the quadriceps and of the lower limb can be assessed by different methods. Dynamometry, considered the gold standard method[33,34] and the maximal repetition test are often used to measure this outcome. The SST in its different variations is an indirect evaluation of muscle strength and endurance for lower limbs, but due to its good applicability it is widely used in clinical practice, also reflecting the patient's functionality[35].

The NMES was effective in increasing quadriceps muscle strength in CKF patients when evaluated by dynamometry or maximal repetition test, and the quality of evidence was considered moderate. This can be explained by the high risk of bias of some studies and different assessment tools used, since, when sensitivity analysis is performed the heterogeneity is practically nil for this outcome. On the other hand, when lower limb muscle strength was assessed by SST, the results were not significant. It was impossible to perform a more robust meta-analysis because different instruments were used for measuring and only two studies included in the quantitative analysis were not enough to show positive results. Thus, the quality of evidence for this outcome was considered low, since sample size is small, confidence intervals are large and therefore there is significant lack of precision. In addition, the risk of bias was also considered serious for SST. It is believed that the small number of

controlled clinical trials that evaluated the effect of NMES on CKF patients for lower limb muscle strength was responsible for the results found.

Corroborating our findings, Medeiros et al.[9], in their systematic review that assessed the effect of inspiratory muscle training on respiratory muscle strength in chronic kidney patients encountered similar difficulties. The authors found few publications in the databases for this population, and, the included studies presented a great heterogeneity of training protocols, which ultimately limited the quality of the evidence.

According to a meta-analysis conducted in this study, NMES increases upper limb muscle strength even when applied to leg muscles. Thomas et al.[36] and Hooker et al.[37] suggest that cardiac output is frequently increased during NMES interventions, as it is regulated by the volumetric overload imposed by increased venous return in leg muscles and not by neural regulation of heart rate.

Dobsak el al.[16] observed that NMES also increases the clearance of uremic toxins in chronic kidney patients during HD, attributing this to increased blood flow in the stimulated peripheral muscles and consequently increased displacement of the toxic substances into plasma. Based on this information, despite being considered a local therapy, it is believed that NMES has systemic effects, since it promotes vasodilation, increased muscle blood flow and increased cardiac output. This may explain in part increased muscle strength of upper limb. However, the quality of evidence for this outcome was considered low. On the contrary of studies evaluating quadriceps strength, those that assessed upper limb strength used the same method of evaluation and yet the heterogeneity presented in the meta-analysis was high (I^2 = 97%). It is believed that the small number of studies included in the quantitative analysis

(only three) and the wide confidence intervals, as well as the biases presented by the studies justify our findings.

All studies that evaluated functional capacity used the 6MWT (except the study of McGregor et al.[24] that used ergospirometry) and observed that it had an increment in CKF patients after the use of NMES alone or in combination with exercise. Meta-analysis did not show heterogeneity ($I^2 = 0\%$) and this supports our convincement that the standardization of evaluation methods increases confidence in the results found. Still, this is a relevant clinical finding since the increase in distance walked in the 6MWT is considered a predictor of survival for CKF patients on HD[38].

There is evidence of positive effects of NMES on outcomes such as functional capacity and muscle strength for the most diverse populations[12], which demonstrates that this intervention is an effective strategy for individuals who do not adapt to exercise-based conventional physical exercise programs[39]. Although there is a large variability of parameters for the application of NMES in the literature, our systematic review has shown that for chronic kidney patients on HD the most commonly used parameters are: frequency 5 to 80 Hz, pulse width between 200-400 μs, session time of 20 to 60 min, intensity adjusted according to patient tolerance, weekly frequency of 2-3 times/week and protocols between 5 and 20 weeks. These parameters are similar to those used in other populations such as patients who have suffered a stroke[40] or who have heart failure[41].

Our study also demonstrated that the muscles stimulated in lower limb are usually quadriceps or quadriceps and gastrocnemius. There is no consensus among the studies on knee angulation for the application of electrical stimulation, but those who describe the

positioning of the lower limbs indicate that the patients were in a supine position, with the knees between 15°[28,29] or 60°[10]. However, the knee angulation that generates the highest torque peak in the quadriceps muscle is 60º[42]. Only Schardong et al.[10] used this joint angle for training with NMES and obtained greater gains in quadriceps muscle strength compared to the other studies.

Only four studies[16,23,27,29] evaluated the quality of life and they had different designs and also used different tools for measurement. Although these questions make quantitative analysis unfeasible, the results found point to some positive effects of NMES on quality of life of CKF patients in three of four studies.

Our systematic review with meta-analysis has several strong points. The research covered several databases, as well as a search in gray literature and, there was no language restriction, thus making it unlikely that any relevant study was forgotten. In addition, we use current tools for bias risk assessment such as ROBINS-I and RoB 2.0 to make the results even more transparent.

Study Limitations

Among the limitations of this review we can cite the small number of RCTs included. In addition, they present an important risk of bias in some dimensions. It can be said that methodological quality is impaired mainly by the absence of patient blinding in all studies, since a control group is used as a comparator. Furthermore, it is not known whether the outcomes assessors were blinded in most studies and the outcomes in question are highly influential if the evaluator or the patient is aware of the intervention received. Finally, the

inability to assess the bias of selective reporting intrigues us if negative results regarding the use of NMES in CKF have not occurred or only have not been reported. These issues generally limit the quality of evidence.

Despite the limitations of the data, the estimates presented here show that NMES seems to be an effective therapy for CKF patients on HD. Our findings may be helpful in supporting the decision-making of physiotherapists, especially in situations where the patient does not fit into conventional rehabilitation programs (exercise-based). Thus, NMES may be an initial strategy within rehabilitation programs for physical conditioning, especially for those who are more debilitated, since it does not require effort on the part of the patient.

CONCLUSIONS

In conclusion, NMES when applied in a chronic form in CKF patients during HD improves the quadriceps muscle strength and functional capacity. The effects of this therapy on upper limb muscle strength and quality of life seem to be positive, however, the quality of evidence is very limited, thus, further RCTs are needed to investigate the real benefits of NMES in these outcomes in patients in the terminal stage of CKD.

CONFLICTS OF INTEREST: All authors completed the ICJME Form and reported no conflict of interest.

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LEGENDS TO FIGURES

Figure 1. Flow diagram of study selection.

Figure 2. The standardized mean difference (SMD) and 95% confidence interval (CI) on quadriceps muscle strength for NMES versus control group.

Figure 3. The standardized mean difference (SMD) and 95% confidence interval (CI) on isometric quadriceps muscle strength evaluated by dynamometry for NMES versus control group.

Figure 4. The mean difference (MD) and 95% confidence interval (CI) on lower limb muscle strength evaluated by sit-and-stand test for NMES versus control group.

Figure 5. The mean difference (MD) and 95% confidence interval (CI) on upper limb muscle strength for NMES versus control group.

Figure 6. The mean difference (MD) and 95% confidence interval (CI) on functional capacity for NMES versus control group.

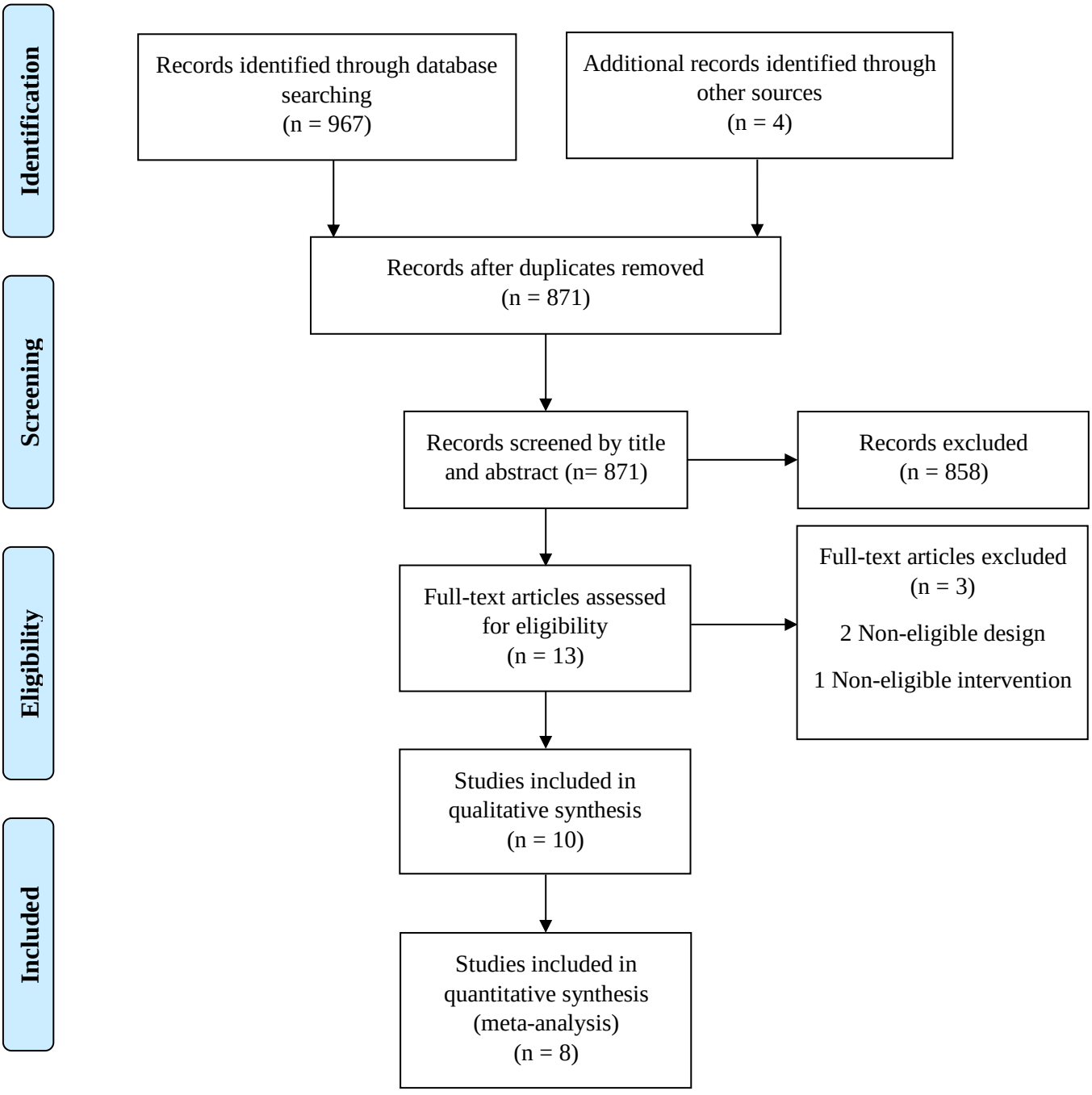
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 967)
Additional records identified through other sources (n = 4)
Records after duplicates removed (n = 871)
Records screened by title and abstract (n= 871)
Records excluded (n = 858)
Full-text articles assessed for eligibility (n = 13)
Full-text articles excluded (n = 3)
2 Non-eligible design
1 Non-eligible intervention
Studies included in qualitative synthesis (n = 10)
Studies included in quantitative synthesis (meta-analysis) (n = 8)

Figure 1

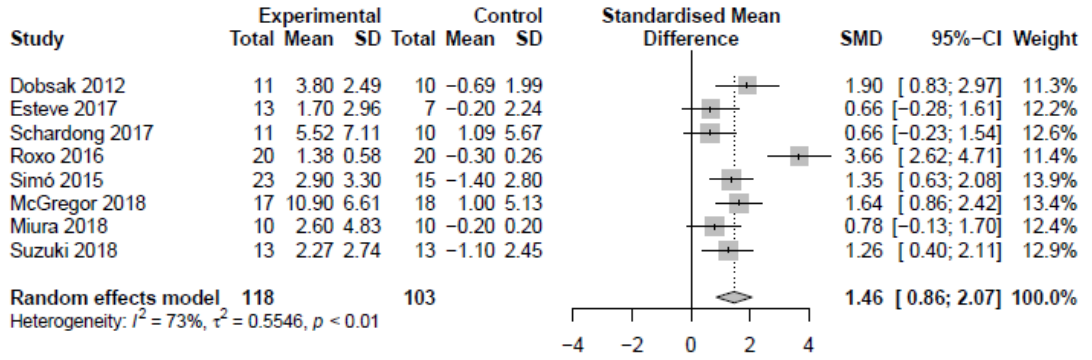

Figure 2

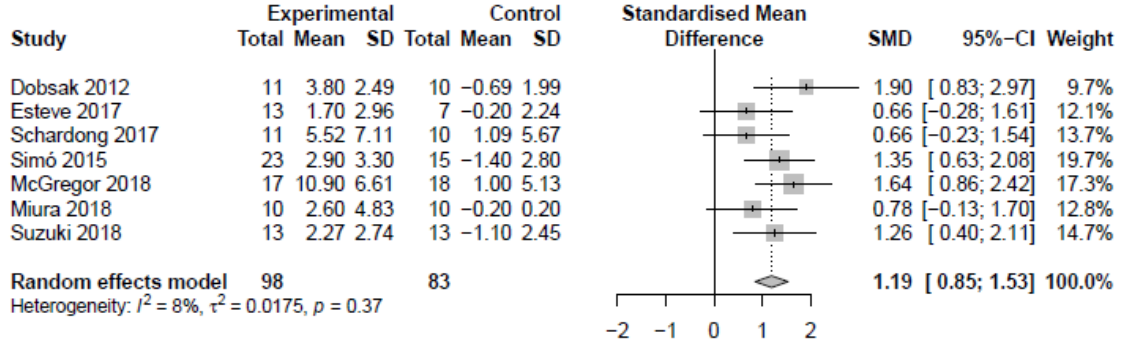

Figure 3

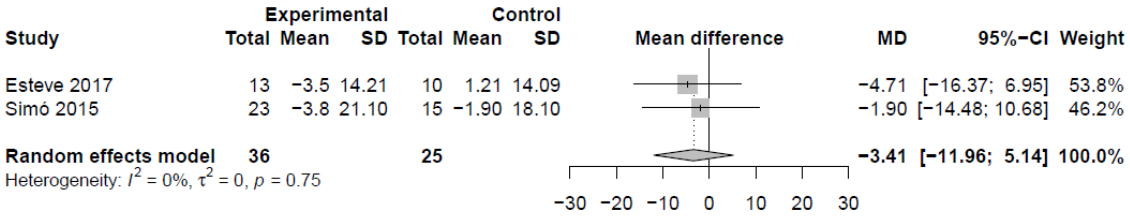

Figure 4

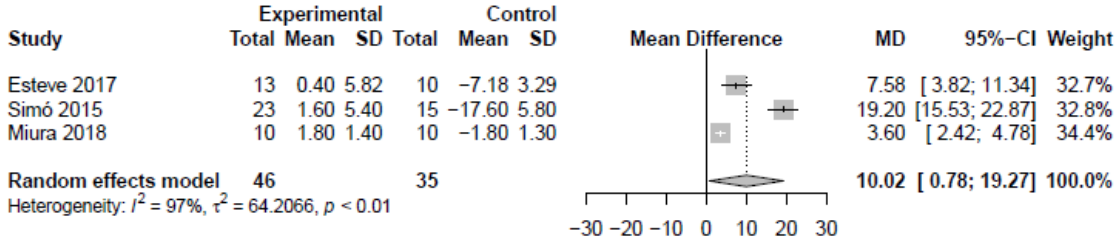

Figure 5

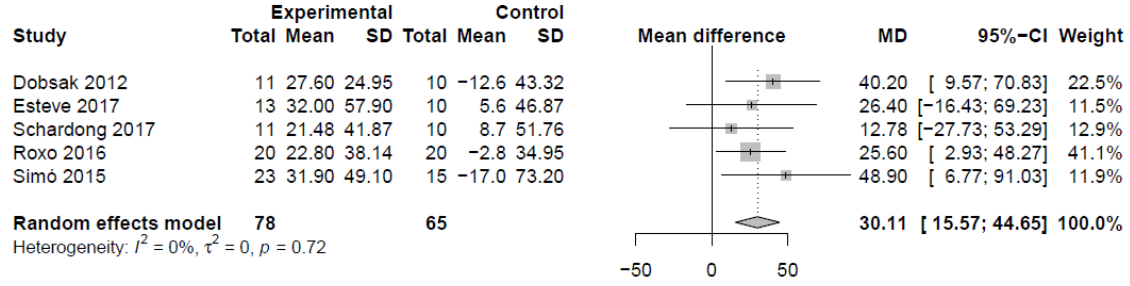

Figure 6

Table 1. Characteristics of included studies

Author, Year	Design	Participants	Intervention	Comparators	Sample (n)	Gender F/M (%)	Age ± SD (years-old)	Protocol	Outcome measures of interest and instruments
Dobsak et al., 2012	Randomized clinical trial	CKF patients on HD	NMES	Control Group	21 patients IG: 11 CG: 10	IG: 54.5/45.5 CG: 40/60	IG: 64.5 ± 8.1 CG: 60.1 ± 8.2	IG: 10 Hz; 200 us pulse width; 20 s TON; 20 s TOFF; 1s rise and fall time; 60 min/session; maximum 60 mA; 3 times/week for 20 weeks; applied on quadriceps and gastrocnemius muscles. CG: No physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by isokinetic dynamometer - Quality of life by SF-36
Esteve et al., 2017	Controlled clinical trial	CKF patients on HD	NMES	Control Group	20 patients IG: 13 CG: 7	IG: 30.8/69.2 CG: 58.3/41.7	IG: 65.7 ± 12.8 CG: 71.6 ± 12.1	IG: 2 – 90 Hz; 1.5-2 s TON; 1.5-0.75 s TOFF; 25-38 min/session; maximum intensity tolerated; 3 times/week for 12 weeks; applied on quadriceps muscle. CG: No physiotherapeutic intervention. Only routine care.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength by STS10 - Upper limb strength by hand grip dynamometer
Jiménez et al., 2013	Clinical trial (Before and after study)	CKF patients on HD	NMES and Exercise program	Not applicable	11 patients	55/45	67.6 ± 16.7	NMES: Parameters of NMES not reported; maximum intensity tolerated by the patient; 2 times/week for 12 weeks; applied on quadriceps muscle. Exercise Program: exercises with balls, weights, elastics and cycle ergometers by 45-50 min.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength by STS10 - Upper limb strength by hand grip dynamometer

Continuation...

Author, Year	Design	Participants	Intervention	Comparators	Sample (n)	Gender F/M (%)	Age ± SD (years-old)	Protocol	Outcome measures of interest
Martos et al., 2011	Clinical trial (Before and after study)	CKF patients on HD	NMES and Exercise program	Not applicable	10 patients	Not reported	66.6 ± 11.5	NMES: 50 Hz; 250 us pulse width; 3 s TON; 6 s TOFF; maximum intensity tolerated by the patient; 3 times/week for 5 weeks; applied on quadriceps muscle. Exercise Program: resistive exercises for lower limbs with weights and elastics (3 series - 15 repetitions).	- Functional capacity by 6MWT - Quadriceps muscle strength by Daniels scale - Lower limb strength STS10 - Quality of life (by KDQOL-SF™
McGregor et al., 2018	Randomized clinical trial	CKF patients on HD	NMES	Control Group	35 patients IG: 17 CG: 18	IG: 18/82 CG: 39/61	IG: 51.5 ± 19.3 CG: 54.3 ± 17.9	IG: 5 Hz; 760 - 857 us pulse width; 60 min/session; maximum intensity tolerated by the patient; 3 times/week for 10 weeks; applied on quadríceps and hamstrings muscles. CG: No physiotherapeutic intervention.	- Functional capacity by ergospirometry - Quadriceps muscle strength by hand-held dynamometer
Miura et al., 2018	Randomized clinical trial	CKF patients on HD	NMES	Control Group	20 patients IG: 10 CG: 10	IG: 30/70 CG: 20/80	IG: 68.6 ± 4.4 CG: 69.9 ± 2.9	IG: 10 Hz; 20 s TON; 20 s TOFF; 60 min/session; 2 times/week for 12 weeks; applied on quadriceps and hamstrings muscles. CG: No physiotherapeutic intervention.	- Quadriceps muscle strength by hand-held dynamometer - Upper limb strength by hand grip dynamometer
Roxo et al., 2016	Randomized clinical trial	CKF patients on HD	NMES	Control Group	40 patients IG: 20 CG: 20	IG: 52.9/47.1 CG: 47.1/52.9	IG: 46.40 ± 15.4 CG: 54.7 ± 19.9	IG: 50 Hz; 350 us pulse width; 2 s TON; 10 s TOFF; 30 min/session; maximum intensity tolerated by the patient; 3 times/week for 8 weeks; applied on quadriceps muscle. CG: No physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by 1RM test

Continuation...

Author, Year	Design	Participants	Intervention	Comparators	Sample (n)	Gender F/M (%)	Age ± SD (years-old)	Protocol	Outcome measures of interest
Schardong et al., 2017	Randomized clinical trial	CKF patients on HD	NMES	Control Group	21 patients IG: 11 CG: 10	IG: 18.2/81.8 CG: 20/80	IG: 59.0 ± 20.0 CG: 64.5 ± 7.6	IG: 80 Hz; 400 us pulse width; 10 s TON; 50-20 s TOFF; 20-34 min/session; maximum intensity tolerated; 3 times/week for 8 weeks; applied on quadriceps muscle. CG: No physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength SST
Simó et al., 2015	Controlled clinical trial	CKF patients on HD	NMES	Control Group	38 patients IG: 23 CG: 15	IG: 41.8/58.2 CG: 49.3/50.7	IG: 67.9 ± 17.5 CG: 72.5 ± 10.1	IG: 2-90 Hz; 4 s – TON; 1.5-2 s rise and 1.5-0.75 s fall time; 30-45 min/session; maximum intensity tolerated by the patient; 12 weeks; applied on quadriceps muscle. CG: No physiotherapeutic intervention.	- Functional capacity by 6MWT - Quadriceps muscle strength by traction dynamometer (load cell) - Lower limb strength (STS10) - Upper limb strength by hand grip dynamometer
Suzuki et al., 2018	Randomized clinical trial	CKF patients on HD	NMES	Control Group	26 patients IG: 13 CG: 13	IG: 7.7/92.3 CG: 7.7/92.3	IG: 66.2 ± 12.8 CG: 65.1 ± 8.1	IG: 20 Hz; 250 us pulse width; 5 s TON; 2 s TOFF; 20 min/session; maximum intensity tolerated (range 30.6-104 mA); 3 times/week for 8 weeks; applied on gluteus and thigh and leg muscles. CG: No physiotherapeutic intervention.	- Quality of life by EQ-5D - Quadriceps muscle strength by hand-held dynamometer - Quality of life (by SF-8)

Legend: F: female; **M:** male; **CKF:** chronic kidney failure; **HD:** hemodialysis; **NMES:** neuromuscular electrical stimulaion; **IG:** intervention group; **CG**: control group; **CYG**: cycling group; **6MWT**: 6-minute walk test; **STS10:** sit to stand to sit 10 test; **SST:** sit-and-stand test; **SF-36**: Medical Outcomes Study 36 – Item Short –Form Health Survey; **KDQOL-SF™**: Kidney Disease and Quality-of-Life Short-Form; **1RM:** one-repetition maximum; **5D:** EuroQol-5 Dimension; **SF-8**: the short form-8 health survey

Table 2. Estimated treatment volume

Study	Intensity	Duty cycle (ON-OFF) (s)	Total treatment time (min)	Number of contractions
Dobsak et al., 2012	MI	20-20	3.600	5.400
Esteve et al., 2017	MI	1,75-1,00	1.134	1.701
Jiménez et al., 2013	MI	NR	NR	___
Martos et al., 2011	MI	3-6	NR	___
McGregor et al et al., 2018	MI	NR	1.800	2.700
Miura et al., 2018	MI	20-20	1.440	2.160
Roxo et al., 2016	MI	2-10	720	1.080
Schardong et al., 2017	MI	10 - 30	648	972
Simó et al., 2015	MI	4 - NR	1350	2.025
Suzuki et al., 2018	67,3 mA	5 - 2	480	720

Legend: MI: maximum intensity tolerated by the patient; NR: not reported.

Table 3. Risk of bias of randomized clinical trials included and evaluated through RoB 2.0

Author, Year	Randomization process	Deviations from intended intervention	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Dobsak et al., 2012						
Functional capacity,	Some concerns	Low	Low	High	Some concerns	High
Quadriceps muscle strength						
Quality of life						
McGregor et al., 2018						
Quadriceps muscle strength	Some concerns	Low	Low	Low	Low	Some concerns
Miura et al., 2018						
Quadriceps muscle strength	Some concerns	Low	Low	Low	Some concerns	Some concerns
Upper limb strength						

Continuation...

Table 3. Risk of bias of randomized clinical trials included and evaluated through RoB 2.0

Author, Year	Randomization process	Deviations from intended intervention	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Roxo et al., 2016						
Functional capacity	Low	Low	Low	High	Some concerns	High
Quadriceps muscle strength						
Schardong et al., 2017						
Functional capacity	Low	Low	Low	High	Low	High
Quadriceps muscle strength						
Lower limb strength						
Suzuki et al., 2018						
Quadriceps muscle strength	Some concerns	Low	Low	Low	Some concerns	Some concerns
Quality of life						

Table 4. Risk of bias of non-randomized clinical trials included and evaluated through ROBINS-I

Study and Outcomes	Confounding	Selection of participants	Measurement of intervention	To departure from intended intervention	Missing date	Measurement of outcomes	Selection of reported results	Overall
Esteve et al., 2017 - *Functional capacity* - *Quadriceps muscle strength* - *Lower limb strength* - *Upper limb strength*	Serious	Serious	Low	Low	Low	No information	No information	Serious
Jiménez et al., 2013 - *Functional capacity* - *Muscle strength*	Critical	Serious	Serious	Low	Low	No information	No information	Critical
Martos et al., 2011 - *Functional capacity* - *Muscle strength* - *Quality of life*	Critical	Serious	Low	Low	Low	No information	No information	Critical
Simó et al., 2015 - *Functional capacity* - *Quadriceps muscle strength* - *Lower limb strength* - *Upper limb strength* - *Quality of life*	Moderate	Moderate	Low	Low	Moderate	No information	No information	Moderate

Table 5. Quality of evidence evaluated through GRADE system

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NMES**	**Control**	**Absolute (95% CI)**		
Functional capacity (assessed with: Six-minute walk test)											
5	Randomized trials	Serious [a]	Not serious	Not serious	Not serious	None	78	65	MD **30.11 higher** (15.57 higher to 44.65 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quadriceps muscle strength (assessed with: Dinamometry and one maximum repetition test)											
8	Randomized trials	Serious [a]	Not serious [b]	Not serious	Not serious [b]	None	118	103	SMD **1.46 SD higher** (0.86 higher to 2.07 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower limbs muscle strength (assessed with: Sit-and-stand test)											
2	Randomized trials	Serious [a]	Not serious	Not serious	Serious [c]	None	36	25	MD **-3.41 lower** (-11.96 lower to 5.14 higher)	⊕⊕◯◯ LOW	CRITICAL
Upper limbs muscle strength (assessed with: Dinamometry)											
3	Randomized trials	Serious [a]	Not serious [d]	Not serious	Serious [c]	None	46	35	MD **10.02 higher** (0.78 higher to 19.27 higher)	⊕⊕◯◯ LOW	IMPORTANT

Continuation...

Quality of life									
3	Randomized trials	Serious [e]	Not serious	Not serious	Serious [f]	None	The studies used different instruments to evaluate the quality of life making it impossible to perform a metanalysis. Dobsak et al. (2012) used the SF-36 questionnaire and verified positive effects on mental health but not on physical aspects. Simó et al. (2015) used the EuroQol-5D questionnaire and found a significant improvement in the usual activities performance and in general health evaluation. Suzuki et al. (2018) used the SF-8 questionnaire and did not observe change in quality of lifeafter NMES.	⊕⊕◯◯ LOW	IMPORTANT

Legend: CI: confidence interval; **MD:** mean difference; **SMD:** standardized mean difference. **a**.The majority of studies do not clearly describe the blinding of patients, therapists and assessors. Furthermore, two studies (Esteve et al., 2017 and Simó et al., 2015) were not randomized, only controlled. **b.** Performing sensitivity analysis to inconsistency is reduced to 8% and CIs overlap. When the article evaluating dynamic force (Roxo et al., 2016) is taken from the meta-analysis, there is no inconsistency and the imprecision becomes smaller. **c**. Confidence interval (CI) is large and small sample size. **d**. Although the heterogeneity is high ($I^2 = 97\%$), this is caused by a large IC that was penalized in the item "Imprecision". **e**.The studies do not clearly describe the blinding of patients, therapists and assessors. Furthermore, one study (Simó et al., 2015) were not randomized, only controlled. **f**. Small sample size.

Chart 1. Search strategy performed in MEDLINE (PubMed)

Patient (#1)
"Renal Insufficiency, Chronic" [MESH] OR "Chronic Renal Insufficiencies" OR "Renal Insufficiencies, Chronic" OR "Chronic Renal Insufficiency" OR "Kidney Insufficiency, Chronic" OR "Chronic Kidney Insufficiency" OR "Chronic Kidney Insufficiencies" OR "Kidney Insufficiencies, Chronic" OR "Chronic Kidney Diseases" OR "Chronic Kidney Disease" OR "Disease, Chronic Kidney" OR "Diseases, Chronic Kidne" OR "Kidney Disease, Chronic" OR "Kidney Diseases, Chronic" OR "Chronic Renal Diseases" OR "Chronic Renal Disease" OR "Disease, Chronic Renal" OR "Diseases, Chronic Renal" OR "Renal Disease, Chronic" OR "Renal Diseases, Chronic"
Patient (#2)
"Kidney Failure, Chronic" [MESH] OR "End-Stage Kidney Disease" OR "Disease, End-Stage Kidney" OR "End Stage Kidney Disease" OR "Kidney Disease, End-Stage" OR "Chronic Kidney Failure" OR "End-Stage Renal Disease" OR "Disease, End-Stage Renal" OR "End Stage Renal Disease" OR "Renal Disease, End-Stage" OR "Renal Disease, End Stage" OR "Renal Failure, End-Stage" OR "End-Stage Renal Failure" OR "Renal Failure, End Stage" OR "Renal Failure, Chronic" OR "Chronic Renal Failure" OR "ESRD"
Intervention (#3)
"Electric Stimulation" [MESH] or "Electric Stimulation" or "Electrical Stimulation" or "Electrical Stimulations" or "Stimulation, Electrical" or "Stimulations, Electrical" or "Stimulation, Electric" or "Electric Stimulations" or "Stimulations, Electric"
Intervention (#4)
"Electric Stimulation Therapy" [MESH] or "Electric Stimulation Therapy" or "Therapeutic Electrical Stimulation" or "Electrical Stimulation, Therapeutic" or "Stimulation, Therapeutic Electrical" or "Therapeutic Electric Stimulation" or "Electric Stimulation, Therapeutic" or "Stimulation, Therapeutic Electric" or "Electrical Stimulation Therapy" or "Stimulation Therapy, Electrical" or "Therapy, Electrical Stimulation" or "Therapy, Electric Stimulation" or "Stimulation Therapy, Electric" or "Electrotherapy" or "Interferential Current Electrotherapy" or "Electrotherapy, Interferential Current" or "microcurrente stimulation" or "high voltage"
Intervention (#5)
"Functional Electrical Stimulation"
Intervention (#6)
"Neuromuscular Electrical Stimulation"
Search Strategy: #1 OR #2 AND #3 OR #4 OR #5 OR #6

Chart 2. Search strategy performed in COCHRANE (Central)

Patient (#1)
"Renal Insufficiency, Chronic" [MESH]
Patient (#2)
"Kidney Failure, Chronic" [MESH]

Intervention (#3)
"Electric Stimulation" [MESH]
Intervention (#4)
"Electric Stimulation Therapy" [MESH]
Search Strategy: #1 OR #2 AND #3 OR #4

Chart 3. Search strategy performed in EMBASE

Patient (#1)
"Chronic Kidney Failure"
Patient (#2)
"Electrostimulation"
Intervention (#3)
*"*Functional Electrical Stimulation"
Intervention (#4)
"Neuromuscular Electrical Stimulation"
Intervention (#5)
"Electrotherapy"
Search Strategy: #1 AND #2 OR #3 OR #4 OR #5

Chart 4. Search strategy performed in PEDro

Patient (#1)
"Chronic Kidney Disease"
Intervention (#2)
"Neuromuscular Electrical Stimulation"
Search Strategy: #1 AND #2

Chart 5. Search strategy performed in Scientific Electronic Library Online

Patient (#1)
"Kidney Failure, Chronic"
Intervention (#2)
*"*Functional Electrical Stimulation"
Intervention (#3)
"Neuromuscular Electrical Stimulation"
Search Strategy: #1 AND #2 OR #3

5 ARTIGO II

Effects of Photobiomodulation on Functional Capacity, Muscle Strength and Architecture, Perception of Pain and Fatigue, and Quality of Life of Patients with Chronic Kidney Failure: Randomized Clinical Trial

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ABSTRACT

Photobiomodulation (PBM) has been used in different populations as a strategy to attenuate muscle fatigue and improve exercise performance, however, there is no evidence regarding the effect of long-time use of this therapy (chronic effect) on patients with chronic kidney failure (CKF). The objective of this study was to evaluate the effects of PBM on functional capacity, muscle strength and architecture, pain perception, fatigue and quality of life of chronic kidney patients on hemodialysis (HD). For this, a randomized clinical trial (RCT) was conducted in which the intervention group (IG, n = 14) received along eight weeks 24 infrared laser applications (810 nm, 5 diodes x 200 mW, 30 J/application site, 8 application sites/leg) in the quadriceps (6 application sites/180 J) and gastrocnemius (2 application sites/60 J) muscles, during HD. The control group (CG, n = 14) received only routine nursing care. Functional capacity was assessed by the six-minute walk test (6MWT) and lower limb muscle strength by the sit-and-stand test (SST10). The quadriceps muscle architecture was evaluated by ultrasonography, the perception of pain by numerical scale, and fatigue by the modified Borg effort subjective perception scale. Quality of life was measured by the EQ-5D and KDQOL-SF^{TM} questionnaires. There was an increase in the distance covered on the 6MWT for the IG when compared to the CG [50.7 m (CI95% 15.63; 85.72), p=0.01]. The time to performe the SST10 decreased for the IG when compared to the CG [-7.4 s (CI95% -4.54; -10.37), p=0.00]. No significant differences were observed between the groups for muscle architecture, pain perception, fatigue and quality of life outcomes. In conclusion, PBM therapy when applied for eight weeks in the lower limb of chronic kidney patients on HD improves functional capacity and muscle strength without causing adverse effects.

Keywords: Renal Insufficiency, Chronic; Renal Dialysis; Low-Level Light Therapy.

INTRODUCTION

Chronic kidney failure (CKF) causes systemic manifestations in the individual that also affect muscular homeostasis (1). The muscle fibers of patients with CKF present morphological and functional alterations possibly due to chronic uremia and to the state of metabolic acidosis. These changes consist in reducing the number of capillaries and contractile proteins, in the increase of cellular oxidation and in enzymatic modifications (2).

Muscle atrophy, particularly of type II fibers (2), is highly prevalent in patients undergoing hemodialysis (HD) (3) and associated with other comorbidities such as cardiovascular diseases (4), bone mineral disease (5), anemia (6) and peripheral neuropathy (7) are responsible for the reduction of physical capacity (8, 9) and functional independence (10), as well as for the increase in mortality rates in this population (11). Moreover, muscle atrophy specifically implies a reduction of peripheral muscle strength, increased fatigue and reduced functional capacity, leading to a sedentary lifestyle and worse quality of life (12).

Photobiomodulation (PBM) therapy, through low level laser (LLL) and light emitting diodes (LEDs), has demonstrated largely positive effects on the improvement of muscle performance and on the delay in fatigue time, in healthy individuals and athletes (13, 14). Mechanisms that lead to improved muscle performance due to the use of LLL and LEDs are not fully understood, but are presumed to be due to increased cytochrome c oxidase enzyme activity (15), local blood flow (16, 17), minimizing oxidative stress (18) and accelerated lactate removal (19). Still, studies in patients with chronic obstructive pulmonary disease (20) and heart failure (21) have also demonstrated benefits on quadriceps muscle strength and perceived fatigue after a single PBM session.

A recent randomized crossover trial (22), demonstrated for the first time the acute effect of PBM on palmar grip strength in chronic kidney patients during HD. The findings suggest that infrared LLL (850 nm) at doses of 60 J (3 sites of application, 20J/site) and 90 J (3 sites of application, 30 J/site) generates a better therapeutic response to this outcome, increasing muscle strength. However, to the best of our knowledge, to date, there are no studies on the effects of this long-term therapy for the lower limbs of patients with CKF on HD on physical and functional outcomes. Thus, the objective of this study was to

evaluate the effects of PBM on the functional capacity, strength and muscle architecture of the lower limbs, perception of pain and fatigue, and quality of life of chronic kidney patients on HD.

PATIENTS AND METHODS

Design and ethical aspects

This study is a randomized clinical trial (RCT), conducted in patients with CKF, and submitted to PBM therapy through LLL. Functional capacity was considered the primary endpoint and lower limb muscle strength, quadriceps muscle architecture, pain and fatigue perception, and quality of life were considered secondary endpoints. The project was reviewed and approved by the Human Research Ethics Committees of the Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) hospital and of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFSCPA) (CAAE: 65845317.1.0000.5335; report number: 2.030.610) and thus implemented in accordance with the ethical standards of the Declaration of *Helsinki*, revised in 2013 in Brazil. Additionally, the project was registered in the ClinicalTrials.gov system (NCT03250715 identifier) and informed consent was obtained from all patients prior to any procedure.

Eligibility criteria

Patients with CKF on HD for a period equal to or greater than three months, of both sexes, aged between 18 and 80 years old, adequate urea clearance (URR≥65%) and weekly dialysis frequency of three times/week were included in the study. Exclusion criteria were: cognitive dysfunction that prevented performing the evaluations, as well as inability to understand the informed consent form; epidermal lesions at the site the PBM application; patients with active carcinoma, stroke sequelae; recent acute myocardial infarction (two months); uncontrolled hypertension (SBP>230 mmHg and DBP>120 mmHg); IV grade heart failure according to the *New York Heart Association* or decompensated; unstable angina; deep venous thrombosis in the lower limbs; incapacitating osteoarticular or musculoskeletal disease; uncontrolled diabetes (glycemia>300mg/dL); febrile state and/or infectious disease and smokers.

Procedures

Initially, all the patients from the HD outpatient of Santa Clara hospital at ISCMPA were invited verbally to participate in the study. When there was an interest, electronic records were consulted to check

the eligibility criteria. If the patient was included, an interview was conducted prior to physical and functional assessments to collect identification data, risk factors for chronic kidney disease (CKD), demographic, anthropometric, biochemical data, primary disease and medications used. All the procedures were performed between October 2017 and September 2018 at the ISCMPA dialysis unit.

Randomization

Eligible patients were randomized (1:1 allocation ratio) into two groups: intervention group (IG) or control group (CG). Randomization occurred through the website www.random.org. The sequence of numbers was generated by a researcher "blinded" to the study and it was kept confidential until the beginning of the intervention to guarantee the concealment of the allocation.

Evaluations

All patients were evaluated before the intervention or at follow-up and after eight weeks. They were instructed not to perform exercise prior to the evaluations. The evaluations occurred prior to the second weekly dialysis session, always by the same evaluator.

Functional capacity evaluation

The six-minute walking test (6MWT) was used to evaluate functional capacity following the recommendations of the *American Thoracic* Society (23). The patient was instructed to walk as far as possible, for six minutes, in a 30-meter corridor, and the distance covered was recorded in meters. Every minute the patient was verbally encouraged by standard phrases. Vital signs were checked at the beginning and end of the test as a safety measure.

Lower limbs muscle strength evaluation

The muscle strength of the lower limbs was evaluated by the sit-and-stand test (SST10). The SST10 is an indirect and functional measure to quantify the muscle strength (24, 25) and it was performed in a chair without arms, 44.5 cm high and 38 cm deep (26). The patient began the test seated, arms crossed in front of the chest and back resting on the chair. The patient was instructed to stand up and return to the seated position as soon as possible in order to perform 10 complete and consecutive repetitions, being verbally encouraged (27). The time to perform the 10 repetitions was recorded by the evaluator.

Muscle architecture evaluation

Muscle architecture was assessed by the acquisition of ultrasound images of the vastus lateralis (VL), rectus femoris (RF) and vastus medial (VM) muscles using a high resolution ultrasound device (Vivid-i, GE, Stamford, CT, USA) and a linear array ultrasonic probe (38 mm, 3–12 MHz). The thickness of quadriceps (VL, RF and VM) and the echogenicity of RF muscle of both legs were specifically evaluated.

The midpoint between the greater trochanter and the lateral condyle of the femur was used as a reference point to evaluate the VL and RF, while measurements of the VM were performed at 25–30% of this distance, according to the characteristics of the patients (28). Three images were obtained with the ultrasound transducer longitudinally positioned on the muscle fibers of each of the knee extensor muscles to evaluate the thickness (29) and three images were obtained with the transducer positioned transversally on the RF to evaluate echogenicity (30). In addition, a bubble level was attached to the ultrasound probe to ensure a minimum inclination during data collection of the echogenicity (30).

To standardize the measurement sites the anatomical points were marked on plastic sheets and the measurements were performed always by the same examiner. All images were subsequently analyzed using the ImageJ software (National Institutes of Health, Bethesda, MD, USA). The distance between the deep and the superficial aponeuroses was measured at five different points in each longitudinal ultrasound image to muscle thickness (28). To measure echogenicity a square with a 0,5 cm^2 area was positioned at the mid-point of rectus femoris for the calculation (gray scale histogram 0 = full black picture; 255 = full white Picture (30). The mean value of each muscle architecture variable obtained from the three recorded ultrasound images was considered for subsequent statistical analysis (28).

Perception of pain and fatigue evaluation

The perception of muscle pain in the lower limbs was evaluated through the visual analog scale. The patient was asked about the intensity of their pain within a range of 0 to 10, where 0 indicates no pain and 10 maximum pain (31). To evaluate the perception of fatigue in lower limbs the modified Borg effort subjective perception scale was used, where 0 indicates no effort or fatigue and 10 indicates maximum effort (32, 33). Both scales were applied before and immediately after the 6MWT.

Quality of life evaluation

Quality of life was measured using two questionnaires.

The *EuroQol-5D health questionnaire* (EQ-5D) is a generic instrument for measuring health-related quality of life. It evaluates five dimensions: mobility, personal care, habitual activities, pain/discomfort and anxiety/depression and it allows to generate a general index of the value of an individual's health status, where 1 indicates the best state of health (perfect health) and 0 the worst state of health (death) (34, 35).

The *Kidney Disease and Quality-of-Life Short-Form questionnaire* (KDQOL-SF^{TM}) includes specific items about CKD in addition to the SF-36 questionnaire. The specific part about kidney disease includes 43 items divided into 11 dimensions: symptoms/problems; effects of kidney disease on daily life; overload imposed by kidney disease; work condition; cognitive function; quality of social interactions; sexual function and sleep; it also includes three additional scales: social support, dialysis staff encouragement and patient satisfaction. The SF-36 consists of 36 items, divided into eight dimensions: physical functioning, limitations caused by physical health problems, limitations caused by emotional health problems, social functioning, mental health, pain, vitality, general health perceptions. Each category generates a score between 0 and 100, with higher scores corresponding to a better quality of life status (36). The patients were instructed to complete the questionnaires during the HD session and the physiotherapist only assisted when there were doubts.

Intervention

PBM therapy by LLL occurred between the 2nd and 3rd hour of the HD session (37), three times/week, for eight weeks, totaling 24 aplications.

The patients were positioned in dorsal decubitus, with the knees at 60º on a foam wedge (38) on the dialysis armchair. Prior to the LLL application, the Flag and Homans tests were performed. The PBM therapy was applied through properly calibrated probe cluster laser, containing five diodes (Thor® Photomedicine, DD2, London/UK). Six points were demarcated in the quadriceps (two points in the distal region of the VM muscle, two points in the center of the RF muscle and two points in the distal region of the VL muscle) and two points in the belly of the gastrocnemius muscle, bilaterally (20, 39), through palpation. After the first session, the laser application sites were copied on plastic sheets, considering the patella as a reference, in order to ensure that the other applications were performed in the same places. The treatment was performed with the probe fixed in contact with the skin, at an angle of 90º and the parameters

adopted were: wavelength 810 nm; output power 1000 mW (200 mW per diode); total area of the cluster 8,5 cm^2; beam area 0.029 cm^2; power density 34.5 W/cm^2 (6.9 W/cm^2 per diode); dose 30 J/application site (6 J/diode); energy density 1.034,5 J/cm^2 (206.9 J/cm^2 per diode); time 30 seconds; continuous emission mode; total dose 240 J/leg (180 J for quadriceps; 60 J for gastrocnemius) and 480 J/session (14). The patients and the physiotherapist used protection goggles for radiation during the applications and vital signs were monitored as a safety measure.

The CG was only evaluated at the beginning and at the end of the follow-up, receiving no type of physical therapy intervention, only routine care from the nursing team.

Statistical analysis

The sample calculation was performed through the website www.lee.dante.br and it was based on an RCT conducted with patients with CKF on HD (37). To calculate the difference of the means and standard deviations between the groups, the distance walked in the 6MWT was used and an alpha error of 5% and power of 80% was adopted, resulting in 14 patients per group.

Statistical analysis was performed using SPSS software version 23. Data with symmetrical distribution are presented as means and standard deviation and data with asymmetric distribution as median and interquartile range. To verify the normality of the data the *Shapiro-Wilk* test was used. The baseline characteristics of the patients were compared by *Student's* t-test for independent samples or by the *Mann-Whitney* test according to the normality of the data. Categorical variables were compared by the chi-square test. To evaluate the post-intervention effect within the same group, we used the paired *Student's* t test or *Wilcoxon's* test. To verify the effect of the therapy between the groups the *Student's* t test for independent samples or the *Mann-Whitney* test were used and the comparisons were made using the values of the difference between the pre and post intervention moments. The estimate of the effect of the intervention on the outcomes evaluated was analyzed using the *Cohen* test, where <0.2 represents a trivial effect, > 0.2 a small effect, > 0.5 a moderate effect and above 0.8 a large magnitude of effect (40). The significance level adopted was 5% ($p < 0.05$) and the analysis was performed by protocol.

RESULTS

Thirty-six patients with CKF on HD were evaluated for eligibility and possible admission into the study. Twenty-eight met the inclusion criteria and finalized the protocol. Admission of the patients and group composition can be seen in detail in figure 1.

Demographic, anthropometric, clinical and biochemical data, as well as primary disease, and risk factors for CKD in both groups at the initial moment of the study are shown in table 1. The control and intervention groups did not present significant differences for these variables and for the functional capacity, muscle strength and architecture, as well as for perception of pain and fatigue, prior to the intervention. Quality of life, with the exception of the dialysis team stimulation domain (p=0.02) of the KDQOL-SF^{TM} questionnaire, also did not differ between groups at baseline.

Functional capacity increased for the treated group after eight weeks of FBM therapy (p=0.00), but the same was not observed for GC (p=0.67). When comparing the two groups, there was a significant difference of 50.7 m (CI95% 15.63; 85.72; p=0.01) in the distance covered in the 6MWT favorable to the IG (table 2, figure 2).

In relation to lower limb muscle strength, IG showed a significant reduction in the time to perform the 10 repetitions of the SST after therapy (p=0.00). CG did not show any change in this outcome over eight weeks (p=0.61). Still, there was a significant difference and favorable to the IG [-7.4 s (CI95% -4.54; -10.37), p=0.00] when the two groups were compared (table 2, figure 3).

Regarding the muscle architecture of the femoral quadriceps, the CG presented a reduction in the thickness of the VM muscle (p=0.03) over eight weeks. There were no significant changes for the other muscles in relation to thickness (*CG* – Right VL: p=0.06; Left VL: p=0.97; Right RF: p=0.05; Left RF: p=0.93; Left VM: p=0.64; *IG* – Right VL: p=0.98; Left VL: p=0.49; Right RF: p=0.36; Left RF: p=0.67; Right VM: p=0.26; Left VM: p=0.29) and neither for the echogenicity of the RF muscle (*CG* – Right RF: p= 0.29; Left RF: p=0.40; *IG* – Right RF: p=0.65; Left RF: p=0.62) in none of the groups over time. There was also no difference when CG and IG were compared for the thickness measurements of the right VL (p=0.17), left VL (p=0.68), right RF (p=0.35), left RF (p=0.77), right VM (p=0.68), left VM (p=0.89) and echogenicity of the right RF (p=0.65) and left RF (p=0.83) after treatment (table 2).

Regarding the perception of pain in the lower limb after the 6MWT, there was a tendency to reduce the pain numerical score for the treated group, but this was not significant (p=0.22). On the other hand, CG presented a significant increase in pain levels (p=0.03) over time. When compared, the groups did not present a different behavior for this outcome (p=0.09) (table 2).

The perception of fatigue in the lower limb after the 6MWT did not change over time for the CG (p=0.15) and for the IG (p =0.10) even when one group is compared to the other (p=0.05) (table 2).

There was improvement in quality of life when evaluated by the EQ-5D questionnaire for the group that received PBM therapy after 8 weeks of treatment (p=0.01). The same did not occur with CG (p=0.49). There were also no significant differences between IG and CG (p=0.08) at the end of the protocol (table 3).

When the quality of life was evaluated by the KDQOL-SF^{TM} questionnaire an increase was observed for emotional wellness (IG: p=0.03; CG: p=0.09), social functioning (IG: p=0.01; CG: p=0.24) and vitality (energy/fatigue) (IG: p=0.00; CG: p=0.45) domains only for the IG over time. For the pain domain, both groups improved after eight weeks of follow-up (IG: p=0.00; CG: p=0.01). There were no significant differences between groups for any of the dimensions of the KDQOL-SF^{TM} (table 3).

Regarding the safety of this therapy, no changes were observed in patients' vital signs and adverse effects during laser radiation applications, as well as in the interval between them. About the adherence of the patients to the protocol, this was considered satisfactory, since there were no losses due to intolerance to PBM therapy.

DISCUSSION

This study demonstrated for the first time that PBM therapy when applied as monotherapy for eight weeks in the quadriceps and gastrocnemius muscles increases functional capacity and lower limb muscle strength. Furthermore, PBM seems to modulate the perception of pain, to improve specific aspects of the quality of life of patients with CKF on HD and have no effects on muscle architecture.

Our findings showed that PBM with LLL increased the distance covered by the 6MWT in 50.7 m when compared to the CG, ensuring a large effect size (d=1.12) and an improvement in functional capacity. On the other hand, Stein et al. (41) applied LLL on the quadriceps muscle of patients with heart disease, with wavelength (850 nm), number of application sites (8 sites) and dose (30 J/site) very similar to those

defined in our study and the authors did not find significant results for this outcome. Although populations (chronic kidney and cardiac disease patients) have similar physical and functional limitations, the absence of positive effects in this study may be related to the volume of application (a single application *vs* 24 applications). Also, unlike the present study, we chose to radiate the gastrocnemius muscle beyond the quadriceps, since it also plays an important role in gait (14), which may has contributed to the increase in distance covered in the 6MWT.

Corroborating our findings, Melo et al. (42) used LLL (810 nm, 200 mW, 4-6 J/site, 6 application sites) in elderly women with osteoarthritis of the knee and, even using a lower dose, they also obtained an increase in the distance covered in the 6MWT after eight weeks of intervention (2 times/week, 16 applications).

Functional capacity was considered the primary endpoint of this study, since it is an independent predictor of mortality. In chronic kidney patients, a distance equivalent to 100 meters in the 6MWT implies a 5.3% increase in the survival rate (43). In this sense, it can be said that our finding, besides being significant, also has clinical relevance.

The SST10 which consists of an indirect and functional measure of muscle strength, and is widely used in clinical practice (24, 25, 44), demonstrated that the PBM has positive effects on this outcome, since the IG presented a reduction of 7.4 seconds to perform the test when compared to the CG, with a large effect size (d=1.99). This result is relevant, since the impairment of the physical performance of the lower limbs in functional tests is strongly associated with increased mortality in chronic kidney patients (45).

There are studies that demonstrate the increase of muscle strength after a session (acute effect) of PBM in patients with CKF (22) and also when this therapy was used for a long period (chronic effect) but associated with exercise in other populations (46). This agrees with our results, however, this was the first study to demonstrate the positive effect of PBM on lower limb muscle strength when radiation is applied for a long time and as monotherapy in chronic kidney patients.

As expected, muscle architecture did not show changes after PBM therapy, except for the reduction of right VM thickness to CG over time, however, this can be attributed to chance or to the sensitivity of the ultrasound technique. According to the literature and to the best of our knowledge, PBM induces changes

in the enzymatic metabolism of cellular mitochondria (oxidase c cytochrome via) but no structural alterations (15, 47). Thus, a possible effect on muscle architecture could occur indirectly, since by improving the functional capacity of this patient he could become more active. Still, neuromuscular electric stimulation (NMES) as demonstrated by our group (48) or physical exercise may be more specific strategies to avoid muscle atrophy which is an inherent process of CKD. In addition, the absence of findings regarding echogenicity is probably related to the volumetric variation that this patient weekly suffers as result of the HD sessions.

Regarding the perception of pain in the lower limbs, there was a tendency to reduce it in the group submitted to PBM, but not significantly. On the other hand, the CG presented an increase in the pain threshold in the lower limb during the follow-up with a large effect size (d=1,59). Although there was no significant difference between the groups after eight weeks of treatment, the findings suggest a likely protective effect of LLL for pain of the lower limb.

Melo et al., (42) performed 16 applications of LLL (810 nm; 4-6 J/point) in the knees of elderly women with osteoarthritis and observed a reduction in the visual analogic scale (VAS) score after the 6MWT. On the other hand, Vanin et al. (49) in a study with athletes performed only one therapeutic laser application on the quadriceps muscle, prior to a resistance exercise protocol, and they did not obtain a reduction of pain levels. It is reiterated that the wavelength (810 nm) and the dose (30 J/site) used by Vanin et al. (49) are the same as those adopted in our study, however, the authors did not use only the VAS but also the algometer to measure this outcome. Based on this evidence, it is believed that for the perception of pain, the parameters adopted were not the only determinants. Besides the population evaluated, the application volume and measurement instrument (numerical scales) may influence the results, since scales are subjective and pain is a relative and individual experience.

The perception of fatigue was also evaluated in our study using numerical scale and significant alterations were not identified after PBM treatment for this outcome. However, the effect size was considered large when the two groups were compared (d=0.95), indicating a tendency to reduce the perception of fatigue in the IG and increase in the CG.

Corroborating our findings, Miranda et al. (50), in a study evaluating the effect of LEDs (660 and 850 nm; 41.7 J/application site) on the quadriceps muscle function of COPD patients, did not observe any change in the perception of fatigue after isometric exercise, when it was evaluated using of modified Borg's scale of effort subjective perception. On the other hand, the endurance time assessed through a loading cell increased after PBM therapy compared to the sham group. Therefore, once again, the subjectivity of the evaluation instrument adopted in our study can influence the results.

Although modified Borg's scale of effort subjective perception is not a direct measure of fatigue, we can not refute that the findings regarding this outcome may also be related to the parameters adopted. In a later study, Miranda et al. (20), used the same scale to measure fatigue in patients with COPD and obtained significant results for this outcome. However, two light sources (LLL and LEDs) with different wavelengths (LLL: 905 nm, LEDs: 875 and 640 nm) were used simultaneously, which could be a hypothesis for the improvement of fatigue.

Regarding quality of life, when the patients were evaluated by EQ-5D, IG showed a significant improvement in this outcome after eight weeks of PBM with a large effect size (d=0.84). There was no difference between groups for quality of life at the end of the follow-up, however, the effect size was considered moderate (d=0.69), indicating a tendency for improvement favorable to the treated group.

In addition, improvement in some aspects of quality of life was observed over time when patients were evaluated by KDQOL-SF^{TM}. There was a significant increase with a moderate effect size for emotional wellness (d=0.56) and social functioning (d=0.79) dimensions to IG and this can be attributed to the fact that the patient is engaged in a rehabilitation program and feels assisted by the health staff. Furthermore, there was an increase with a large effect size for the pain (d=1.03) and vitality (energy/fatigue) (d=1.18) dimensions. These variables are directly related to the biological/therapeutic effects of PBM (analgesic and anti-inflammatory effect) (47) and therefore the findings are justified. Overall, the absence of significant differences between groups for quality of life can also be related to the intervention time (only eight weeks) and to the sample size, which was calculated for the primary outcome of this RCT (functional capacity). Finally, other studies (51, 52) used different techniques for the rehabilitation of this population and they

found results similar to ours for quality of life. In this sense, this is a complex outcome and it probably involves more than one approach for that occur relevant changes.

Anyway, the findings in our study are positive and promising, but further studies are needed, since the best therapeutic window (dose-response) for the treatment of the lower limb of chronic kidney patients is not yet known. However, it is reiterated that the dose used in our study is in accordance with the recommendations proposed by Leal-Junior et al. (53) for large muscle groups when the goal is to improve performance during physical exercise.

Finally, to date, it is believed that the effects of PBM on improving physical performance are due to the increase in the enzymatic activity of oxidase c cytochrome (15), vasodilatation (16), improvement of collateral circulation, increase of the level of oxygen in the tissue and therefore of adenosine triphosphate (ATP) in peripheral muscle mitochondria (15, 17, 54).

Among the limitations of this RCT we can mention the absence of a placebo comparator and follow up to verify the duration of the treatment effect. However, it should be mentioned that biochemical outcomes as mediators of inflammation, oxidative stress and DNA damage are being analyzed by our group as proposed in the registration protocol (ClinicalTrials.gov: NCT03250715) and will be published in future. These, in turn, can elucidate the findings found in this study, minimizing these fragilities.

CONCLUSION

PBM therapy when performed as monotherapy for eight weeks improves the functional capacity and lower limb muscle strength of chronic kidney patients on HD. In addition, it seems to influence the perception of pain and specific aspects of quality of life.

No adverse effects were observed for the use of PBM by LLL during the protocol, therefore, it can be considered a safe and prophylactic strategy for the impairment of physical capacity, as well as an adjuvant therapy for a conventional rehabilitation programs.

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TABLES AND FIGURES

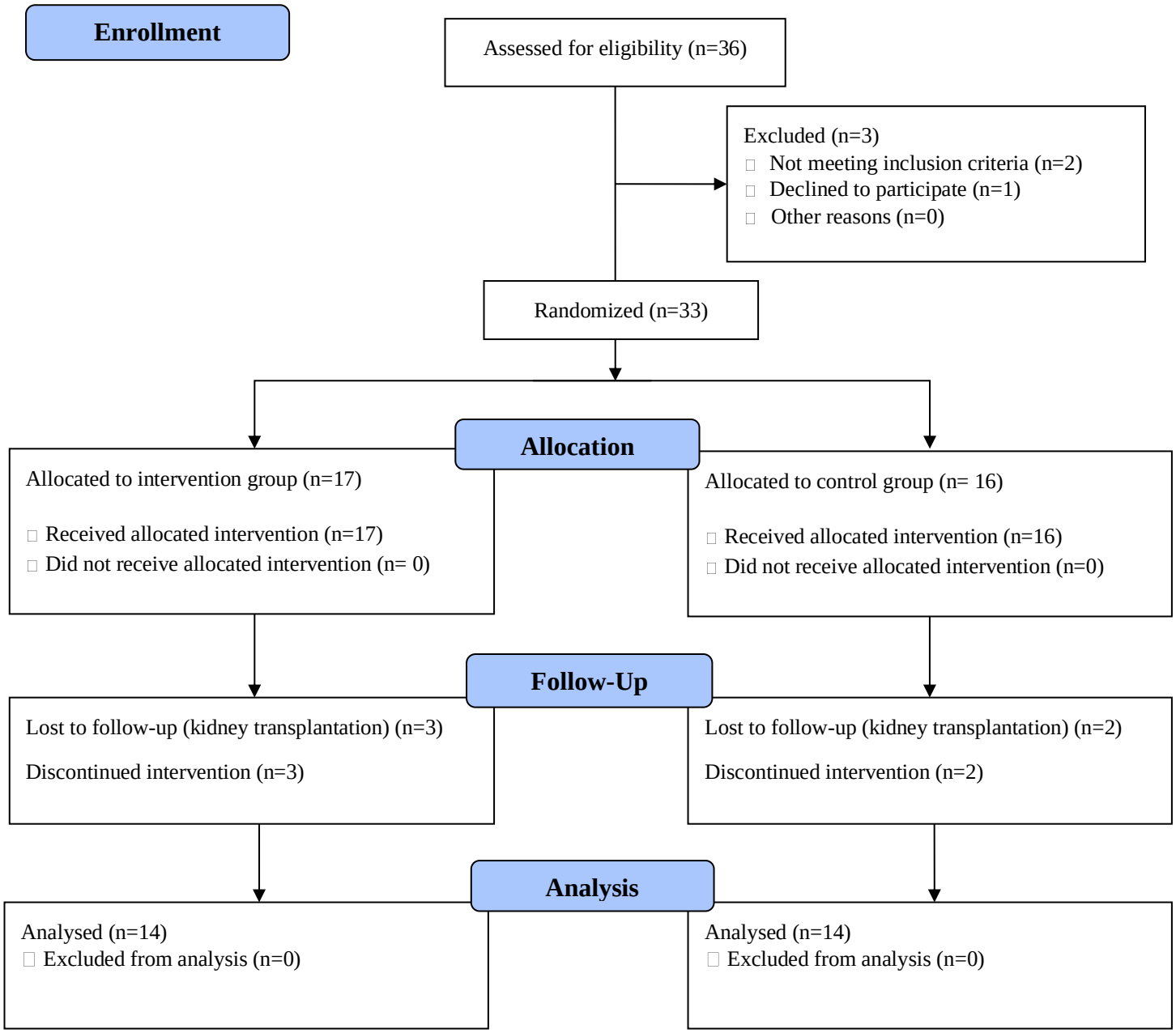

FIGURE 1. *Flowchart of patients' admission and group composition.*

TABLE 1. *Characteristics of patients in the study admission*

	Control group (n=14)	Intervention group (n=14)
Sex (F/M)	7/7	5/9
Age (years)	58.1 ± 16.9	53.0 ± 17
Dry weight (kg)	67.6 ± 12.9	67.1 ± 15
Wet weight (kg)	70.5 ± 13.7	69.3 ± 15.5
BMI (kg/m^2)	25.5 ± 5.1	24.6 ± 4.4
HD time (months)	32 (11.8 – 70.3)	48 (8.8 – 105)
URR (%)	72.5 (69.2 – 76.6)	74.6 (65 – 77.1)
Primary disease		
- Glomerulonephritis	2	0
- Hypertension	4	2
- Diabetes mellitus	1	2
- FSG	0	2
- Polycystic kidney disease	0	1
- Nephrolithiasis	2	2
- Other	4	1
- Unknown	1	4
Risk factors		
- Ex-smoker	1	1
- Hypertension	13	13
- Sedentary lifestyle	12	12
- Diabetes mellitus	4	2
- Heart disease	1	6
- FH heart disease	0	3
- Peripheral vascular disease	1	1
Serum biochemistry		
- Predialysis urea (mg/dL)	144.3 ± 34.5	171.1 ± 45.6
- Postdialysis urea (mg/dL)	40.5 ± 13.4	45.4 ± 23.1
- Creatinine (mg/dL)	9.3 ± 2.6	10.4 ± 3.3
- Albumin (mg/dL)	4.0 ± 0.3	3.9 ± 0.3
- Hemoglobin (g/dL)	11.2 ± 1.7	10.7 ± 1.4
- Hematocrit (%)	34.3 ± 5.8	33.5 ± 4.9

Legend: F: female; M: male; BMI: body mass index; HD: hemodialysis; URR: urea reduction rate; FSG: focal segmental glomerulosclerosis; FH: family history. Data are expressed as mean ± standard deviation; median and interquartile range (P25-P75) or frequency.

TABLE 2. *Values for functional capacity, muscle strength, pain perception, fatigue and muscle architecture before and after PBM*

	Control group (n=14)			Intervention group (n=14)			
	Pre	Post	d1	Pre	Post	d1	d2
Functional capacity							
- 6MWT (m)	440.3 ± 76.2	446.1 ± 79.3	0.12	428.5 ± 104.9	485 ± 106.9 #	1.41	1.12
Muscle strength							
- SST10 (s)	24.8 ± 6.2	24.3 ± 7.2	0.14	27 ± 7.7	19.1 ± 5.0 #	1.88	1.99
Muscle architecture							
- Thickness right VL (cm)	1.38 ± 0.25	1.28 ± 0.30	0.54	1.45 ± 0.35	1.45 ± 0.25	0.01	0.54
- Thickness left VL (cm)	1.28 ± 0.35	1.27 ± 0.29	0.01	1.47 ± 0.34	1.49 ± 0.34	0.19	0.01
- Thickness right RF (cm)	0.86 ± 0.18	0.76 ± 0.25	0.56	0.92 ± 0.33	0.88 ± 0.29	0.26	0.36
- Thickness left RF (cm)	0.78 ± 0.22	0.77 ± 0.27	0.02	0.80 ± 0.28	0.78 ± 0.27	0.12	0.11
- Thickness right VM (cm)	1.04 ± 0.33	0.94 ± 0.28 *	0.63	1.12 ± 0.45	1.05 ± 0.31	0.32	0.16
- Thickness left VM (cm)	1.09 ± 0.27	1.07 ± 0.33	0.13	1.04 ± 0.31	1.00 ± 0.32	0.29	0.05
- Echogenicity right RF (a.u)	63.71 ± 22.11	59.70 ± 17.81	0.29	65.92 ± 19	64.29 ± 22.44	0.12	0.18
- Echogenicity left RF (a.u)	65.72 ± 21.56	62.09 ± 22.11	0.23	66.04 ± 24.67	63.77 ± 23.97	0.14	0.08
Pain	0 (0 – 2.5)	3 (0.75 – 4.25) *	1.59	3 (0 – 5)	0 (0 – 5.25)	0.80	0.47
Fatigue	2.5 (0 – 3.25)	3 (1 - 4)	0.19	3 (2 - 5)	1.5 (0 – 4.25)	0.58	0.95

Legend: 6MWT: six-minute walking test; SST10: sit-and-stand test of 10 repetitions; VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis. Data are expressed as mean ± standard deviation or median and interquartile range (P25-P75). *: within group difference; #: within and between groups difference; d1: effect size for within group difference; d2: effect size for difference between groups. Significance level $p<0.05$.

TABLE 3. *Values for quality of life before and after intervention with PBM*

	Control group (n=14)			Intervention group (n=14)			
	Pre	Post	d1	Pre	Post	d1	d2
EQ-5D index	0.636 ± 0.15	0.658 ± 0.12	0.19	0.604 ± 0.17	0.713 ± 0.16 *	0.84	0.69
KDQOL-SF™							
- Symptoms /Problems	71.9 (62-81.3)	71.9 (64.6-79.7)	0.11	75.9 (59.9-89.1)	81 (72.4-90.1)	0.33	0.21
- Effects of CKD on daily life	75 (81.3-79.7)	70.3 (61.7-82)	0.04	67 (53.1-85.2)	71 (58.6-82)	0.19	0.14
- Burden imposed by the CKD	37.5 (18.8-45-3)	50 (29.7-64.1)	0.52	46.4 (25-70.3)	50.4 (29.7-71.9)	0.15	0.29
- Work status	0 (0-50)	0 (0-50)	0.10	32.1 (0-50)	35.7 (0-62.5)	0.27	0.00
- Cognitive function	86.7 (71.7-100)	90 (80-100)	0.08	73.8 (58.3-100)	81.4 (71.7-88.3)	0.54	0.30
- Quality of social interactions	80 (63.3-88.3)	80 (70-95)	0.21	71.4 (53.3-88.3)	79 (56.7-95)	0.43	0.17
- Sexual funtion	100 (50-100)	100 (0-100)	0.46	73.2 (75-100)	55.4 (0-100)	0.26	0.17
- Sleep	62.5 (46.9-86.3)	62.5 (46.9-75.6)	0.14	73.9 (56.3-90.6)	80.4 (66.9-98.1)	0.49	0.53
- Social support	66.7 (12.5-100)	66.7 (58.3-100)	0.15	71.4 (62.5-100)	82.1 (62.5-100)	0.32	0.09
- Dialysis staff encouragement	68.8 (40.6-87.5) #	87.5 (43.8-100)	0.20	87.5 (84.4-100) #	75 (75-100)	0.32	0.50
- Patient satisfaction	58.3 (50-87.5)	66.7 (50-100)	0.16	77.4 (66.7-83.3)	81 (66.7-87.5)	0.20	0.00
+ Physical functioning	60 (42.5-77.5)	55 (38.8-77.5)	0.12	56.4 (40-76.3)	57.5 (33.8-80)	0.07	0.20
+ Physical function	50 (0-56.3)	50 (18.8-100)	0.29	42.9 (0-81.3)	60.7 (25-100)	0.50	0.08
+ Emotional wellness	68 (47-86)	84 (65-89)	0.41	67.1 (49-92)	77.4 (65-89) *	0.56	0.07
+ Social functioning	75 (62.5-100)	93.8 (71.9-100)	0.36	60.7 (37.5-81.3)	80.4 (62.5-100) *	0.79	0.49
+ Mental health	66.7 (25-100)	100 (33-100)	0.37	59.5 (33.3-100)	71.4 (58.3-100)	0.28	0.06
+ Pain	45 (39.4-60)	67.5 (52.5-82.5) *	0.93	54.3 (35-67.5)	76.1 (55-100) *	1.03	0.13
+ Vitality (energy/fatigue)	52.5 (42.5-61.3)	55 (40-70)	0.21	44.3 (23.8-55)	61.8 (48.8-77.5) *	1.18	0.53
+ General health perception	47.5 (38.8-61.3)	47.5 (35-67.5)	0.03	49.6 (28.8-65)	55 (32.5-76.3)	0.32	0.23

Legend: EQ-5D: EuroQol-5D Health Questionnaire; KDQOL-SF™: Kidney Disease and Quality-of-Life Short-Form; CKD: chronic kidney disease. -: specific items on CKD; +: general items. Data are expressed as mean ± standard deviation or median and interquartile range (P25-P75). *: within group difference; #: between groups difference. Significance level $p<0.05$

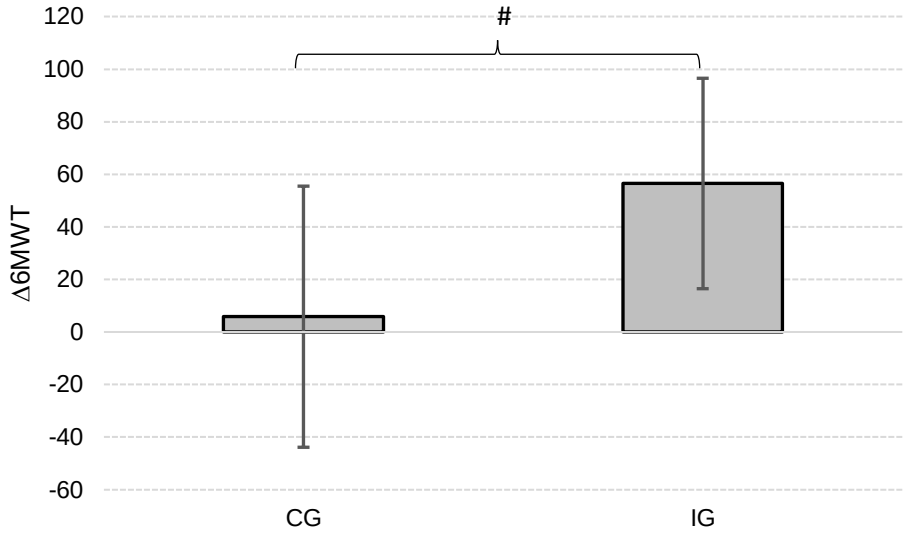

FIGURE 2. Mean difference and CI95% for distance covered (meters) in six-minute walk test (6MWT) between control (CG) and intervention (IG) groups after photobiomodulation. #: significance level p=0.01.

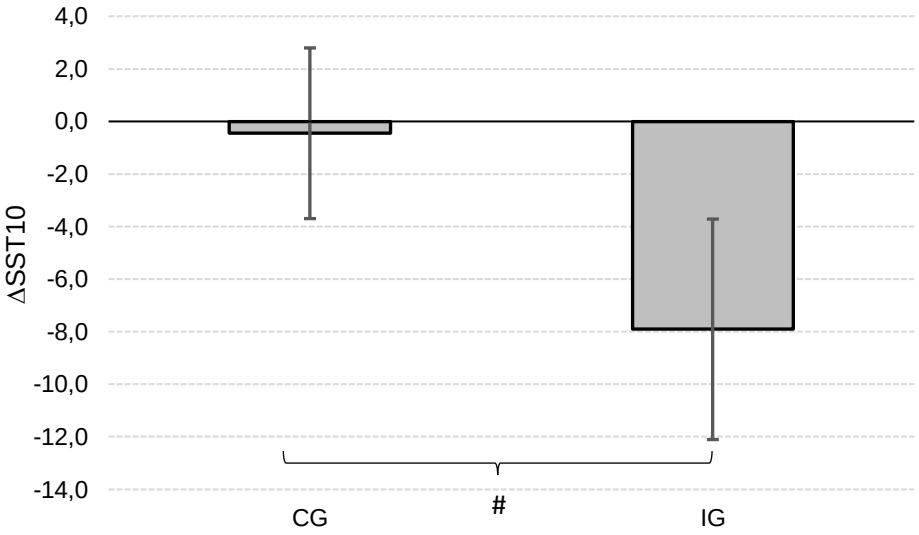

FIGURE 3. Mean difference and CI95% for time (seconds) in sit-and-stand test of 10 repetitions (SST10) between control (GC) and intervention (GI) groups after photobiomodulation. #: significance level p=0.00

6 CONCLUSÃO

A EENM e a FBM quando utilizadas por longo período em membros inferiores melhoram a capacidade funcional e a força muscular de pacientes com IRC em HD.

A EENM parece ter efeitos positivos sobre a força muscular de membros superiores, entretanto, mais estudos são necessários para confirmar essa hipótese, uma vez que a qualidade da evidência disponível é muito limitada.

A FBM quando utilizada como monoterapia, por oito semanas, em membros inferiores de pacientes com IRC não altera a arquitetura e tampouco a qualidade muscular do quadríceps femoral. Além disso, esta terapia parece modular a percepção de dor em membros inferiores, entretanto, os achados encontrados neste trabalho não suportam a mesma hipótese para a fadiga muscular.

A EENM e a FBM quando utilizadas por longo período parecem ter efeitos positivos sobre alguns aspectos da qualidade de vida de pacientes com IRC em HD, entretanto, a qualidade da evidência é limitada e mais estudos se fazem necessários para confirmar os reais benefícios sobre este desfecho.

Por fim, a EENM e a FBM podem ser consideradas estratégias promissoras dentro dos programas de reabilitação para pacientes com IRC, uma vez que, são modalidades terapêuticas alternativas ao exercício convencional, seguras, bem toleradas e capazes de melhorar a capacidade física desta população.

ANEXO A – Parecer consubstanciado do Comitê de Ética em Pesquisa com Seres Humanos

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITOS DA ESTIMULAÇÃO ELÉTRICA FUNCIONAL E DA LASERTERAPIA DE BAIXA POTÊNCIA SOBRE A CAPACIDADE FUNCIONAL E SOBRE O DANO AO DNA DE PACIENTES COM INSUFICIÊNCIA RENAL CRÔNICA EM HEMODIÁLISE: ENSAIO CLÍNICO RANDOMIZADO

Pesquisador: Rodrigo Della Méa Plentz

Área Temática:

Versão: 2

CAAE: 65845317.1.0000.5335

Instituição Proponente: Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.030.610

Apresentação do Projeto:

A doença renal crônica (DRC) consiste em lesão renal e perda progressiva e irreversível da função dos rins e em sua fase mais avançada (fase terminal) é chamada de insuficiência renal crônica (IRC). Apesar da hemodiálise (HD) substituir algumas das funções renais perdidas, os pacientes sofrem de algumas alterações que caracterizam a síndrome urêmica, sendo elas: neuropatia motora periférica, osteomalácia, miopatias cardíaca e

musculoesquelética, anemia, entre outras alterações. Considerando que a capacidade do paciente em HD se exercitar é baixa, o objetivo deste estudo é verificar os efeitos da eletroestimulação funcional (EEF) e da laserterapia de baixa potência (LBP) sobre a capacidade funcional, dano ao DNA, força muscular de membros inferiores, arquitetura muscular de quadriceps, dor muscular e percepção de fadiga de membros inferiores, perfil

inflamatório, estresse oxidativo e qualidade de vida de pacientes com IRC em HD. Para isso os pacientes serão randomizados em três grupos: grupo controle, grupo LBP e grupo EEF+LBP. O grupo controle será apenas avaliado e reavaliado. Os demais grupos além das avaliações receberão os

respectivos protocolos três vezes por semana, por 8 semanas, durante a HD. Serão realizadas as

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Telefone: (51)3214-8571 **Fax:** (51)3214-8571 **E-mail:** cep@santacasa.tche.br

seguintes avaliações pré-intervenção, após 4 e 8
semanas de terapia: teste de caminhada de seis minutos (TC6M) para avaliação da capacidade funcional; ensaio alcalino do cometa para avaliação do dano ao DNA, teste de sentar e levantar (TSL-10) e dinamometria por célula de carga para avaliação de força muscular de membros inferiores; ultrassonografia de quadriceps para arquitetura muscular; escala visual analógica para dor; escala de percepção subjetiva de esforço de Borg para
fadiga; medida de interleucinas 6 (IL-6) e 10 (IL-10), fator de necrose tumoral (TNF alfa), proteína C reativa (PCR) e marcadores de dano muscular (lactato, creatina quinase) para o perfil inflamatório; medidas de carbonilação proteica, superóxido dismutase, catalase, sulfídricos totais e diclorofluoresceína diacetato para o estresse oxidativo e aplicação dos questionários Kidney Disease and Quality-of-Life Short-Form (KDQOL-SFTM)
e EQ-5D para qualidade de vida. Os resultados esperados ao final do protocolo são: maior distância percorrida no TC6M; redução do dano ao DNA, incremento na força de membros inferiores; manutenção da massa muscular; redução dos níveis de dor e fadiga assim como do perfil inflamatório e dos níveis de estresse oxidativo, além de melhora da qualidade de vida para o grupo que foi submetido às modalidades terapêuticas EEF e LBP.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar os efeitos da estimulação elétrica funcional e da laserterapia de baixa potência sobre a capacidade funcional e sobre o dano ao DNA de pacientes com insuficiência renal crônica (IRC) em hemodiálise (HD).

Objetivo Secundário:

• Avaliar os efeitos da estimulação elétrica funcional e da laserterapia de baixa potência sobre a força muscular de membros inferiores;

• Avaliar os efeitos da estimulação elétrica funcional e da laserterapia de baixa potência sobre a arquitetura muscular do quadríceps;

• Avaliar os efeitos da estimulação elétrica funcional e da laserterapia de baixa potência sobre a dor muscular e fadiga de membros inferiores;

• Avaliar os efeitosda estimulação elétrica funcional e da laserterapia de baixa potência sobre o perfil inflamatório;• Avaliar os efeitos da estimulação elétrica funcional e
da laserterapia de baixa potência sobre o estresse oxidativo;

• Avaliar os efeitos da estimulação elétrica funcional e da laserterapia de baixa potência
sobre a qualidade de vida de pacientes com IRC em HD.

Avaliação dos Riscos e Benefícios:

Riscos:

As avaliações físicas que serão realizadas apresentam um risco mínimo levando em consideração que são submáximas. A coleta de sangue pode
gerar dor momentânea na região do braço em função da punção na fístula arteriovenosa, assim como podem ocorrer hematomas, entretanto, os
pacientes seriam submetidos à punção de qualquer forma para dialisar. A aplicação da LBP não causa queimaduras e alterações na pele, logo não apresenta risco. A EEF pode gerar efeitos semelhantes aos do exercício físico após a sessão como cansaço, dor muscular, ou algum desconforto relacionado à utilização da corrente elétrica durante a aplicação.

Benefícios:

Os benefícios residem no fato do paciente conhecer sua situação de saúde a partir das avaliações, receber um tratamento fisioterapêutico e ainda contar com a possibilidade de melhorar a sua capacidade funcional e força das pernas, manter a massa muscular, reduzir a dor e a fadiga dos membros inferiores, o dano ao DNA, o perfil inflamatório e o estresse oxidativo das suas células.

Comentários e Considerações sobre a Pesquisa:

A solicitação das pendências ao TCLE, foram atendidas.

Considerações sobre os Termos de apresentação obrigatória:

Apresentados e adequados.

Conclusões ou Pendências e Lista de Inadequações:

A solicitação das pendências ao TCLE, foram atendidas.

Considerações Finais a critério do CEP:

Após reavaliação do protocolo acima descrito, o presente comitê não encontrou óbices quanto ao desenvolvimento do estudo em nossa Instituição e poderá ser iniciado a partir da data deste parecer.

Obs.: 1 - O pesquisador responsável deve encaminhar à este CEP, Relatórios de Andamento dos Projetos desenvolvidos na ISCMPA. Relatórios Parciais (pesquisas com duração superior à 6 meses), Relatórios Finais (ao término da pesquisa) e os Resultados Obtidos (cópia da publicação).

2 – Para o início do projeto de pesquisa, o investigador deverá apresentar a chefia do serviço (onde

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será realizada a pesquisa), o Parecer Consubstanciado de aprovação do protocolo pelo Comitê de Ética.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_875469.pdf	24/04/2017 18:17:52		Aceito
Outros	Carta_ao_revisor_relator.pdf	24/04/2017 18:15:48	Rodrigo Della Méa Plentz	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_versao2.docx	24/04/2017 18:14:14	Rodrigo Della Méa Plentz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Termo_Consentimento_Livre_Esclarecido_versao2_UFCSPA.pdf	24/04/2017 18:12:20	Rodrigo Della Méa Plentz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Termo_Consentimento_Livre_Esclarecido_versao2_ISCMPA.pdf	24/04/2017 18:09:56	Rodrigo Della Méa Plentz	Aceito
Outros	Termo_compromisso_entrega_relatorio_UFCSPA.pdf	14/03/2017 17:01:37	Rodrigo Della Méa Plentz	Aceito
Outros	Termo_anuencia_responsavel_setor_UFCSPA.pdf	14/03/2017 17:00:18	Rodrigo Della Méa Plentz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_UFCSPA.pdf	13/03/2017 20:39:09	Rodrigo Della Méa Plentz	Aceito
Outros	Declaracao_isencao_onus_instituicao.jpeg	13/03/2017 20:33:00	Rodrigo Della Méa Plentz	Aceito
Outros	Declaracao_compromisso_utilizacao_dados_material_biologico.jpeg	13/03/2017 20:31:20	Rodrigo Della Méa Plentz	Aceito
Outros	Declaracao_utilizacao_dados_prontuarios.jpeg	13/03/2017 20:30:25	Rodrigo Della Méa Plentz	Aceito
Outros	Declaracao_confidencialidade_sujeito.jpeg	13/03/2017 20:25:50	Rodrigo Della Méa Plentz	Aceito
Outros	Formulario_inscricao.jpeg	13/03/2017 20:22:16	Rodrigo Della Méa Plentz	Aceito
Cronograma	Cronograma.jpeg	13/03/2017 20:18:31	Rodrigo Della Méa Plentz	Aceito
Orçamento	Orcamento.jpeg	13/03/2017 20:17:37	Rodrigo Della Méa Plentz	Aceito

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Continuação do Parecer: 2.030.610

Outros	Declaracao_autorizacao_chefia.jpeg	13/03/2017 20:16:43	Rodrigo Della Méa Plentz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	13/03/2017 20:08:25	Rodrigo Della Méa Plentz	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Doutorado.docx	13/03/2017 20:07:19	Rodrigo Della Méa Plentz	Aceito
Folha de Rosto	Folha_Rosto.pdf	13/03/2017 20:05:10	Rodrigo Della Méa Plentz	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 25 de Abril de 2017

Assinado por:
ELIZETE KEITEL
(Coordenador)

ANEXO B – *Normas Archives of Physical Medicine and Rehabilitation*

Introduction

Archives of Physical Medicine and Rehabilitation publishes original articles that report on important trends and developments in physical medicine and rehabilitation and in the wider interdisciplinary field of rehabilitation. *Archives of Physical Medicine and Rehabilitation*brings readers authoritative information on the therapeutic utilization of physical and pharmaceutical agents in providing comprehensive care for persons with disabilities and for chronically ill individuals. *Archives* began publication in 1920, publishes monthly, and is the official journal of the ACRM | American Congress of Rehabilitation Medicine. Its content is cited more often than any other rehabilitation journal.

A steadily increasing rate of submissions has forced the *Archives* to adopt a policy of restricting its manuscripts to topics that proved new information that may alter clinical practice or represent influential advances in the research. *Archives* will not review studies involving animal models, healthy normal samples, or small case reports, except in unusual circumstances. We may make exceptions when the clinical implications for populations of persons with chronic illness or disability are compelling. In addition, we will not review studies that report psychometric information of well-established instruments for language-specific applications.

Types of papers

Original Research: Present new and important basic and clinical information, extend existing studies, or provide a new approach to a traditional subject. Manuscripts should be limited to 3000 words of text (Introduction through Conclusions). Figures, tables, and references should be limited to the number needed to clarify, amplify, or document the text.

Brief Reports: Provide preliminary communications of new data, research methods, new ideas, and techniques. Manuscripts should be limited to 1500 words of text (or 1200 words plus 1-2 figures or tables, Introduction through Conclusions), and no more than 10 references. Brief reports should be accompanied by the appropriate reporting guideline and checklist.

The *Archives* will **not** consider case reports or animal studies for publication. Please do not submit them.

Commentaries (by Invitation): Focus on issues in physical medicine and rehabilitation. Manuscripts should be limited to 2000 words of text (Introduction through Conclusions). The Editorial Board reserves the right to ensure that the author is qualified, through education and professional experience, to write knowledgeably and appropriately about a particular subject before accepting a Commentary for publication. The Editorial Board will choose the author(s) for Invited Commentaries and the author(s)' identity will be anonymous until publication. Authors of the subject article may submit a response for a subsequent issue.

Editorials: Editorials published in *Archives* may only be written by the elected officers of ACRM, or by members of the Editorial Board. Prior to publication, all editorials are approved by the Editorial Board's Executive Committee. Editorials do not represent the opinions or positions of ACRM or the Editorial Board. Editorials should be limited to 1000 words of text.

Information/Education: The ACRM Communications Committee has developed a new feature, Information/Education Pages, which appear in the Organization News section of *Archives*.
These fact sheets are printed as tear-out pages. They are designed to provide consumer-friendly information on topics relevant to rehabilitation medicine, including basic background or overview, similar to a Wikipedia entry, or brief how-to suggestions. They are targeted toward people with disabilities, their caregivers, or clinicians; and are designed so that a practitioner can tear out and copy, or download the pages, to make them available to patients and caregivers.

Authors are invited to submit Information/Education Page manuscripts or proposals to the *Archives*' Editorial Office (ArchivesMail@archives.acrm.org). The ACRM Communications Committee will assess subject matter, content, and target reading level then provide feedback on suitability and instructions on how to proceed directly to the author. Note that this should not be considered an official peer review of the content. For more information go to http://www.acrm.org/publications/archives-of-pm-r/information-education-pages/.

Letters to The Editor: Letters are published at the discretion of the Editorial Board and should be directly related to the published article on which it comments. Letters may not reference unpublished studies or reference "in press" studies that are not publicly available. The Editorial Board reserves the right to solicit a response from the authors of the cited article. Letters must be limited to roughly 500 words of text, 1 table, and no more than 5 references.

Measurement Tools: These instrument summaries, which appear in the Organization News section of *Archives*,

are designed to facilitate the selection of outcome measures by trained clinicians. The information contained in this summary represents a sample of the peer-reviewed research available at the time of the summary's publication. The information contained in these summaries does not constitute an endorsement of the instrument for clinical practice. The views expressed are those of the summary authors and do not represent those of authors' employers, instrument owner(s), the *Archives*, the Rehabilitation Measures Database or the United States Department of Health and Human Services. Authors are invited to submit proposals for new Measurement Tools to the *Archives'*editorial office (Archivesmail@archives.acrm.org) and the office will coordinate with the ACRM Measurement Networking Group for the Rehabilitation Measures Database to determine if the proposal is suitable for publication in the *Archives*. The Networking Group can assist authors with formatting their article to meet the Measurement Tools requirements.

Review Articles (Meta-Analyses): The Editorial Board welcomes state-of-the-art review articles. Manuscripts should be limited to 5000 words of text (Introduction through Conclusions), exclusive of references.
The *Archives* strongly prefers systematic reviews of the literature.

Special Communications: Provide information or an objective analysis of issues in physical medicine and rehabilitation that does not qualify as a research or clinical paper or commentary. Manuscripts are peer reviewed and should be limited to 5000 words of text, exclusive of references.

Before You Begin

Ethics in Publishing

Authorship
Manuscripts should have no more than 8 authors; a greater number requires written justification. The order of authorship is a joint decision of the coauthors. *Archives* follows the *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* guidelines [1], which state authorship credit should be based only on substantial contributions to (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Participation solely in the acquisition of data does not justify authorship, nor does general supervision of the research group. *Archives* may require authors to justify the assignment of authorship. Increasingly, multicenter trials are attributed to a corporate author. All members of the group who are named as authors, either in the authorship position below the title or in a footnote, must fully meet the criteria for authorship as defined above. Group members not meeting these criteria should be listed, with their permission, in the Acknowledgments. Acknowledgments to other investigators for advice or data must be documented by written authorization specifically granting permissions to the authors.

Changes in authorship: After a manuscript has been submitted, any addition, deletion, or change to the order of the authors must be submitted in writing [2] to the Editorial Office (ArchivesMail@archives.acrm.org). This written statement, explaining the change and listing the old and new author orders, must be submitted with all authors copied (including those who have been removed, if applicable). The corresponding author should instruct all copied authors to respond with their approval of the change in author order. Failure to respond or failure of all authors to agree to the change may lead to suspension of review/publication of the article.

ICMJE form
Archives requires that all authors fill out the ICMJE form. For both new submissions and revisions, the peer-review process will not begin until these documents are completed correctly and submitted as per the instructions below.

Step 1: *Archives* requires the author submitting the manuscript to complete and upload an ICMJE Form for Disclosure of Potential Conflicts of Interest. By this act, the author submitting the manuscript will serve as the guarantor for all coauthors in presenting accurate disclosures for the author group. The guarantor is expected to consult with all coauthors about the disclosures he/she provides. Any disclosure (i.e. actual or perceived conflict of interest) must be described on the title page of the manuscript.

Step 2: At the point an editor seeks revision of a manuscript, *Archives* will require, with submission of the revised manuscript, original copies from all coauthors of the ICMJE form. Review of the revision will not commence until the editors have fully and accurately received the completed ICMJE forms from all coauthors. The editors expect the guarantor's group disclosure at submission to be consistent with the individual disclosures received at the revision stage. A written explanation will be required if this is not the case. If it is not possible to provide ICMJE forms from all co-authors at the revision stage, please contact the Editorial Office (ArchivesMail@archives.acrm.org) for alternative instructions.

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As of January 1, 2017 the *Archives* will ***only*** consider clinical trials that have been registered before the first patient is enrolled.

For our purposes, a clinical trial is defined as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (http://www.who.int/ictrp/en). Thus, cohort and retrospective studies without an intervention do not require registration, and neither do observational studies of clinical care. However, studies of human subjects with prospective assignment of an intervention by the investigators, regardless of the size of the trial or method of assignment, must be registered.

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Click on the checklist that applies to your manuscript, download it to your computer, fill it out electronically, "save as," and upload it with your manuscript when you submit. Links to mandatory flow diagrams also are provided. Below are the most commonly used checklists but please note that the Equator Network provides many others (e.g. TRIPOD, SRQR, etc.) and it is up to the authors to select the one most appropriate for their study.

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Abstract

For articles reporting original data (Original Articles, Brief Reports) and Review Articles (including Meta-Analyses), a structured abstract is required (see the Instructions for Structured Abstracts). Authors should make sure the key elements from the Reporting Guideline (eg. CONSORT, PRISMA, etc.) they followed for their manuscript are included in the abstract as well as the body of the paper.
Structured abstracts for Original Research and for Systematic Reviews/Meta-Analyses should be no more than 300 words in length.
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All abstracts must include provide 1 to 10 Keywords identified by the author. Keywords must be selected from the US National Library of Medicine's (NLM) *Medical Subject Headings*, which is available at http://www.nlm.nih.gov/mesh/MBrowser.html.

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Main Manuscript

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Specify any general use computer programs used. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlation," or "sample." Define statistical terms, abbreviations, and symbols.

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Include the subsection (Level 2 heading), "Study Limitations" to discuss the limitations of the study.

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