UNIVERSIDADE FEDERAL DE MINAS GERAIS
Faculdade de Odontologia
Colegiado de Pós-Graduação em Odontologia

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PROPOSTA DE NOVO PROTOCOLO DE FOTOBIOMODULAÇÃO PROFILÁTICA PARA MUCOSITE ORAL E OROFARÍNGEA INDUZIDA POR QUIMIOTERAPIA: *UM ESTUDO CLÍNICO RANDOMIZADO*

Belo Horizonte
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Orientador: Prof. Ricardo Alves de Mesquita
Coorientadora: Profa. Tarcília Aparecida da Silva

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PROPOSTA DE NOVO PROTOCOLO DE FOTOBIOMODULAÇÃO PROFILÁTICA PARA MUCOSITE ORAL E OROFARÍNGEA INDUZIDA POR QUIMIOTERAPIA: UM ESTUDO CLÍNICO RANDOMIZADO

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“I owned every second that this world could give
I saw so many places, the things that I did
With every broken bone
I swear I lived”
One Republic

RESUMO

A terapia de fotobiomodulação (TFBM) é amplamente utilizada em contextos oncológicos, mas a falta de padronização das avaliações é a principal barreira para otimizar os protocolos clínicos. Este estudo tem o objetivo de investigar os efeitos clínicos frente a utilização da TFBM na prevenção da mucosite oral e orofaríngea (MO) induzida por quimioterápicos e e/ou transplante de células-tronco hematopoiéticas (TCTH) em pacientes adultos. Foi realizado um ensaio clínico randomizado, no qual os participantes foram designados para três grupos de TFBM. O Grupo 1 recebeu TFBM profilática intraoral, o Grupo 2 recebeu TFBM intraoral e orofaríngea, e o Grupo 3 recebeu TFBM intraoral, orofaríngea e extraoral, desde o primeiro dia da infusão de QT até o dia D+10. Foram avaliadas a ocorrência e gravidade da MO, odinofagia e presença de sinais de infecções na cavidade oral. Também foram avaliadas informações sobre o regime de QT, tipo de TCTH, doença de base, exames hematológicos e dados sociodemográficos. Foram incluídos no estudo 60 pacientes. A distribuição por gênero foi igual (50%) em toda a amostra e a faixa etária variou de 18 a 74 anos. 70% dos indivíduos foram submetidos apenas à QT, enquanto 30% foram submetidos a TCTH. O agente quimioterápico mais utilizado foi a Citarabina (43,3%). A MO foi observada em 43,3% dos pacientes, principalmente nos graus I e II. A odinofagia foi relatada em apenas 23,3% dos indivíduos. A mucosa jugal foi o local mais afetado pela MO (35%). Na análise multivariada, observou-se que o tipo de TCTH influenciou diretamente a ocorrência da MO. Os indivíduos submetidos a TCTH alogênico tiveram 1,93 vezes mais chances de desenvolver MO ($p < 0,001$). O Grupo 3 apresentou uma frequência maior de MO, embora em graus menores. Além disso, esse grupo era composto por metade da população submetida a TCTH, tinha a maior porcentagem de uso de melfalano e a menor contagem média de leucócitos. Todos os três protocolos demonstraram eficácia na prevenção e redução da MO, apresentando boa tolerância e nenhuma toxicidade relatada. Defendemos a utilização da TFBM como uma abordagem segura e eficaz para a profilaxia da MO induzida pela QT em adultos submetidos a QT/TCTH.

Palavras-chave: quimioterapia; transplante de células-tronco hematopoiéticas; mucosite oral; mucosite orofaríngea; fotobiomodulação.

ABSTRACT

Proposal of a prophylactic photobiomodulation protocol for chemotherapy-induced oral and oropharyngeal mucositis: a randomized clinical trial

Photobiomodulation Therapy (PBMT) is widely used in oncological contexts, but the lack of standardized evaluations is the main barrier to optimizing clinical protocols. This study aims to investigate the clinical effects of PBMT in the prevention of oral and oropharyngeal mucositis (OM) induced by chemotherapy and/or hematopoietic stem cell transplantation (HSCT) in adult patients, as well as to explore and correlate potential risk factors associated with this toxicity. A randomized clinical trial was conducted, in which participants were assigned to three PBMT groups. Group 1 received intraoral prophylactic PBMT, Group 2 received intraoral and oropharyngeal PBMT, and Group 3 received intraoral, oropharyngeal, and extraoral PBMT from the first day of chemotherapy infusion until D+10. The occurrence and severity of OM, odynophagia, and the presence of signs of oral cavity infections were evaluated. Information regarding the chemotherapy regimen, type of HSCT, underlying disease, hematological examinations, and sociodemographic data were also assessed. The study included 60 patients. Gender distribution was equal (50%) across the entire sample, and the age range varied from 18 to 74 years. 70% of individuals underwent chemotherapy alone, while 30% underwent HSCT. The most commonly used chemotherapeutic agent was Cytarabine (43.3%). OM was observed in 43.3% of patients, mainly in grades I and II. Odynophagia was reported in only 23.3% of individuals. The buccal mucosa was the most affected site by OM (35%). In the multivariate analysis, it was observed that the type of HSCT directly influenced the occurrence of OM. Individuals undergoing allogeneic HSCT had 1.93 times more chances of developing OM ($p < 0.001$). Group 3 presented a higher frequency of OM, although in milder grades. Additionally, this group consisted of half of the population who underwent HSCT, had the highest percentage of melphalan use, and the lowest mean leukocyte count. All three protocols exhibited efficacy in the prevention and reduction of OM, displaying good tolerance and no reported toxicity. We assert the utilization of PBMT as a safe and effective approach for CT-induced OM prophylaxis in adults undergoing CT/HSCT.

Keywords: chemotherapy; hematopoietic stem cell transplantation; oral mucositis; oropharyngeal mucositis; photobiomodulation.

LISTA DE ABREVIATURAS E SIGLAS

5-FU	5-Fluorouracil
AlGaInP	*Alumínio-Gálio-Índio-Fósforo*
ATP	Adenosina Trifosfato
DNA	*Deoxyribonucleic Acid*
HC-UFMG	Hospital das Clínicas da Universidade Federal de Minas Gerais
HSV-1	Herpes-Vírus Simples
IARC	International Agency for Research on Cancer
INCA	Instituto Nacional de Câncer
J	Joule
J/cm²	Joule por Centímetro Quadrado
LASER	*Light Amplification by Stimulated Emission of Radiation*
MASC/ISOO	Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology
MO	Mucosite Oral e/ou Orofaríngea
MTX	Metotrexato
mW	Miliwatt
nm	Nanômetro
OMS	Organização Mundial de Saúde
OMS	Organização Mundial de Saúde
PAS	Ácido periódico de Schiff
QT	Quimioterapia
ROS	Espécies Reativas de Oxigênio
RT	Radioterapia
SPSS	Statistical Package for the Social Sciences
TCTH	Transplante de Células Tronco Hematopoiéticas
TFBM	Terapia de Fotobiomodulação
TGF- β1	Fator de Crescimento Transformador Beta 1

SUMÁRIO

1 CONSIDERAÇÕES INICIAIS

O câncer é amplamente reconhecido como o principal desafio de saúde pública global, destacando-se como uma das principais causas de mortalidade e, portanto, como uma das principais barreiras para o aumento da expectativa de vida em todo o mundo (IARC, 2020). Em muitos países, essa condição patológica é responsável pela primeira ou segunda causa de morte prematura antes dos 70 anos (INCA, 2019). Segundo as estimativas mais recentes para o Brasil, referentes ao ano de 2022, é esperado que ocorram aproximadamente 704 mil novos casos de câncer a cada ano no período de 2023 a 2025 (INCA, 2022). Além disso, a distribuição da incidência por região geográfica revela que as Regiões Sul e Sudeste concentram cerca de 70% dos casos, sendo que metade deles está localizada na Região Sudeste.

No que diz respeito às neoplasias hematológicas, como linfomas e leucemias, essas também são frequentemente diagnosticadas na população adulta, de acordo com as estimativas para o Brasil (INCA, 2019). Vale ressaltar que, excluindo os tumores de pele não melanoma, a leucemia ocupa a décima posição entre os tipos de câncer mais comuns, enquanto o linfoma não Hodgkin está na nona posição para homens e mulheres na Região Sudeste (6,68/100 mil e 5,96/100 mil, respectivamente). De modo geral, o risco de desenvolver ambas as condições aumentam com o avanço da idade (INCA, 2022).

Atualmente, há uma ampla variedade de tratamentos antineoplásicos disponíveis, e a seleção do tratamento a ser aplicado em um paciente é determinada pelo tipo de câncer, sua localização, estágio de desenvolvimento e outros fatores relevantes (MEDRADO *et al.,* 2015). A quimioterapia (QT), que é considerada uma terapia sistêmica, pode ser utilizada em combinação com outras modalidades terapêuticas, visando prevenir a disseminação tumoral ou reduzir o tamanho inicial do tumor (HARTNER *et al.,* 2018). Além disso, o transplante de células-tronco hematopoiéticas (TCTH) é um procedimento terapêutico que envolve a infusão intravenosa de células progenitoras do tecido hematopoiético. Esse procedimento é utilizado com o objetivo de restaurar a função da medula óssea em pacientes que apresentam danos medulares decorrentes de aplasia, causas benignas primárias, malignidades neoplásicas ou para permitir o aumento das doses de quimioterapia e/ou

radioterapia no tratamento de neoplasias hematológicas (KNIGHT *et al.,* 2016; SILVA JUNIOR *et al.,* 2009;)

Por se tratar de uma terapia sistêmica, além a imunossupressão, a QT pode causar alterações em mucosa oral que podem causar decréscimo considerável na qualidade de vida do paciente, causando inclusive interrupção do tratamento (HESPANHOL *et al.,* 2010). Além disso, o regime intensivo de condicionamento prévio ao TCTH e a subsequente recuperação imunológica lenta tornam os pacientes submetidos a esse procedimento suscetíveis ao desenvolvimento de uma série de efeitos adversos, tais como vômitos, diarreia, toxicidade hepática e complicações bucais (WEISSHEIMER *et al.,* 2017). As estruturas da cavidade oral são altamente sensíveis aos efeitos tóxicos dos agentes quimioterápicos, resultando em complicações frequentes, como mucosite oral e orofaríngea (MO), xerostomia, infecções bacterianas, virais e fúngicas, bem como neurotoxicidade (HESPANHOL *et al.,* 2010; HONG *et al.,* 2019; SROUSSI *et al.,* 2017; WANI *et al.,* 2018).

A MO é considerada um efeito adverso prevalente e clinicamente significativo observado em pacientes submetidos a altas doses de QT e TCTH e acompanhado por muitas alterações complexas da mucosa e da submucosa (CINASEURO *et al.,* 2017; WEISSHEIMER *et al.,* 2017; SONIS *et al.,* 2011). De acordo com a estimativa de Sonis (2021), dos 1,8 milhão de indivíduos que seriam diagnosticados com doenças malignas no ano de 2021 nos Estados Unidos, quase a metade teria algum grau de MO (SONIS, 2021).

Tal toxicidade caracteriza-se pela inflamação e ulceração da mucosa oral, que se torna edemaciada, eritematosa e friável, resultando em dor, desconforto, disfagia e debilidade sistêmica (HESPANHOL *et al.,* 2010; SILVA *et al.,* 2021). Frequentemente acompanhada de dor severa em orofaringe (MOMO *et al.,* 2017), a MO afeta principalmente as superfícies mucosas não queratinizadas, incluindo os revestimentos internos dos lábios e bochechas, o palato mole, a superfície ventral da língua, bem como a faringe e todo o trato gastrointestinal (FERREIRA *et al.,* 2015; NOIRRIT-*ESCLASSAN et al.,* 2019). Seu aparecimento ocorre entre 5-10 dias após a administração da droga e apresenta resolução de 90% dos casos em cerca de 2-3 semanas após o término do tratamento. Em síntese, ela ocorre em 40% a 76% dos pacientes sob QT (HESPANHOL *et al.,* 2010) e em pacientes submetidos ao TCTH,

começa a ser evidenciada entre o D+ 7 e D+ 10, podendo durar em média de 2 a 4 semanas (ANTUNES *et al.,* 2013; INCA, 2020).

Por ser um evento biológico complexo, diversos autores discutem sobre as vias moleculares e celulares que levam o aparecimento da MO (SHETTY *et al.,* 2022). Sonis descreve como evento biológico que ocorre em cinco fases: iniciação, sinalização, amplificação, ulceração e cicatrização (SONIS, 2007, 2009, 2021). O Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) revisa periodicamente a literatura relacionada à patogênese da MO, mecanismos e novas abordagens terapêuticas e destila isso em perspectivas resumidas e recomendações para pesquisa (ELAD *et al.,* 2020).

Os principais mecanismos descritos em 2004 e 2013 por Sonis continuam sendo fundamentais para o início da lesão. O primeiro ponto-chave é que a MO não se restringe apenas à camada epitelial da mucosa, mas abrange também os tecidos submucosos mais profundos (CINAUSERO *et al.,* 2017). Dessa forma, a QT ou a radiação causarão danos ao epitélio basal e à submucosa, por meio da clivagem do DNA e, consequentemente, da geração de espécies reativas de oxigênio. A clivagem do DNA ativa fatores de transcrição como o p53 e o fator NF-κB, que estão associados às funções anti e pró-apoptóticas. Uma vez ativados, ocorre um aumento de muitas citocinas pró-inflamatórias, como o fator de necrose tumoral-α (TNF-α), interleucina 6 e IL-1β, bem como COX-2, que iniciam um sinal para reduzir a oxigenação das células epiteliais, causando danos nas células epiteliais basais, tecido conjuntivo e endotélio (SHETTY *et al.,* 2022). Além disso, existem danos não relacionados ao DNA, que resultam da ativação da enzima esfingomielinase, com consequente ativação da via da ceramida, levando à apoptose de células epiteliais. Todos esses eventos levam à liberação de metaloproteinases da matriz, que, por sua vez, afetam a matriz de colágeno, gerando efetivamente danos teciduais (CINAUSERO *et al.,* 2017; SHETTY *et al.,* 2022). Clinicamente, é possível observar o desprendimento do epitélio, além de sinais inflamatórios, úlceras e formação de pseudomembrana. As úlceras servem como porta de entrada para microorganismos, causando uma liberação adicional de citocinas inflamatórias que perpetuam a cascata inflamatória. A neutropenia associada à QT prejudica a função das células imunes e do epitélio. A cicatrização geralmente é caracterizada por proliferação, migração e diferenciação epitelial estimuladas pela matriz extracelular CINAUSERO *et al.,* 2017; SHETTY *et al.,* 2022).

Notavelmente, as complicações diretas ou indiretas desta toxicidade se apresentam em forma de sintomatologia dolorosa, que resultam em uma maior necessidade de analgésicos sistêmicos, sangramento e muita das vezes necessidade de nutrição parenteral e hospitalização prolongada, influenciando negativamente a qualidade de vida desses pacientes (BARRACH *et al.,* 2015; SROUSSI *et al.,* 2017).

Segundo a estimativa do INCA, cerca de 70% dos indivíduos com neoplasias malignas em tratamento antineoplásico apresentam complicações orais decorrentes de toxicidade direta ou indireta, que podem levar à colonização da mucosa oral por bactérias, vírus e fungos (INCA, 2020; MÜLLER *et al.,* 2019). Nos últimos anos, tem sido realizada uma extensa investigação para explorar as correlações entre a MO e outras infecções orais, particularmente no contexto da mielossupressão e inflamação. Estes estudos destacaram o papel significativo desempenhado pela ruptura das barreiras da mucosa, que permite a entrada da flora oral endógena e de agentes patogénicos virais (CLEVERSON *et al.,* 2014; CHEN *et al.,* 2010). Um estudo abrangente realizado por Chen *et al*. forneceu provas convincentes de que, para além dos sinais clínicos de infecções normalmente observados em doentes submetidos a QT, *Candida spp*. e Herpes simples vírus (HSV-1) são os principais contribuintes para o desenvolvimento de MO. Além disso, outro autor demonstrou que cepas bacterianas presentes na microbiota de indivíduos com neoplasias malignas aderem à superfície da cavidade oral e orofaringe (BUNETEL *et al.,* 2019).

Pesquisas apontam alguns fatores como responsáveis pelo aumento de risco da incidência e gravidade da MO, podendo estarem relacionados tanto ao tratamento quanto ao paciente (VILLA E SONIS, 2015). Esses fatores incluem o tipo de tratamento antineoplásico (KAUARK-FONTES *et al.,* 2022), o regime de quimioterapia (SHI et al., 2016), a saúde bucal prévia ao tratamento (GURGAN et al., 2014; SURESH et al., 2016;), a idade do paciente (MARTINS et al., 2022) e os marcadores de imunidade local (CLEVERSON *et al.,* 2014; SURESH *et al.,* 2016).

A QT pode ser agressiva para a mucosa devido aos seus efeitos sobre as células pouco diferenciadas ou aquelas com alta taxa de mitose (DAMASCENA *et al.*, 2018). É considerada diretamente tóxica para a região oral (VELTEN *et al.,* 2017) e ocasionalmente certos medicamentos são secretados pela saliva, causando danos à cavidade oral (MORAIS *et al.,* 2014). Ademais, a incidência e a severidade da lesão nas mucosas dependem do tipo de QT utilizada (SHI *et al.,* 2016), e cada agente

quimioterápico apresenta sua mucotoxicidade (SONIS *et al.,* 2021). Os agentes antimetabólitos, como o metotrexato (MTX) e citarabina, agentes alquilantes (ciclofosfamida e melfalano), antraciclinas (daunorrubicina e doxorrubicina) e taxanos tendem a estar mais associados a toxicidades em mucosa. Uma revisão recente (CURRA *et al.,* 2018) constatou que a citarabina, o 5-fluoracil (5-FU) em alta dose, os agentes alquilantes e compostos à base de platina são frequentemente associados ao desenvolvimento de MO.

No que tange os tratamentos voltados para minimizar os danos da MO, a terapia de fotobiomodulação (TFBM) se tornou uma terapia reconhecida no tratamento dessas lesões (BOWEN *et al.,* 2019; MARTINS *et al.,* 2020; NUNES *et al.,* 2020; RAMOS-PINTO *et al.,* 2021; ZADIK *et al.,* 2019). Os efeitos clínicos incluem analgesia, efeito anti-inflamatório, potencial regenerativo dos tecidos, neovascularização e cicatrização acelerada de feridas (CURRA *et al.,* 2015; MARTINS *et al.,* 2019; PASSARELLA & KARU *et al.,* 2014). O efeito produzido pela TFBM se baseia na capacidade de modulação de diversos processos metabólicos, mediante a conversão da energia luminosa aportada pela TFBM através de processos bioquímicos e fotofísicos (ZECHA *et al.,* 2016). Tais efeitos biológicos incluem: ativação na produção de ATP, auxílio na multiplicação de fibras colágenas, formação de enzimas especificas, auxílio ao sistema linfático, benefícios no desenvolvimento de novos vasos sanguíneos (microcirculação) e aumento significativo na síntese de proteínas e de DNA (PASSARELLA & KARU *et al.,* 2014), além de acelerar a migração epitelial, contribuindo para a cicatrização das lesões (MARTINS *et al.,* 2021; WAGNER *et al.,* 2016; ZECHA *et al.,* 2016).

Uma vez bem estabelecida para o tratamento da MO, diversos estudos têm demonstrado a redução da intensidade da MO quando usado a TFBM de forma preventiva ao tratamento antineoplásico (NUNES *et al.,* 2020; SOTO *et al.,* 2015; WEISSHEIMER *et al.,* 2017; ZADIK *et al.,* 2019). Neste cenário, protocolos baseados em evidências clínicas desenvolvidos pela MASCC/ISO recomendam que a TFBM seja relevante na redução da dor na incidência de MO em pacientes submetidos a altas doses de QT e condicionamento de TCTH (ELAD *et al.,* 2020; LALLA *et al.,* 2014; SUNG *et al.,* 2017; WEISSHEIMER *et al.,* 2017; ZADIK *et al.*, 2019).

Em consonância com os estudos acima citados, tem sido reportado que os comprimentos de onda de 660nm a 970nm têm um efeito benéfico na prevenção da

MO induzida por QT em pacientes oncológicos (GOBBO *et al.,* 2018; NUNES *et al.,* 2020; RAMOS-PINTO *et al.,* 2021; WEISSHEIMER *et al.,* 2017; ZECHA *et al.,* 2016). Ademais, a aplicação de TFBM extraoral pode prevenir eficazmente o início precoce da MO (KAUARK-FONTES *et al.,* 2022), e autores referem melhoria nos resultados funcionais relacionados à dieta disfagia, porém permanecem incertos sobre o protocolo ideal (SOTO *et al.,* 2015). Desta forma, persistem desafios em termos de administração da dosagem adequada para aplicação extraoral e de determinação da dosimetria ideal para o tratamento de tecidos orais (ZADIK *et al.,* 2019).

Considerando as dificuldades relacionadas ao acesso à orofaringe utilizando as técnicas tradicionais existentes e com o objetivo de fornecer energia com maior eficiência a essa região, que frequentemente é afetada, o presente estudo clínico tem como propósito investigar os efeitos clínicos de três protocolos de TFBM na prevenção da mucosite oral e orofaríngea induzida por quimioterapia e transplante de células-tronco hematopoiéticas em pacientes adultos.

2 OBJETIVOS

2.1 Objetivo geral

Investigar os efeitos clínicos frente a utilização da TFBM na prevenção da MO induzida por quimioterápicos e pelo TCTH em pacientes adultos.

2.2 Objetivos específicos

a) Avaliar comparativamente o efeito clínico em três diferentes protocolos da TFBM na prevenção de MO induzida por quimioterápicos e TCTH.
b) Avaliar os efeitos clínicos de prevenção da mucosite orofaríngea através da fibra óptica adicionada nos protocolos;
c) Investigar e correlacionar potenciais fatores de risco associados à MO;
d) Avaliar os parâmetros bioquímicos sanguíneos dos pacientes inseridos nos momentos D0, D+3, D+10 e D+15;
e) Investigar a ocorrência de infecções fúngicas, virais e bacterianas em cavidade oral, assim outras alterações orais provenientes do tratamento antineoplásico (Ex: alterações secundárias à plaquetopenia).

3 METODOLOGIA EXPANDIDA

3.1. Considerações éticas

O presente estudo foi submetido aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (UFMG) (Número do parecer: 5.904.127/ CAAE: 64244422.9.0000.5149) e ao Comitê de Ética em Pesquisa do Hospital das Clínicas da UFMG (HC-UFMG), obedecendo ao exigido pela legislação brasileira do Conselho Nacional de Saúde sobre diretrizes e normas regulamentadoras de pesquisa envolvendo seres humanos (Resolução 466/2012) e foi realizado de acordo com os princípios éticos da Declaração de Helsinque (BELSEY, 1978). Todos os participantes receberam informações detalhadas sobre a pesquisa. Indivíduos adultos selecionados para o estudo, que concordaram em participar, assinaram o Termo de Consentimento Livre e Esclarecido.

3.2 Desenho do estudo

Este estudo foi do tipo estudo clínico randomizado.

3.3 Critérios de elegibilidade

Para a inserção no presente estudo, foram considerados os pacientes com os seguintes critérios de inclusão:

a) Adultos, maiores de 18 anos, de ambos os sexos, portadores de neoplasias malignas ou doenças hematológicas em tratamento no HC-UFMG;
b) Indivíduos sob regime quimioterápico que exigisse internação ou indivíduos submetidos a TCTH (autólogo e alogênico);
c) Indivíduos com a capacidade de cooperar com o tratamento, ou seja, com capacidade mental e física para tomada de decisões para aceitar participar do projeto e receber o tratamento proposto.

Os seguintes critérios de exclusão foram seguidos:

a) Pacientes crianças ou adolescentes (0-17 anos);
b) Pacientes que apresentarem neoplasias de glândulas salivares ou síndrome de Sjögren ou doenças crônicas com comprometimento salivar (Histoplasmose, Linfoma MALT, Lúpus Eritematoso Sistêmico, Amiloidose), programados a receber outro tipo de terapia antineoplásica (ex., RT ou QT/RT);
c) Indivíduos que não tiveram tempo de internação suficiente para realizar o protocolo de TFBM (D0 ao D+10).

3.4 Grupos de estudo

Os participantes da pesquisa foram selecionados para uma sequência de randomização criada usando números aleatórios gerados por computador (Excel 2019; *Microsoft Corp*) e alocados em três grupos:

a) Grupo 1: participantes que receberam TFBM profilática intraoral;
b) Grupo 2: participantes que receberam TFBM profilática intraoral e em orofaringe;
c) Grupo 3: participantes que receberam TFBM profilática intraoral, em orofaringe e extraoral.

3.5 Protocolo da TFBM profilática e terapêutica intraoral e extraoral para MO

Para este projeto foram utilizados equipamentos da DMC Equipamentos (São Carlos, SP, Brasil), para todos os protocolos de TFBM. Não existem conflito de interesse entre os pesquisadores e a empresa DMC.

O protocolo proposto da TFBM de uso profilático intraoral consistiu na irradiação de 6 dias por semana (segunda à sábado), do D0 até o D+10, em todos os grupos, sendo o D0 o primeiro dia da infusão da QT ou do condicionamento do TCTH. No grupo 1, foi realizada a aplicação profilática de TFBM em 22 pontos pré-determinados em todas as membranas mucosas da cavidade oral. No grupo 2, além dos 22 pontos pré-determinados nas mucosas da cavidade oral, foram irradiados

bilateralmente 2 pontos na orofaringe utilizando um aparelho LASER acoplado a uma fibra óptica, de 10.5 cm, desenvolvida para este estudo, permitindo então deposição de energia na orofaringe a partir de uma distância. O Grupo 3 também teve os mesmos 24 pontos pré-determinados (22 na cavidade oral, 2 pontos na orofaringe), porém acrescido de 2 pontos extra-orais (infravermelho) bilateralmente, localizados abaixo do ângulo da mandíbula, com o intuito de prevenir a odinofagia. A aplicação da TFBM foi efetuada por um dentista previamente calibrado (F.V.H)

A TFBM intra e extra-oral foi utilizada em modo de contato com o equipamento. Adicionalmente, foi utilizado um laser de fibra óptica de 10,5 cm para irradiação orofaríngea. A fibra óptica foi posicionada à distância da orofaringe, assegurando uma proximidade sem contato direto, de modo a evitar o desencadeamento de um reflexo de vômito no paciente.

Para a irradiação intraoral e orofaríngea, foi utilizado o LASER de diodo de Alumínio-Gálio-Índio-Fósforo (AlGaInP) com um comprimento de onda de 660nm (vermelho visível). Na irradiação intraoral, os seguintes parâmetros foram utilizados: potência de 100mW, energia de 2J por ponto, exposição de 20 segundos e área de spot de 0.028cm^2. Já para a irradiação orofaríngea, a potência foi de 200mW, energia de 2J por ponto, exposição de 10 segundos e área de spot de 0.0078cm^2.

Para irradiação extraoral, o protocolo da TFBM foi realizado pontualmente, na região abaixo do ângulo da mandíbula próximo às tonsilas palatinas, bilateralmente, com o mesmo aparelho de LASER utilizado na irradiação intraoral, porém no comprimento de onda de 808nm, potência de 100mW, atingindo uma dose de energia tecidual de 6J/cm^2 (60 s/local).

Todos os participantes do projeto que desenvolveram MO foram tratados exclusivamente com TFBM intraoral e em orofaringe, independente do grau/severidade e a TFBM foi aplicada exclusivamente nas lesões. O protocolo de TFBM para o tratamento da MO intraoral consistiu na irradiação diária pontual em todas as mucosas lesionadas da cavidade oral, com o mesmo dispositivo, no comprimento de onda de 660nm, potência de 100mW, atingindo uma dose de energia tecidual de 4J/cm^2 (40 s/local), iniciando assim que as lesões aparecerem finalizado quando apresentassem resolução clínica (NUNES *et al.,* 2020).

Adicionalmente, aqueles que desenvolveram também odinofagia receberam TFBM extraoral com os mesmos parâmetros da aplicação profilática. Todos os

pacientes foram também orientados sobre higiene bucal, sendo o acompanhamento com reforço da saúde bucal realizado durante todo o período de internação e, caso necessário e liberado pela equipe médica, os pacientes poderiam fazer a adequação de meio bucal e profilaxia.

3.6 Coleta de dados e avaliação da MO

Foram registradas informações pertinentes relacionadas ao sexo, idade, doença de base, outras condições sistêmicas e medicamentos em uso pelos participantes. No que diz respeito aos regimes de QT administrados durante o período de internação, foram contabilizados os fármacos mucotóxicos utilizados por cada indivíduo, assim como as respectivas doses. A classificação dos agentes quimioterápicos quanto à mucotoxicidade foi estabelecida com base em estudos previamente realizados na literatura científica e nas informações contidas nos folhetos descritivos dos medicamentos.

Em relação aos parâmetros clínicos, foram registrados a presença e o grau de MO. Ademais, também foi examinado a ocorrência de sinais de infecções fúngicas, virais ou bacterianas na cavidade oral, assim como sinais de alterações secundárias à trombocitopenia e desidratação labial. Os dados referentes à odinofagia foram registrados com base nos sintomas relatados pelos participantes e as suspeitas clínicas de infecções oportunistas associadas à MO foram confirmadas através de raspado e ácido periódico de Schiff (PAS).

A avaliação clínica da ocorrência e severidade da MO e/ou outras condições orais acima citadas foi realizada por outro dentista calibrado (J.A.A.A), e este avaliador não teve conhecimento das atribuições dos grupos, assegurando um processo de avaliação cego.

As informações sobre a localização anatômica das lesões de MO foram consideradas nos seguintes sítios: lábios, mucosa labial, comissura labial, mucosa jugal, vestíbulo, assoalho da boca, língua (borda lateral, ventral, dorso), trígono retromolar, palato e orofaringe. A análise da localização anatômica foi realizada com base no número de lesões, não no número de indivíduos, uma vez que um mesmo paciente poderia apresentar lesões em mais de um local anatômico.

A severidade da MOO foi graduada de acordo com a escala da OMS. (WHO, 1979).

Na qual:

Grau 0 Nenhuma alteração

Grau 1 Presença de eritema, alimentação sólida

Grau 2 Presença de eritema, úlceras, alimentação sólida

Grau 3 Presença de úlceras e alimentação líquida

Grau 4 Presença de úlceras e alimentação via oral impossibilitada

Além disso, foram registrados os episódios de neutropenia febril ocorridos durante o tratamento. Também foram coletadas as contagens absolutas de neutrófilos e leucócitos nos momentos D0, D+3, D+10 e D+15 como fatores hematológicos. Esses exames já eram realizados diariamente como parte do protocolo do serviço do HC-UFMG, portanto, os pacientes não foram submetidos a nenhuma intervenção adicional para a sua realização.

3.7 Análise estatística

Todas as análises estatísticas foram realizadas utilizando o software Statistical Package for the Social Sciences (SPSS) (IBM SPSS Statistics for Windows, versão 25.0, Armonk, Y: IBM Corp). As diferenças entre os grupos de TFBM foram avaliadas por meio do teste qui-quadrado para dados categóricos. Para as variáveis quantitativas, utilizou-se o teste de Kruskal-Wallis. Todas as variáveis com um valor de $p < 0,20$ na análise univariada foram incluídas na análise multivariada. Um valor de $p \leq 0,05$ foi considerado estatisticamente significativo.

4 RESULTADOS

ARTIGO

Os resultados estão apresentados em forma de artigo científico, submetido ao periódico Lasers in Medical Science. As informações e normas da revista estão contidas no Anexo B.

Proposal of a prophylactic photobiomodulation protocol for chemotherapy-induced oral and oropharyngeal mucositis: a randomized clinical trial

Abstract

Purpose: Photobiomodulation therapy (PBMT) is widely used in oncology settings, but lack of standardization of assessments is the main barrier to optimizing clinical protocols. This study analyzed three PBMT protocols for preventing oral and oropharyngeal mucositis (OM) in patients undergoing chemotherapy (CT) and/or hematopoietic stem cell transplantation (HSCT).

Methods: This is a preliminary randomized blind clinical trial. Group 1 received intraoral prophylactic PBMT; Group 2 received of intraoral and oropharyngeal PBMT; and Group 3 received of intraoral, oropharyngeal and extraoral PBMT. The applications were from the first day of CT until day+10. Clinicodemographic data, CT regimens, types of HSCT, hematological exams, occurrence/severity of OM, odynophagia, and OM-related opportunistic infections were assessed.

Results: Sixty participants (age range: 18–74 years) were included. 70% of patients underwent CT, while 30% HSCT. About 43.3% of patients had OM, while odynophagia was reported by 23.3%. Both Groups 1 and 2 revealed better results. In the multivariate analysis, HSCT directly influenced the occurrence of OM. Individuals who had undergone allogeneic HSCT were 1.93 times more likely to develop OM (p<0.001). Group 3 exhibited a higher frequency of OM, albeit in lower grades. This group consisted of half of the population who had undergone HSCT, had the highest percentage of melphalan use, and the lowest mean leukocyte count.

Conclusion: The three proposed protocols were effective in preventing and reducing OM, with good tolerance and no reported adverse effects. PBMT is a safe and effective approach to OM prophylaxis in adults undergoing CT/HSCT.

Keywords: chemotherapy; hematopoietic stem cell transplantation; oral mucositis; oropharyngeal mucositis; photobiomodulation

Introduction

Oral and oropharyngeal mucositis (OM) is a prevalent outcome in individuals undergoing high-dose chemotherapy (CT), radiotherapy (RT), and hematopoietic stem cell transplantation (HSCT) [1-3]. OM manifests as pain, discomfort, and functional impairments in eating, swallowing, and speaking, which can potentially limit antineoplastic treatment and impact overall quality of life [3, 4]. OM primarily affects the non-keratinized mucosa, including the inner linings of the lips and buccal mucosa, soft palate, ventral surface of the tongue, oropharynx, and gastrointestinal tract [3, 5, 6]. Furthermore, OM may be associated with the occurrence of local and systemic infections and contribute to unfavorable health outcomes [7].

Risk factors for OM can be attributed to the specific treatment regimen and/or individual patient profile [8]. The occurrence and severity of OM depends on the type of CT [8], type of HSCT, as well as the presence of myelosuppression [1]. In recent decades, efforts have been made to gain a better understanding of the pathobiology of OM and its associated risk factors [2, 3, 6, 8]. Currently, important strategies have been made available for OM prophylaxis, including cryotherapy, growth factor therapy, inhibitors of inflammation and cytokine production, and photobiomodulation therapy (PBMT) [2, 3, 6, 9, 10].

PBMT, also known as low-level laser therapy, stimulates and promotes positive tissue processes, such as wound healing, regeneration, and immune responses, and mitigates negative aspects, such as inflammation, pain, and abnormal immune responses [9-11]. Compelling evidence supports the use of PBMT in preventing and reducing the severity of OM in individuals undergoing HSCT, as indicated by guidelines established by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). These panel recommendations have also indicated the use of PBMT as an adjunctive intervention for OM in adult HSCT patients undergoing high-dose CT conditioning [9, 12]. Conversely, previous studies have shown that extraoral application of PBMT can also effectively prevent early onset of OM and has the advantage of application in shorter treatment sessions compared to intraoral PBMT [10, 13]. However, challenges persist in terms of administering the proper dosage for extraoral application and determining the optimal dosimetry for treating oral tissues [10].

Revisiting the last 20 years of clinical studies of PBMT for mitigation of OM, it has become evident that the main barrier to optimizing clinical protocols of PBMT for OM is the lack of standardization in clinical protocols; thus, additional randomized clinical trials with well-described methods are needed [14]. The purpose of this blind randomized clinical trial was to examine the effects of three distinct PBMT protocols for OM prophylaxis

in adult patients undergoing CT and/or HSCT. Additionally, we sought to identify potential risk factors associated with OM.

Materials and Methods

Study design, sampling, setting, and period of recruitment

This is a preliminary randomized blind clinical trial. The study was carried with the adult population of oncology and hematological patients from the Oncology and Hematopoietic Stem-Cell Transplantation services of the Hospital das Clínicas of the Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. A total of 92 hospitalized patients receiving CT were recruited from July 2021 to March 2023. **Figure 1** portrays the study flowchart. The inclusion criteria were as follows: patients aged ≥18 years, diagnosed with malignant neoplasms or hematological diseases, undergoing chemotherapy/conditioning regimen for HSCT who required hospitalization. Patients with salivary gland neoplasms, Sjögren syndrome, or chronic diseases with salivary involvement (e.g., histoplasmosis, MALT lymphoma, systemic lupus erythematosus, or amyloidosis) scheduled to receive another type of antineoplastic therapy (e.g., RT or CT/RT) were excluded. Those who did not have sufficient hospitalization time to perform the PBMT protocol (10 days) were also excluded.

Allocation of participants to intervention groups

Participants were randomly assigned to three groups of prophylactic PBMT. Group 1 received intraoral prophylactic PBMT; Group 2 received both intraoral and oropharyngeal PBMT; and Group 3 received intraoral, oropharyngeal, and extraoral PBMT. Throughout the study, the outcome assessor was kept unaware of group assignments, ensuring a blinded assessment process.

The proposed protocol for prophylactic intraoral PBMT consisted of irradiation six days per week (Monday to Saturday), from day 0 (D0) until day 10 (D+10), in all groups, with D0 being the first day of CT/HSCT conditioning. **Figure 2** illustrates the laser devices used in patients. In Group 1, prophylactic PBMT was spot-on at 22 predefined points along the mucous membranes of the oral cavity **(Figure 3A)**. For Group 2, 22 pre-defined points were irradiated on all the mucous membranes of the oral cavity, plus two points of the oropharynx irradiated bilaterally with the laser device coupled to a 10.5 cm optical fiber that, at a distance, allowing the operator to deposit energy in the oropharynx **(Figures 3A–3B)**. Group 3 had the same 24 pre-defined points (22 in the oral cavity, two points in the oropharynx – **Figures 3A–3B**) plus two extra-oral points (infrared), bilaterally, in the

region below the mandible angle to prevent odynophagia **(Figure 3C)**. Device information, irradiation parameters, and treatment standards of the PBMT groups are described in **Table 1**.

On the day of CT initiation, all patients received oral examinations to confirm that there were no OM lesions. The application of PBMT was performed by a previously calibrated dentist (F.V.H.), while the clinical assessment of OM and/or other oral conditions (e.g. candidiasis, herpes simplex virus [HSV]) was done by one dentist (J.A.A.A.). Clinically suspected opportunistic infections associated with OM were confirmed by cytopathological examination. The severity of OM was scored according to the World Health Organization (WHO) classification: grade 0 (none), grade I (oral soreness, erythema), grade II (oral erythema, ulcers, solid and liquid diet tolerated), grade III (oral ulcers, liquid diet only), and grade IV (oral alimentation impossible) [15].

Participants who had developed OM were treated with intraoral and oropharyngeal PBMT, regardless of degree/severity. PBMT was applied exclusively to the lesions. The PBMT protocol for the treatment of intraoral OM consisted of daily spot irradiation at a wavelength of 660 nm on all the lesioned mucosae of the oral cavity, with the same device, with power of 100 mW, reaching a dose of tissue energy of 4 J/cm^2 (40 s/location), and total energy of 100 J/cm^2 starting as soon as the lesions appeared and ending when clinical resolution was observed [11]. Those who had also developed odynophagia received extraoral PBMT as shown in **Figure 2C**. Preventive strategies, such as monitoring of oral hygiene were used before and during CT to attenuate OM [11].

Data collection

Information on sex, age, baseline disease, other systemic conditions, and medications in use was recorded. Regarding the CT schemes taken during hospitalization, the amount of drugs for each individual and their respective doses were registered. The chemotherapeutic agents used, separated by intervention groups, are shown in **Supplementary Table 1**.

As for the clinical parameters, the presence/degree of OM, the presence of signs of fungal, viral or bacterial infections in oral cavity, and signs of alterations secondary to thrombocytopenia and labial dehydration were recorded. Data on odynophagia were recorded according to the symptoms mentioned by the individuals.

The anatomical site of OM lesion was considered as follows: lips, labial mucosa, labial commissure, buccal mucosa, vestibule, floor of the mouth, tongue (lateral border, ventral, dorsal), retromolar trigone, palate, and oropharynx. The anatomical site was not analyzed in terms of number of patients, but rather in terms of number of lesions, i.e., the same patient may have been affected at more than one anatomical site.

Data on episodes of febrile neutropenia during treatment were collected. As a standard of care in the unit, blood counts are performed daily; thus, absolute neutrophil and leukocytes counts were also collected on days 0, 3, 10, and 15.

Statistical analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp). Descriptive, bivariate, and multivariate analyses were carried out. Differences among the PBMT groups were analyzed using chi-square test in analysis of categorical data. The Kruskal-Wallis test was used for quantitative variables. All variables with a p-value <0.20 in the bivariate analysis were then entered into the multivariate analysis. A p-value ≤0.05 was considered statistically significant.

Ethical issues

The study was approved by the Ethics Committee on Human Research of the Institution (No. 5904127) and the participants agreed with the publication of the research in accordance with the Declaration of Helsinki.

Results

Clinicopathological and antineoplastic regimens

A total of 92 internalized patients receiving CT were enrolled in the study; however, 32 were excluded for the reasons shown in **Figure 1**. In total, data of 60 patients were analyzed in the study. The proportion of male and female patients in the sample was the same (50% each) and the age ranged from 18 to 74 years, with a mean age of 44.2 (±16.2) years. The main baseline diseases were myeloid leukemias (30%), followed by lymphoid leukemias (26.7%), and multiple myeloma (16.7%). Regarding the type of treatment, 42 (70%) patients underwent CT as the main treatment and 18 (30%) underwent HSCT (i.e., 83% autologous and 17% allogeneic). Forty-one (68.3%) individuals remained alive with disease **(Supplementary Table 2)**. **Supplementary Table 3** presents the systemic conditions observed in the individuals, among whom cardiovascular and endocrine diseases were the most frequent (>20%).

Chemotherapeutic agents were administered extensively across all groups. The agents most used within the sample were cytarabine (43.3%), daunorubicin (26.7%), melphalan (21.7%), and methotrexate (MTX) (20%). Prophylaxis against graft-versus-host disease (GVHD) with MTX was implemented exclusively in patients

undergoing allogeneic transplantation (5%). Classification of CT agents as mucotoxic or non-mucotoxic was determined based on existing literature studies and drug description leaflets. The total count of chemotherapeutic agents administered to each patient was documented. The mean number of administered mucotoxic chemotherapies was higher in Group 2 (2.34) compared to Group 1 (1.64) (p=0.043) **(Table 2)**.

Evaluation of OM and risk factors

All three prophylactic PBMT protocols were well tolerated with no adverse effects. OM was observed in 43.3% of the entire sample **(Supplementary Table 2)** and illustrated in **Figure 4**. In Group 1, 30% had OM, predominantly mild, grades I–II (20%). Eight individuals in Group 2 had OM, four (18.2%) grade I, three (13.6%) grade II and one (4.5%) grade IV. In Group 3, patients had a higher percentage of OM (61.1%), but predominantly in mild grades, i.e., I and II (33.3% and 11.1%, respectively) **(Table 3)**. All individuals who had developed OM received therapeutic PBMT. Group 2 included the largest population submitted to cytarabine (45.5%) and vincristine (27.3%), while the three groups had almost the same number of patients submitted to MTX regimens. The use of melphalan in Group 3, whose participants exhibited the highest rates of OM, was higher than in Group 1 and Group 2 (p=0.005) **(Supplementary Table 1)**. In addition, of the 13 patients who had undergone treatment with this chemotherapeutic agent, 37.5% had some degree of OM (p=0.024), even if in lower degrees (I–II).

With respect to anatomical location, the site most affected by OM lesions among all subjects was the buccal mucosa (18.3%). Specifically, the preferred site continues to be the buccal mucosa (25%) in Group 1, floor of the mouth (18.2%) in Group 2, and hard/soft palate in Group 3 (44.4%) **(Table 3)**, although no statistically significant difference among groups was observed (p>0.05). Regarding odynophagia, Groups 2 and 3 had the same number (n=5) of affected individuals, with a lower incidence in Group 1 (20%) **(Table 3)**.

Considering HSCT, Group 3 was statistically different from Groups 1 and 2 (p=0.015). In Groups 1 (85.0%) and 2 (77.3%), most patients did not undergo HSCT, while in Group 3, 50.0% of individuals underwent autologous HSCT **(Table 3)**. Multivariate analysis demonstrated that the type of HSCT had a direct impact on the occurrence of OM. Individuals who had undergone allogeneic HSCT were 1.93 times more likely to develop OM than those who had not undergone HSCT (OR=1.93; CI=1.58–2.36; p<0.001). Also, those who had undergone autologous HSCT were 1.59 times more likely to develop OM than individuals who had not undergone HSCT (OR=1.59; CI=1.24–2.06; p<0.001) **(Table 4)**.

Table 2 also shows the association of quantitative variables and PBMT groups. Individuals in Group 2 used a higher amount of mucotoxic CT agents than individuals in Groups 1 and 3 (p=0.043). For age and lower

count of leukocytes, no significant differences among groups were observed (p>0.05). **Figure 5** illustrates the mean values of neutrophils and leukocytes across all patients, revealing a significant decline starting from D+3. The nadir is observed on D+10, succeeded by a subsequent escalation until D+15.The lowest count of neutrophils was reduced in individuals in Group 3 in comparison to individuals in Group 1 and those in Group 2, but without significant differences (p>0.05).

Regarding the factors that can increase the severity of OM, we tested in a multivariate analysis, the influence of HSCT, oral candidiasis, age, amount of chemotherapy, and the lowest neutrophil rate. HSCT demonstrated a significant result. The severity of OM among individuals who had undergone HSCT was 2.80 times higher than among individuals who had not undergone HSCT (OR=2.80; CI=1.44–5.74; p=0.003) **(Supplementary Table 4)**.

Occurrence of opportunistic infections and other oral alterations

Patients exhibited 14 episodes of oral candidiasis, being seven (31.8%) in Group 2, six (30%) in Group 1, and one in Group 3 **(Table 3)**. Five episodes of HSV (8.3%) and two cases (3.33%) of both infections (oral candidiasis and HSV) were also observed. No significant associations between the establishment of OM with viral and/or fungal infections were observed as well (p>0.05).

Other oral alterations were also observed; 17 patients (28.3%) had labial dehydration, 12 (20%) had changes secondary to thrombocytopenia, such as petechiae, and six (10%) patients experienced hyperkeratosis secondary to CT.

Discussion

OM represents an acute adverse effect commonly associated with cytotoxic antineoplastic treatments and is undoubtedly considered one of the most debilitating and prevalent oral outcomes in individuals undergoing CT or HSCT [16]. It is no longer considered an isolated concern, but rather acknowledged as a significant source of distressing physical, psychological, economic, and systemic burden across its entire spectrum [6]. Consequently, it is of utmost importance to effectively control OM and prioritize the development of interventions that can support patients undergoing antineoplastic therapy [1]. Previous studies have demonstrated the efficacy of PBMT in promoting deep healing and increasing the proportion of mature collagen, thereby aiding in the prevention of OM [11]. However, it should be noted that PBMT parameters and protocols vary significantly across studies [5,

9, 17]. In this sense, the present study aimed to evaluate the clinical effects of intraoral, oropharyngeal, and extraoral irradiation with PBMT in the prevention of OM in an adult population undergoing CT and/or HSCT.

The MASCC/ISOO guidelines have endorsed PBMT as one of the recommended preventive modalities for OM [9, 12]. Authors have identified beneficial effects of wavelengths ranging from 660 nm to 970 nm in the prevention of CT-induced OM in cancer patients [1, 9, 11]. In our study, we selected a red-spectrum wavelength of 660 nm for intraoral irradiation (22 points, 2 J/point), an infrared wavelength of 808 nm for extraoral irradiation (two points, 6 J/point) and an oropharyngeal irradiation with a 10.5cm optic fiber (2 points, 2 J/point). Encouraging results have been found because less than half of the patients developed some degree of OM. All three protocols demonstrated efficacy in preventing and reducing the severity of OM, with good tolerance and no reported toxicity.

According to the results obtained here, in Group 3, the patients had a higher percentage of OM (61.1%), but predominantly in mild grades I and II (33.3% and 11.1%, respectively). To better understand why this group was most affected, we also explored the associated risk factors that may have led to these outcomes. Considering the robust evidence on the effectiveness of PBMT in the treatment of OM in the literature [9], the development and severity of OM can be attributed to multiple factors related to both the treatment and the patient [8]. These factors include the type of antineoplastic treatment [8], CT regimens [18], pre-existing oral conditions [19], patient age [20], and markers of immunity [21]. Hence, a higher OM rate in Group 3 can be attributed to several factors. First, half of the population in this group underwent HSCT and also had the highest percentage of regimen with melphalan, a chemotherapeutic agent well known for its mucotoxicity [22]. Furthermore, individuals in Group 3 exhibited the lowest mean leukocyte count, indicating an impaired immune system, which may further contribute to the development and severity of OM [23].

Patient-related risk factors for OM have been a matter of debate in recent years, and a possible relationship between age and female sex and the development and severity of OM has been suggested [8, 20]. Younger cancer patients are considered to be more susceptible to the occurrence of CT-induced OM due to factors, such as faster cell turnover rate, higher number of growth factor receptors in the epithelium, and faster epithelial mitotic rate [24]. These factors may contribute to the greater vulnerability of young individuals to the toxic effects of antineoplastic therapy [25]. Among patients who developed OM, a slightly higher incidence (43.3%) was observed in younger individuals, although no significant differences were found in the severity of the lesions. These findings are in line with those reported in the study of Shouval et al. [26], with a heterogeneous cohort, encompassing individuals who had received different antineoplastic regimens.

Patients undergoing HSCT are significantly more prone to develop adverse effects, including those affecting the oral cavity. This increased susceptibility can be attributed not only to the conditioning regimen administered prior to transplantation, but also to the slow immune recovery experienced afterwards [1]. It has been documented that 70% to 86.8% of patients undergoing HSCT experience these adverse effects [27]. In the current study, 78% of HSCT patients had OM, but in lower grades. We can consider that these findings demonstrate that PBMT is effective in reducing the severity of OM, which is consistent with the findings of studies published elsewhere [1, 9]. In addition, severe OM was observed more frequently in the allogenic transplantation group as previously reported [10], and the severity of OM among patients undergoing HSCT was 2.80 times higher than among individuals not submitted to HSCT. Nevertheless, it is important to note that all patients in the allogeneic group received GVHD prophylaxis with standard-dose of MTX, which also appears to be a risk factor for OM [27].

The onset and severity of mucosal injury vary depending on the type of CT [8, 18], and each chemotherapeutic agent has its own degree of mucotoxicity [28]. Since different CT agents were used in the oncology/HSCT setting, we chose to calculate the mean use of mucotoxic agents for each individual. As result, a higher mean of mucotoxic chemotherapy combinations was observed in in individuals Group 2, among whom 36.4% exhibited OM. Consistently, chemotherapeutic agents highly associated with the development/severity of OM have been described, including cytarabine, high-dose 5-fluorouracil (5-FU), melphalan, alkylating and antimetabolite compounds [8, 18]. The most used chemotherapeutic agent in this study was cytarabine (43.3%), followed by daunorubicin (26.7%), melphalan (21.7%), and MTX (20%). Moreover, individuals who had received cytarabine, busulfan, and melphalan exhibited a higher occurrence of OM compared to those who had not received these chemotherapeutic agents.

A linear relationship between the occurrence of OM, the systemic granulocyte count, and the resolution of OM with recovery of neutrophil has been described [29]. Furthermore, a decrease in leukocyte count may be associated with exacerbation of inflammatory disorders [1, 30] and a significantly higher rate of OM in patients undergoing CT can be attributed to severe myelosuppression [23]. The research results demonstrate a substantial decline in leukocytes and neutrophils between the period of D+3 and D+10, which coincides with the peak appearance of OM lesions, as previously described [1, 30, 31]. Moreover, the group that exhibited the most severe OM lesions also demonstrated the lowest number of neutrophils, and among all individuals, 27% experienced febrile neutropenia.

Correlations between OM and other oral infections have been explored, particularly in the context of myelosuppression and inflammation. Former studies have highlighted the significant role played by the disruption of mucosal barriers, which allows for the entry of endogenous oral flora and viral pathogens [6, 32]. Chen et al. [32] provided compelling evidence that, alongside clinical signs of infections commonly observed in patients undergoing CT, *Candida spp*. and HSV-1 are major contributors to the development of OM. Our data further support these findings, revealing that among patients diagnosed with candidiasis, 57.1% also presented themselves with some degree of OM. Additionally, within the subgroup of patients who underwent HSCT, a recognized high-risk population for infection development [33], approximately one-third (33.3%) experienced fungal infection or co-infection with HSV-1.

The present study features a differentiating aspect regarding the implementation of three distinct PBMT protocols, two of which involve combinations of different laser therapy techniques. It is worth mentioning that the majority of previous studies on OM prevention have primarily focused on intraoral techniques, occasionally incorporating extraoral techniques as well [1, 10, 11, 13]. Interestingly, these two PBMT techniques have already been associated with a reduction of OM severity and augmented biostimulation [10]. Recognizing the challenges associated with accessing the oropharynx using the established techniques, an optical fiber was developed with the purpose of delivering energy to this region, which is typically heavily affected and consequently impairs eating and swallowing. Our findings demonstrate that all groups, regardless of whether they underwent daily irradiation with the optical fiber or not, experienced a frequency of OM below to what is conventionally reported in the literature [1, 10, 13]. Of note, the incidence of odynophagia was observed to be less than 28% in both groups with oropharynx irradiation.

A notable strength of this study relies on its comprehensive description of the implemented protocols and PBMT parameters, facilitating reproducibility. We have proposed an alternative protocol that encompasses the oropharynx, emphasizing the necessity for additional investigations in this domain. Besides, it is essential to acknowledge the limitations posed by the small sample size and the heterogeneity of the chemotherapeutic agents utilized.

Conclusions

In summary, due to the reduction in the occurrence and/or severity of OM through the implementation of the PBMT proposed protocols, patients experienced fewer episodes of oral pain and odynophagia, subsequently leading to a diminished reliance on parenteral nutrition. Our findings support the use of PBMT as a secure and

effective approach for preventing OM in adults undergoing CT/HSCT. The outcomes of this study hold significance for health institutions, given the prominence of oncology patients as a crucial target population in contemporary healthcare.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical Approval: The study was approved by the Ethics Committee of Universidade Federal de Minas Gerais (No. 5904127).

Informed consent: Consent was obtained from all participants.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figures 4a, 4b, 4c and 4d.

Figures legends

Figure 1. Flowchart depicting sample data and participants allocation.

Figure 2. Laser devices used in patients. On the left, optic fiber attached to the laser device used for mucositis prevention in the oropharynx. The device on the right is utilized for both intraoral and extraoral irradiation.

Figure 3. Predefined points used in photobiomodulation therapy (PBMT) prophylaxis protocols. **(A)** Intraoral prophylactic PBMT points. **(B)** Intraoral and oropharyngeal prophylactic PBMT points. **(C)** Extra-oral prophylactic PBMT points located in the region below the mandibular angle.

Figure 4. Examples of oral mucositis (OM) observed among study patients. (A) OM grade I. (B) OM grade II. (C) OM grade III. (D) OM on the soft palate toward the oropharynx.

Figure 5. Mean values of neutrophils and leukocytes at different hospitalization time points (D0, D+3, D+10, and D+15).

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Table 1. Device information, irradiation and preventive parameters

Manufacturer	DMC, São Carlos, SP, Brazil	DMC, São Carlos, SP, Brazil	DMC, São Carlos, SP, Brazil
Preventive protocols	***Intraoral PBMT***	***Extraoral PBMT***	***Oropharyngeal PBMT***
Device information	Therapy XT	Therapy XT	Therapy Sinus Plus
Model identifier	Therapy XT	Therapy XT	Therapy Sinus Plus
Number of emitters	Two	Two	One
Emitter type	InGaAs	InGaAs	InGaAs
Beam delivery system	Fiberoptic	Fiberoptic	Fiberoptic
Irradiation parameters			
Centre wavelength (nm)	660	808	638
Spectral bandwidth (nm)	660±10	808±10	638±5
Operating mode	Continuous wave	Continuous wave	Continuous wave
Radiant power (W)	100mW	100mW	200mW
Beam profile	Gaussian	Gaussian	Gaussian
Treatment parameters			
Beam spot size at target (cm^2)	0.028	0.028	0.0078
Irradiance at target (W/cm^2)	3.57	3.57	25.64
Average exposure duration (s)	20	60	10
Radiant exposure (J/cm^2)	71.42	214.28	512.82
Radiant energy (J)	2	6	4
Number of points irradiated	22	2	2
Application technique	Contact	Contact	Distance
Number and frequency of prophylactic sessions	Six sessions weekly (Monday–Saturday) 1–10 days	Six sessions weekly (Monday–Saturday) 1–10 days	Six sessions weekly (Monday–Saturday) 1–10 days

Note: InGaAs, Indium-Gallium-Arsenide; J, joule; cm^2; nm, nanometers; s, second;square centimeters; W, watts.

Table 2. Comparison of age, amount of mucotoxic chemotherapy (CT) agents, lower neutrophil, and leukocyte counts among the photobiomodulation therapy (PBMT) groups

Variables	**PBMT groups**			***p* value**
	Group 1: n=20 (%)	***Group 2: n=22 (%)***	***Group 3: n=18 (%)***	
Age (median, range, mean, and SD)	49 (20–74); 46.75 ± 15.29[a]	31.5 (18–70); 37.95 ± 17.2[a]	54 (25–66); 49 ± 14.2[a]	0.058
Amount of mucotoxic CT agents	2 (1–4); 1.64 ± 0.75[a]	2 (1–4); 2.34 ± 1.0[b]	2 (1–4); 1.74 ± 0.9[a,b]	**0.043**
Lower neutrophil count (median, range, mean, and SD)	0.1 (0–3.1); 0.4 ± 0.9[a]	0.08 (0–5); 0.9 ± 1.5[a]	0.005 (0–1.8); 0.2 ± 0.5[a]	0.180
Lower leukocyte count (median, range, mean, and SD)	0.25 (0–4.6); 0.8 ± 1.5[a]	0.3 (0–7.4); 1.4 ± 2[a]	0.3 (0–2); 0.5 ± 0.6[a]	0.784

Note: SD, standard deviation.

[a,b]Different superscript letters indicate difference between groups.

[*]Chi-square test. Bold means statistically significant at $p<0.0$

Table 3. Distribution of the clinicodemographic data of patients undergoing chemotherapy or HSCT across the photobiomodulation therapy (PBMT) groups

Variables	PBMT groups			*p* value*
	Group 1: n=20 (%)	*Group 2: n=22 (%)*	*Group 3: n=18 (%)*	
Sex				
Male	7 (35.0)[a]	13 (59.1)[a]	10 (55.6)[a]	0.293
Female	13 (65.0)[a]	9 (40.9)[a]	8 (44.4)[a]	
HSCT				
Non-HSCT	17 (85.0)[a]	17 (77.3)[a,b]	8 (44.4)[b]	
Autologous HSCT	3 (15.0)[a,b]	3 (13.6)[b]	9 (50)[a]	**0.015**
Allogeneic HSCT	0[a]	2 (9.1)[a]	1(5.6)[a]	
Baseline disease				
Leukemias	11 (55.0)[a]	14 (63.6)[a]	9 (50)[a]	
Lymphomas	4 (20.0)[a]	3 (13.6)[a]	4 (22.2)[a]	0.85
Other hematological diseases	5 (25.0)[a]	5 (22.7)[a]	5 (27.8)[a]	
OM				
Yes	6 (30.0)[a]	8 (36.4)[a]	12 (61.1)[a]	**0.032**
No	14 (70.0)[a]	14 (63.6)[a]	6 (33.3)[a]	
Grade OM				
I	2 (10.0)[a]	4 (18.2)[a]	6 (33.3)[a]	
II	2 (10.0)[a]	3 (13.6)[a]	2 (11.1)[a]	**0.048**
III	2 (10.0)[a]	0[a]	4 (22.2)	
IV	0[a]	1 (4.5)[a]	0[a]	
Anatomical location**				
Buccal mucosa	5 (25.0)[a]	2 (9.1)[a]	5 (27.8)[a]	
Labial mucosa	3 (15.0)[a]	2 (9.1)[a]	3 (16.7)[a]	
Lip	1 (5.0)[a]	0[a]	1 (5.6)[a]	
Floor of the mouth	2 (10.0)[a]	4 (18.2)[a]	3 (16.7)[a]	0.920
Dorsal tongue	1 (5.0)[a]	0[a]	0[a]	
Ventral tongue	1 (5.0)[a]	1 (4.5)[a]	0[a]	
Lateral border of the tongue	1 (5.0)[a]	2 (9.1)[a]	4 (22.2)[a]	

Retromolar trigone	0[a]	1 (4.5)[a]	2 (11.1)[a]	
Vestibule	0[a]	1 (4.5)[a]	1(5.6)[a]	
Hard/soft Palate	1 (5.0)[a]	3 (13.6)[a,b]	8 (44.4)[b]	
Oropharynx	1 (5.0)[a]	2 (9.1)[a]	1 (5.6)[a]	
Odynophagia				
Yes	4 (20.0)[a]	5 (22.7)[a]	5 (27.8)[a]	0.705
No	16 (80.0)[a]	17 (77.3)[a]	13 (72.2)[a]	
Oral candidiasis				
Yes	6 (30.0)[a]	7 (31.8)[a]	1 (5.6)[a]	0.09
No	14 (70.0)[a]	15 (68.2)[a]	17 (94.4)[a]	
Febrile neutropenia				
Yes	7(35.0)[a]	4 (18.2)[a]	5 (27.8)[a]	0.717
No	13(65.0)[a]	18 (81.8)[a]	13 (72.2)[a]	

Table 4. Multivariate analysis evaluating the association between the onset of oral and oropharyngeal mucositis and the variables hematopoietic stem-cell transplantation (HSCT), age, mean number of mucotoxic chemotherapy (CT) agents, and lower neutrophil count

Variables	**Oral and oropharyngeal mucositis**		
	OR	**95% CI**	***p* value**
HSCT			
Non-HSCT	1		
Autologous HSCT	1.59	1.24-2.06	**<0.001**
Allogeneic HSCT	1.93	1.58–2.36	**<0.001**
Age	0.99	0.98–1.01	0.879
Mean number of mucotoxic CT agents	1.01	0.87–1.15	0.893
Lower neutrophil count	0.99	0.90–1.11	0.711

Note: CI, confidence interval; OR, odds ratio. Bold means statistically significant at $p<0.05$

Supplementary Table 1. Distribution of chemotherapeutic agents used in patients undergoing chemotherapy or HSCT across the photobiomodulation therapy (PBMT) groups

Chemotherapy agents	**PBMT groups**			***p* value***
	Group 1: n=20 (%)	***Group 2: n=22 (%)***	***Group 3: n=18 (%)***	
Methotrexate	4 (20.0)[a]	5 (22.7)[a]	4 (22.2)[a]	1.000
Cytarabine	10 (50.0)[a]	10 (45.5)[a]	6 (33.3)[a]	0.333
Daunorubicin	7 (35.0)[a]	6 (27.3)[a]	3 (16.7)[a]	0.275
Thioguanine	0	3 (13.6)[a]	1 (5.6)[a]	0.540
Cyclophosphamide	2 (10.0)[a]	6 (27.3)[a]	2 (11.1)[a]	1.000
Busulfan	0	3 (13.6)[a]	3 (16.7)[a]	0.109
Fludarabine	1 (5.0)[a]	3 (13.6)[a]	1 (5.6)[a]	1.000
Melphalan	2 (10.0)[a]	2 (9.1)[a]	9 (52)[b]	**0.005**
Vincristine	5 (25.0)[a]	6 (27.3)[a]	1 (5.6)[a]	0.164
Doxorubicin	1 (5.0)[a]	3 (13.6)[a]	0[a]	0.755
Etoposide	3 (15.0)[a]	1 (4.5)[a]	0[a]	0.104
Mitoxantrone	1 (5.0)[a]	2 (9.1)[a]	0[a]	0.724
Rituximab	1 (5.0)[a]	0[a]	0[a]	0.633
Ifosfamide	0[a]	1 (4.5)[a]	0[a]	1.000
Cisplatin	2 (10.0)[a]	1 (4.5)[a]	0[a]	0.278
Carboplatin	1 (5.0)[a]	0[a]	0[a]	0.633
Vinorelbine	0 (0.0)[a]	1 (4.5)[a]	0[a]	1.000
Gemcitabine	0[a]	1 (4.5)[a]	0[a]	1.000
Bortezomib	0[a]	2 (9.1)[a]	0[a]	1.000
Imatinib	0[a]	0[a]	1 (5.6)[a]	0.300
Sorafenib	0[a]	0[a]	1 (5.6)[a]	0.300
Dasatinib	0[a]	0[a]	1 (5.6)[a]	0.300
MADIT	3 (15.0)[a]	5 (22.7)[a]	2 (11.1)[a]	0.832

Note: HSCT, hematopoietic stem-cell transplantation; OM, oral mucositis.

[a,b]Different superscript letters indicate difference between groups.

*Chi-square test. Bold means statistically significant at $p<0.05$.

Supplementary Table 2. Clinicodemographic data, diagnosis, treatment, and outcome of the evaluated sample (n=60)

Variables	n (%)
Sex	
Male	30 (50.0)
Female	30 (50.0)
Age (years), mean ± SD, range	44.2 ± 16.2 (18–74)
Disease group	
Non-HSCT	42 (70.0)
HSCT	18 (30.0)
Baseline disease	
Myeloid leukemia	18 (30.0)
Lymphoid leukemia	16 (26.7)
Multiple myeloma	10 (16.7)
Non-Hodgkin lymphoma	9 (15.0)
Hodgkin's lymphoma	2 (3.3)
Other hematological diseases	5 (8.3)
Treatment	
Chemotherapy (solely)	42 (70.0)
Autologous HSCT	15 (25.0)
Allogenic HSCT	3 (5.0)
Oral mucositis	
Yes	26 (43.3)
No	34 (56.7)
Grade OM	
Grade I-II	19 (31.7)
Grade III-IV	7 (11.7)
Odynophagia	
Yes	14 (23.3)
No	46 (76.7)
Oral candidiasis	
Yes	14 (23.3)
No	46 (76.7)
Febrile neutropenia	
Yes	16 (26.7)
No	44 (73.3)
Outcome	
Alive with disease	41 (68.3)

Died	19 (31.7)

Note: HSCT, hematopoietic stem cell transplantation; SD standard deviation; OM oral mucositis.

Supplementary Table 3. Data on the systemic conditions data of the evaluated sample (n=60)

Variables	**n (%)**
Cardiovascular system	
No	46 (76.7)
Yes	14 (23.3)
Endocrine system	
No	47 (78.4)
Yes	13 (21.6)
Neurologic/psychiatric conditions	
No	56 (94.4)
Yes	4 (6.6)
Gastrointestinal system	
No	55 (91.7)
Yes	5 (8.3)
Rheumatologic conditions	
No	57 (95.0)
Yes	3 (5.0)
Pulmonary system	
No	59 (98.4)
Yes	1 (1.66)
Hemoglobinopathy	
No	59 (98.4)
Yes	1 (1.6)
Others	
No	54 (90.0)
Yes	6 (10)

Note: *Cardiovascular system:* arterial hypertension; coronary artery disease.

Endocrine system: hypothyroidism; diabetes mellitus; obesity, dyslipidemia; hypercholesterolemia.
Pulmonary system: bronchitis; chronic obstructive pulmonary disease.
Gastrointestinal system: irritable bowel syndrome; colonic diverticular; gastroesophageal reflux disease; cholelithiasis, hepatic steatosis.
Neurologic/psychiatric conditions: anxiety/depression; epilepsy.
Rheumatologic conditions: arthritis; fibromyalgia; lupus.
Others: osteonecrosis, polycystic ovary syndrome; nephrolithiasis; hepatitis B.

Supplementary Table 4. Multivariate analysis evaluating the association between the severity of oral and oropharyngeal mucositis and hematopoietic stem-cell transplantation (HSCT), oral candidiasis, age, mean of mucotoxic chemotherapy (CT) agents, and lower neutrophil count

Variables	Oral and oropharyngeal mucositis		
	OR	**95% CI**	***p* value***
HSCT			
Non-HSCT	1		
HSCT	2.80	1.44–5.74	**0.003**
Oral candidiasis			
No	1		
Yes	1.6	0.72–3.78	0.227
Age	0.99	0.99–1.02	0.278
Mean of mucotoxic CT agents	1.03	0.75–1.40	0.845
Lower neutrophil count	0.99	0.81–1.22	0.984

Note: CI, confidence interval; OR, odds ratio. Bold means statistically significant at $p<0.05$.

Figure 1. Flowchart depicting sample data and participants allocation.

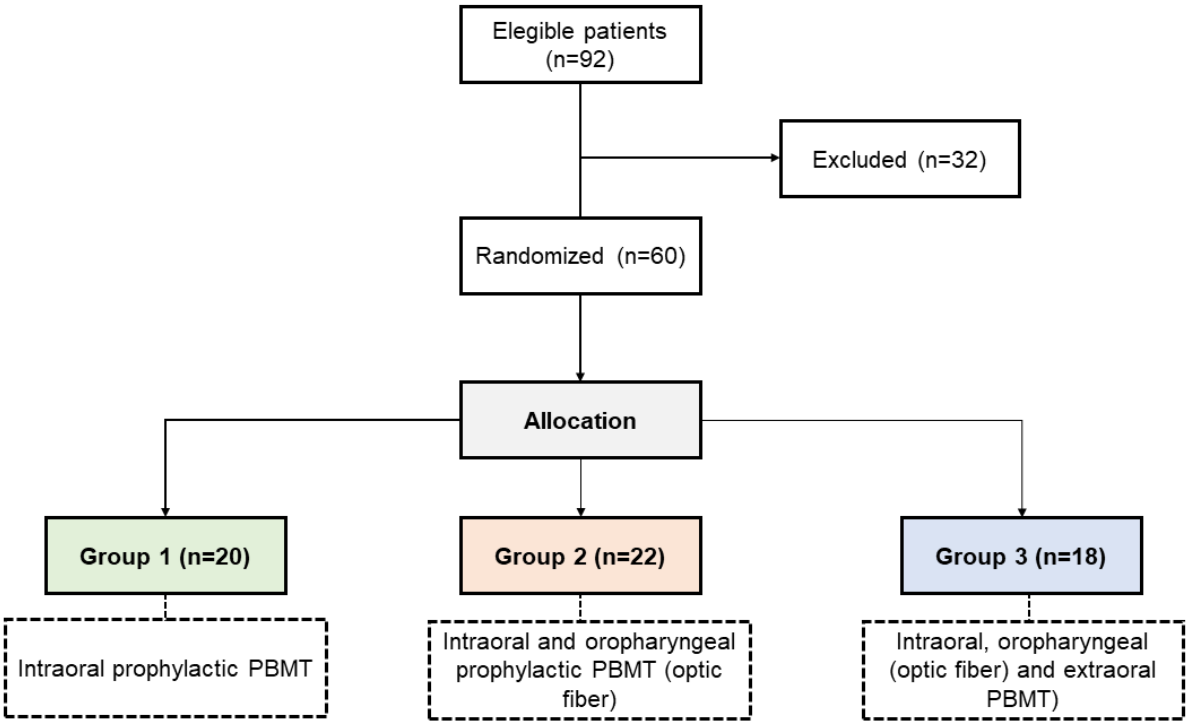


Figure 2. Laser devices used in patients. On the left, optic fiber attached to the laser device used for mucositis prevention in the oropharynx. The device on the right is utilized for both intraoral and extraoral irradiation.

Figure 3. Predefined points used in photobiomodulation therapy (PBMT) prophylaxis protocols. **(A)** Intraoral prophylactic PBMT points. **(B)** Intraoral and oropharyngeal prophylactic PBMT points. **(C)** Extra-oral prophylactic PBMT points located in the region below the mandibular angle.

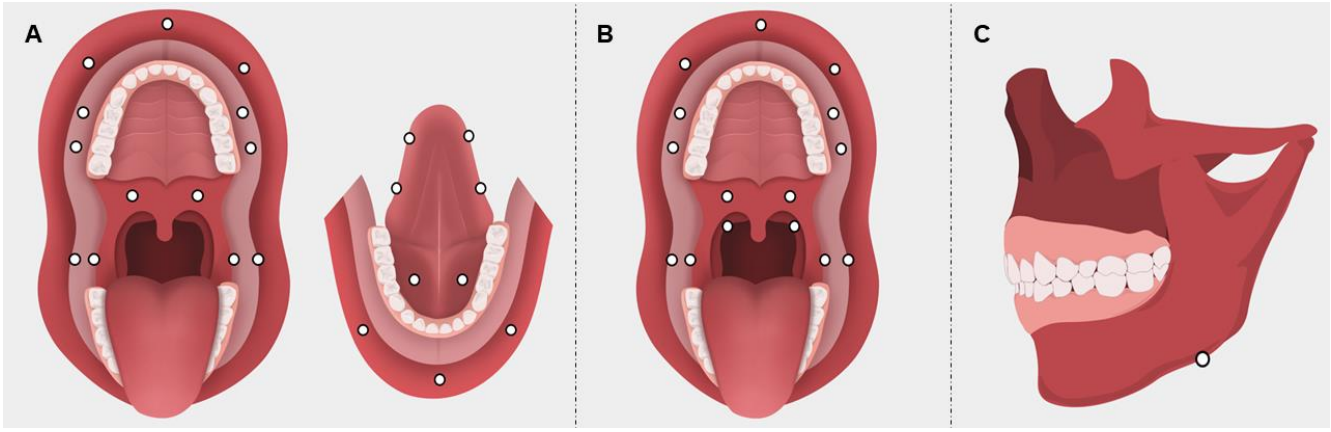


Figure 4. Examples of oral mucositis (OM) observed among study patients. (A) OM grade I. (B) OM grade II. (C) OM grade III. (D) OM on the soft palate toward the oropharynx.

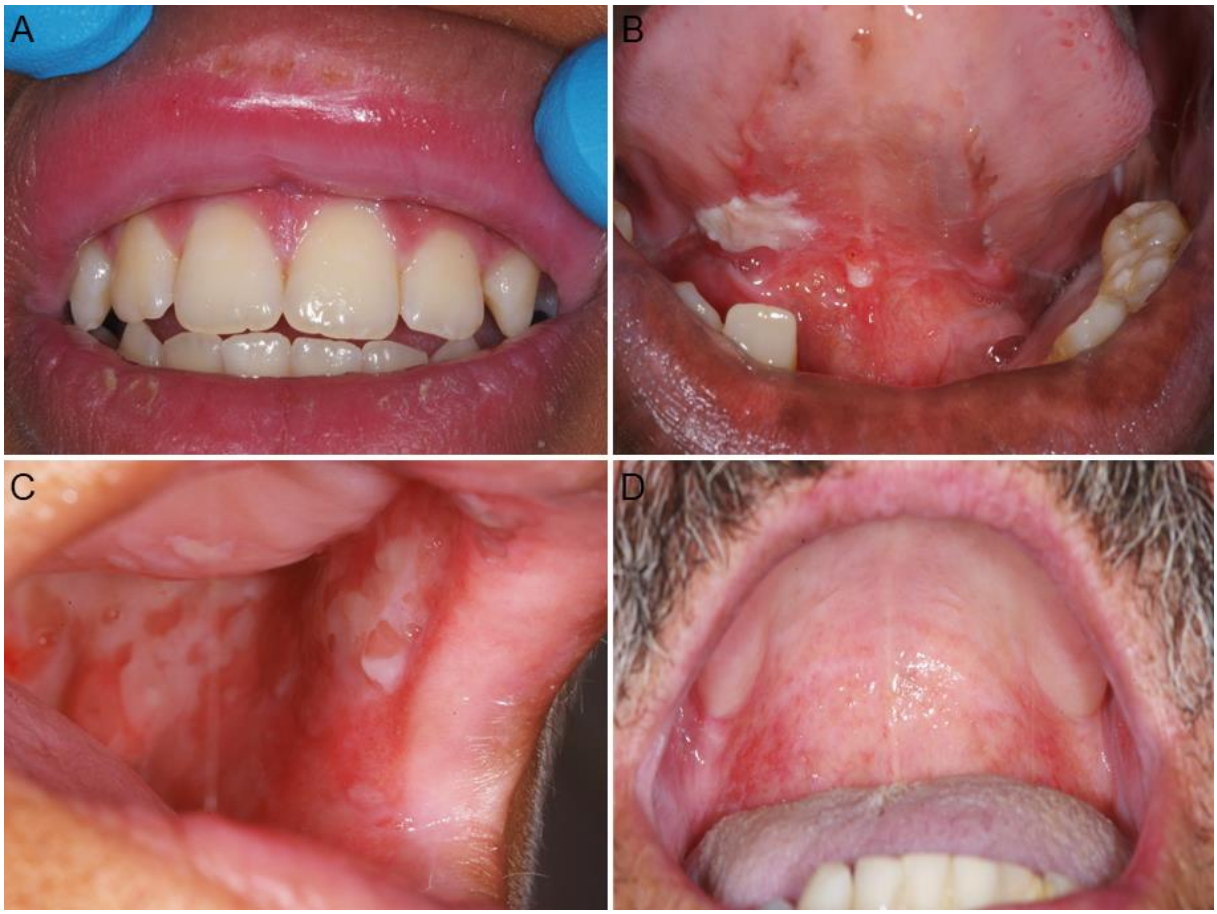
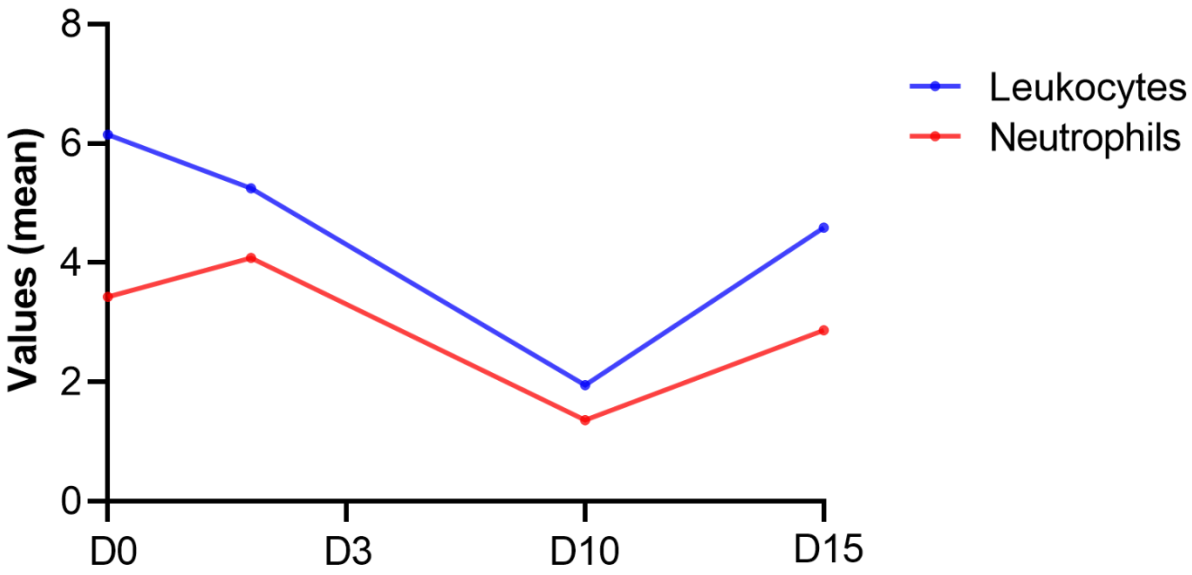


Figure 5. Mean values of neutrophils and leukocytes at different hospitalization time points (D0, D+3, D+10, and D+15)



5 CONSIDERAÇÕES FINAIS

Neste estudo clínico randomizado, constatamos que todos os protocolos propostos de TFBM demonstraram reduzir a incidência e/ou gravidade da MO, resultando em menos episódios de dor oral e odinofagia nos pacientes e, consequentemente, diminuindo a dependência da nutrição parenteral. Nossos resultados respaldam o uso do TFBM como uma abordagem segura e eficaz para a prevenção da MO em adultos submetidos a tratamentos de QT e TCTH. Ademais, os achados deste estudo são relevantes para as instituições de saúde, dada a importância dos pacientes oncológicos como uma população-alvo essencial nos cuidados de saúde contemporâneos.

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ANEXO A - APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: TERAPIA DE FOTOBIOMODULAÇÃO NA MUCOSITE ORAL E OROFARÍNGEA EM ADULTOS: ASPECTOS CLÍNICOS, BIOQUÍMICOS, INFLAMATÓRIOS, MICROBIOLÓGICOS E AVALIAÇÃO DA QUALIDADE DE VIDA.

Pesquisador: Ricardo Alves de Mesquita

Área Temática:

Versão: 1

CAAE: 64244422.9.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.904.127

Apresentação do Projeto:

4.2 A proposta envolve ensaio clínico randomizado para avaliar os efeitos clínicos, bioquímicos, inflamatórios e microbiológicos da terapia de fotobiomodulação (TFBM) no tratamento da mucosite oral e/ou orofaríngea (MOO) induzida por quimioterápicos e pelo transplante de células tronco hematopoéticas (TCTH) em pacientes adultos. Adicionalmente, o impacto da magnitude da MOO na qualidade de vida dessa população bem como da TFBM no tratamento das lesões será avaliado por meio de três instrumentos: Oral Health Impact Profile (OHIP-14), The World Health Organization Quality of Life (WHOQOL-bref) e Hospital Anxiety and Depression Scale (HADS). No período de maio de 2022 a maio de 2023, 78 pacientes adultos de ambos os sexos em tratamento quimioterápico no serviço de Oncologia do Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG), serão aleatoriamente divididos em três grupos (n=26): (1) grupo que receberá TFBM profilática intraoral a partir do primeiro dia de QT; (2) grupo que receberá TFBM profilática intraoral e em orofaringe; e (3) grupo que receberá TFBM profilática intraoral incluindo orofaringe e extraoral. Os parâmetros clínicos e inflamatórios serão avaliados por meio da investigação de citocinas inflamatórias e redes extracelulares de neutrófilos (NET) e de eosinófilos (EET) na saliva. Também será realizado isolamento e identificação de Candida spp. em amostras de saliva. Raspados da mucosa oral serão utilizados para investigação de infecção pelos vírus do herpes simples (HSV-1) e citomegalovírus (CMV). As comparações serão feitas entre os grupos com base

nos desfechos clínicos, inflamatórios e microbiológicos propostos, bem como no impacto na qualidade de vida desses indivíduos. A hipótese do estudo é que a TFBM aplicada nos grupos que utilizarão o dispositivo intraoral, na orofaringe e extraoral será mais eficaz na prevenção da MOO e no desfecho do impacto de uma melhor qualidade de vida desses indivíduos. De maneira geral, os dados podem contribuir com medidas preventivas, tratamento e redução de comorbidades em pacientes com MOO induzida por QT, bem como elucidar os mecanismos da doença, impacto na qualidade de vida e medidas adjuvantes de proteção. O pesquisador indica que serão coletadas informações sobre sexo, idade, doença de base e protocolo quimioterápico utilizado. Todos os pacientes terão um prontuário clínico individual para registro clínico e acompanhamento no momento inicial (D0) e ao final do tratamento com TFBM (D+). As informações sobre a localização anatômica da(s) lesão(es) de MOO serão consideradas da seguinte forma: lábios, mucosa labial, comissura labial, mucosa jugal, vestíbulo, soalho da boca, língua (borda lateral, dorso e ventre), trígono retromolar, palato e orofaringe. A localização anatômica não será analisada em termos do número de pacientes, mas sim em termos do número de lesões apresentadas, ou seja, o mesmo paciente pode ser acometido em mais de um sítio anatômico. A severidade da MOO será graduada de acordo com a escala da OMS (1979), que considera: grau 0 – ausência de mucosite; grau 1 – presença de eritema sem lesões; grau 2 – mucosa ulcerada, mas o paciente se alimenta normalmente com alimentos sólidos e/ou semissólidos; grau 3 – presença de úlceras, dor intensa e alimentação líquida; e grau 4 – paciente requer dieta parenteral e suporte contínuo de analgésicos (WHO, 1979). Detalhes sobre os desfechos dos participantes, ou seja, vivos com doença, sobrevivência livre de doença ou morte, também serão coletados. A pesquisadora anexou os formulários para coleta desses dados no projeto. Não haverá retenção de amostras para armazenamento em bancos.

Serão considerados os seguintes critérios de inclusão para os participantes: Adultos, maiores de 18 anos de ambos os sexos, segundo os critérios de admissão do HC-UFMG (NUNES et al., 2020); Indivíduos sob regime quimioterápico (QUADRO 1) e Indivíduos submetidos a transplante de células-tronco hematopoiéticas (autólogo e alogênico); Indivíduos com a capacidade de cooperar com o tratamento e disponibilidade para colaborar voluntariamente com a pesquisa. Por sua vez os critérios de exclusão são: Pacientes crianças ou adolescentes (0-17 anos); Pacientes que apresentarem neoplasias de glândulas salivares ou síndrome de Sjögren ou doenças crônicas com comprometimento salivar, programados a receber outro tipo de terapia antineoplásica (ex., RT ou QT/RT); Indivíduos em terapia antibiótica profilática; Indivíduos que não conseguirem completar quatro consultas regulares para coleta de dados.

Objetivo da Pesquisa:

Objetivo Primário: Investigar os efeitos clínicos, inflamatórios, bioquímicos e microbiológicos frente a utilização da terapia de fotobiomodulação (TFBM) no tratamento da mucosite oral e/ou orofaríngea (MOO) induzida por quimioterápicos e pelo transplante de células tronco hematopoéticas (TCTH) em pacientes adultos; o impacto na qualidade de vida desses pacientes sobre a magnitude da MOO e da TFBM no tratamento das lesões de MOO.

Objetivo Secundário:

- Avaliar comparativamente o efeito clínico e os parâmetros bioquímicos em diferentes protocolos da TFBM na MOO induzida por quimioterápicos e TCTH, por meio de dados bioquímicos e escores clínicos.

-Avaliar o impacto na qualidade de vida dos pacientes adultos meio da percepção dos próprios pacientes sobre a magnitude da MOO, bem como da TFBM no tratamento das lesões por meio de questionários.

- Avaliar a concentração de citocinas inflamatórias e pró-inflamatórias na saliva por meio de Ensaio de Imunoabsorção Enzimática (ELISA) nos indivíduos com MOO induzida por quimioterápicos e tratados com diferentes protocolos de TFBM.

- Investigar o papel da NET e EET na MOO induzida por quimioterápicos e TCTH, tratados com diferentes protocolos de TFBM, através de quantificações na saliva.

- Isolar e identificar possível presença de Candida spp. em amostras de saliva nos indivíduos com MOO induzida por quimioterápicos/TCTH e tratados com diferentes protocolos de TFBM.

- Investigar e correlacionar infecções virais, em raspados de mucosa oral dos pacientes em QT e TCTH, tratados com diferentes formas de TFBM.

Avaliação dos Riscos e Benefícios:

O pesquisador informa que possíveis riscos da pesquisa são aqueles considerados mínimos, não acarretando danos físicos ou mentais. Os exames clínicos, coleta de amostra e tratamento podem gerar desconforto mínimo. E estão indicados no TCLE (1. Desconforto, como dor, durante a manipulação da boca quando da aplicação do LASER. A forma de minimizá-lo será o manuseio com muito cuidado da boca; 2. Desconforto quando aplicado o LASER em áreas escurecidas (manhas melânicas, tatuagem por amálgama). A forma de evitá-lo será a não aplicação do LASER nestas áreas;

3. Risco de incidência ocular (olho) do feixe de LASER. A forma de evitá-lo serão o direcionamento correto do feixe de LASER para a boca e o uso de óculos adequado ao comprimento de onda e

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Plataforma Brasil

Intensidade de energia pelo paciente; 4. Risco de incidência do feixe de LASER na área da tireoide. A forma de evitá-lo será o direcionamento correto do feixe de LASER para a boca, evitando a região da tireoide; 5. Ao responder os questionários, você poderá se sentir desconfortável com algumas questões que podem lhe trazer lembranças ruins, se isso acontecer, você poderá pausar o preenchimento, não responder a questão ou desistir da participação, sem qualquer penalidade.

Benefícios: A proposta é fundamental para o conhecimento da MOO e TFBM, trazendo assim novas estratégias para controle da MOO. Os dados poderão ser aplicados ao SUS pelo desenvolvimento e implementação de ações efetivas, integradas, sustentáveis e baseadas em evidências. Também, resultará na formação de recursos humanos (residentes e alunos de pós-graduação), com repercussão para qualificação de profissionais de saúde envolvidos na atenção ao paciente. Também proverá ainda mais a experiência da equipe em publicações em conjunto e o fortalecimento do HCUFMG e da FAO-UFMG.

Comentários e Considerações sobre a Pesquisa:

O projeto é de grande relevância dientifica e clinica com potencial pra gerar publicação em periódicos de alto fator impacto, além de gerar protocolos clínicos para a prevenção e tratamento da mucosite oral e/ou orofaríngea (MOO) induzida por quimioterápicos e pelo transplante de células tronco hematopoéticas (TCTH) como relatado pela parecerista da Faculdade de odontologia da UFMG.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados:

-Informações básicas do projeto.

-Folha de rosto assinada

-Projeto detalhado (brochura do investigador)

- TCLE

-Parecer aprovado a referendum pelo Coordenador do Programa de Pós graduação em Odontologia da faculdade de Odontologia da UFMG e pelo Chefe do Departamento de Clínica, Patologia e Cirurgia Odontológicas.

-Carta Resposta ao CEP.

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Continuação do Parecer: 5.904.127

Recomendações:

Alterar a data de execução da pesquisa, que indica que o estudo envolverá 78 pacientes adultos de ambos os sexos em tratamento quimioterápico no serviço de Oncologia do Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG), período de maio de 2022 a maio de 2023.

Conclusões ou Pendências e Lista de Inadequações:

Alterar a data de execução da pesquisa, que indica que o estudo envolverá 78 pacientes adultos de ambos os sexos em tratamento quimioterápico no serviço de Oncologia do Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG), período de maio de 2022 a maio de 2023.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1951874.pdf	14/10/2022 16:10:45		Aceito
Outros	2022MucositeLaserFernadaCartaRespostaaoCEP.docx	14/10/2022 16:10:26	Ricardo Alves de Mesquita	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	2022TermoLivreEsclarecidoMestradoFernandaVieiraHelmlichAjustado.docx	14/10/2022 16:09:41	Ricardo Alves de Mesquita	Aceito
Declaração de Instituição e Infraestrutura	CPCCPGOParecerFERNANDAVIEIRAHELMLICH.pdf	14/10/2022 16:07:24	Ricardo Alves de Mesquita	Aceito
Projeto Detalhado / Brochura Investigador	2022ProjetoMestradoFernandaVieiraHelmlichHC.docx	25/08/2022 17:15:35	Ricardo Alves de Mesquita	Aceito
Folha de Rosto	2022FolhadeRostoCEPFernandaVieiraHelmlich.pdf	25/08/2022 16:58:02	Ricardo Alves de Mesquita	Aceito

Endereço: Av. Presidente Antonio Carlos, 6627 2º. Andar Sala 2005 Campus Pampulha
Bairro: Unidade Administrativa II CEP: 31.270-901
UF: MG Município: BELO HORIZONTE
Telefone: (31)3409-4592 E-mail: coep@prpq.ufmg.br

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BELO HORIZONTE, 20 de Fevereiro de 2023

Assinado por:
Corinne Davis Rodrigues
(Coordenador(a))

Endereço: Av. Presidente Antonio Carlos, 6627 2º. Andar Sala 2005 Campus Pampulha
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

ANEXO B- Normas da revista onde o artigo foi submetido

Lasers in Medical Science
ISSN on-line: 1435-604X
Qualis: A2
Fator de Impacto: 2.555

Normas da revista:

A Lasers in Medical Science publica artigos sobre as aplicações médicas e odontológicas de novas tecnologias LASER, sistemas de fornecimento de luz, sensores para monitorizar os efeitos do laser, interações básicas entre o laser e os tecidos e a modelação das interações entre o laser e os tecidos. Para além das aplicações de laser, a LIMS apresenta artigos relacionados com a utilização de interações entre a luz e os tecidos sem laser.

Editorial Procedure
Double-blind peer review
This journal follows a double-blind reviewing procedure. Authors are therefore requested to submit:

A blinded manuscript without any author names and affiliations in the text or on the title page. Self-identifying citations and references in the article text should be avoided.

A separate title page, containing title, all author names, affiliations, and the contact information of the corresponding author. Any acknowledgements, disclosures, or funding information should also be included on this page.

Title Page
Please make sure your title page contains the following information.

Title: The title should be concise and informative.

Author information

The name(s) of the author(s)
The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
A clear indication and an active e-mail address of the corresponding author
If available, the 16-digit ORCID of the author(s)
If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

Purpose (stating the main purposes and research question)
Methods
Results
Conclusion
For life science journals only (when applicable)
Trial registration number and date of registration for prospectively registered trials
Trial registration number and date of registration followed by “retrospectively registered”, for retrospectively registered trials

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Statements and Declarations

The following statements should be included under the heading "Statements and Declarations" for inclusion in the published paper. Please note that submissions that do not include relevant declarations will be returned as incomplete**.**

Competing Interests: Authors are required to disclose financial or non-financial interests that are directly or indirectly related to the work submitted for publication. Please refer to “Competing Interests and Funding” below for more information on how to complete this section.

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs

Text Formatting

Manuscripts should be submitted in Word.

Use a normal, plain font (e.g., 10-point Times Roman) for text.

Use italics for emphasis.

Use the automatic page numbering function to number the pages.

Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Use the equation editor or MathType for equations.

Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX. We recommend using Springer Nature’s LaTeX template.

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols. Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

Journal article

Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

Article by DOI

Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

Book

South J, Blass B (2001) The future of modern genomics. Blackwell, London

Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

Dissertation

Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see ISSN.org LTWA

Tables

All tables are to be numbered using Arabic numerals.

Tables should always be cited in text in consecutive numerical order.

For each table, please supply a table caption (title) explaining the components of the table.

Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

Supply all figures electronically.

Indicate what graphics program was used to create the artwork.

For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.

Vector graphics containing fonts must have the fonts embedded in the files.

Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

LineArt

Definition: Black and white graphic with no shading.

Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.

All lines should be at least 0.1 mm (0.3 pt) wide.

Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.

Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art

Definition: Photographs, drawings, or paintings with fine shading, etc.

If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.

Halftones should have a minimum resolution of 300 dpi.

Combination Art

Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.

Combination artwork should have a minimum resolution of 600 dpi.

Color Art

Color art is free of charge for online publication.

If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.

If the figures will be printed in black and white, do not refer to color in the captions.

Color illustrations should be submitted as RGB (8 bits per channel)

Figure Lettering

To add lettering, it is best to use Helvetica or Arial (sans serif fonts).

Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

Avoid effects such as shading, outline letters, etc.

Do not include titles or captions within your illustrations.

Figure Numbering

All figures are to be numbered using Arabic numerals.

Figures should always be cited in text in consecutive numerical order.
Figure parts should be denoted by lowercase letters (a, b, c, etc.).
If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

Figure Captions

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

Figures should be submitted within the body of the text. Only if the file size of the manuscript causes problems in uploading it, the large figures should be submitted separately from the text.
When preparing your figures, size figures to fit in the column width.
For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.
For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm**.**

Permissions

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that

Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that all figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)

Any figure lettering has a contrast ratio of at least 4.5:1

Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as Supplementary Information, authors should read the journal’s Research data policy. We encourage research data to be archived in data repositories wherever possible.

Submission

Supply all supplementary material in standard file formats.

Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.

To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

High resolution (streamable quality) videos can be submitted up to a maximum of 25GB; low resolution videos should not be larger than 5GB.

Audio, Video, and Animations

Aspect ratio: 16:9 or 4:3

Maximum file size: 25 GB for high resolution files; 5 GB for low resolution files
Minimum video duration: 1 sec
Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

Text and Presentations

Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
A collection of figures may also be combined in a PDF file.

Spreadsheets

Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

Specialized Formats

Specialized format such as .pdb (chemical), wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting Multiple Files

It is possible to collect multiple files in a .zip or .gz file.

Numbering

If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

Supplementary Information (SI) will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

The manuscript contains a descriptive caption for each supplementary material
Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk).

Ethical Responsibilities of Authors

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation is helped by following the rules of good scientific practice, which include*:

The manuscript should not be submitted to more than one journal for simultaneous consideration.
The submitted work should be original and should not have been published elsewhere in any form or language (partially or in full), unless the new work concerns an expansion of previous work. (Please provide transparency on the re-use of material to avoid the concerns about text-recycling (‘self-plagiarism’).
A single study should not be split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (i.e. ‘salami-slicing/publishing’).

Concurrent or secondary publication is sometimes justifiable, provided certain conditions are met. Examples include: translations or a manuscript that is intended for a different group of readers.

Results should be presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation (including image-based manipulation). Authors should adhere to discipline-specific rules for acquiring, selecting, and processing data.

No data, text, or theories by others are presented as if they were the author's own ('plagiarism'). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks (to indicate words taken from another source) are used for verbatim copying of material, and permissions secured for material that is copyrighted.

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Back to top

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