UNIVERSIDADE FEDERAL DE ALFENAS

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ABORDAGENS TERAPÊUTICAS PARA CICATRIZAÇÃO DO PALATO APÓS A REMOÇÃO DE ENXERTO GENGIVAL

ALFENAS/MG
2023

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Dissertação apresentada à banca como parte dos requisitos para obtenção do título de Mestre em Ciências Odontológicas, pela Universidade Federal de Alfenas - UNIFAL-MG. Área de concentração: Odontologia.

Orientadora: Profa. Dra. Suzane Cristina Pigossi

Co-orientador: Prof. Dr. Guilherme José Pimentel Lopes de Oliveira

ALFENAS/MG
2023

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Biblioteca Central

Oliveira, Jovânia Alves .
Abordagens terapêuticas para cicatrização do palato após a remoção de enxerto gengival / Jovânia Alves Oliveira. - Alfenas, MG, 2023.
186 f. : il. -

Orientador(a): Suzane Cristina Pigossi.
Dissertação (Mestrado em Ciências Odontológicas) - Universidade Federal de Alfenas, Alfenas, MG, 2023.
Bibliografia.

1. Cicatrização. 2. Autoenxerto. 3. Palato. I. Pigossi, Suzane Cristina, orient. II. Título.

Ficha gerada automaticamente com dados fornecidos pelo autor.

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A Presidente da banca examinadora abaixo assina a aprovação da Dissertação apresentada como parte dos requisitos para a obtenção do título de Mestre em Ciências Odontológicas pela Universidade Federal de Alfenas. Área de concentração: Odontologia.

Aprovada em: 28 de julho de 2023.

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Documento assinado eletronicamente por **Suzane Cristina Pigossi**, **Usuário Externo**, em 01/08/2023, às 14:47, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

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Dedico este trabalho aos meus pais, Maria do Carmo e Francisco, minha madrinha, Maria Imaculada, minha irmã, Gabriela e ao meu noivo, Everton, por todo amor, apoio e fé creditados em mim, na busca pelos meus sonhos.

AGRADECIMENTOS

A minha família, que tanto me apoiou, amparou, incentivou e tornou possível a realização dessa conquista. Agradeço imensamente, meus pais, Maria do Carmo e Francisco, minha madrinha, Maria Imaculada, minha tia, Maria Lúcia, minha irmã, Gabriela e meu cunhado, Paulo Henrique.

Ao meu noivo, Everton, muito obrigada por sempre me fazer acreditar e estar ao meu lado em todos os momentos. Seu amor, parceria e incentivo me tornam mais forte para enfrentar qualquer obstáculo.

A minha orientadora, Profª. Drª. Suzane Cristina Pigossi, obrigada por toda sua amizade, ensinamentos, paciência, confiança e carinho dedicados a mim em todos esses anos. Sua generosidade e dedicação ao ensinar me inspiram e motivam a continuar trilhando esse caminho.

Ao meu co-orientador Prof. Dr. Guilherme José Pimentel Lopes de Oliveira, por toda sua contribuição e suporte na realização do trabalho.

A todos os meus amigos que estiveram presente durante essa caminhada e tornaram meus dias mais alegres. Em especial, as minhas primas/amigas/colegas de quarto, Roberta, Ana Luísa e Júlia.

Aos meus amigos da pós-graduação que levarei por toda vida, Marcela Iunes, Thaísa Carrera, Lélio Soares, Henrique Felizardo e Letícia Siqueira; e meus queridos amigos e professores, Daniel Almeida e Hugo Gaêta por todo suporte e companheirismo, que sem dúvidas contribuíram muito para minha formação.

As alunas de iniciação científica, Monalisa, Júlia, Alyne e Mayra por toda colaboração e dedicação durante o desenvolvimento desse trabalho.

Aos pacientes, pela confiança e disponibilidade para participar da pesquisa. Suas individualidades foram essenciais para o meu aprendizado e crescimento pessoal e profissional.

Ao Programa de Pós-Graduação em Ciências Odontológicas da Universidade Federal de Alfenas e seus professores, por todos os ensinamentos, suporte e incentivo para obtenção desse título.

Ao Prof. Dr. João Adolfo da Costa Hanemann, pelos conselhos e oportunidade de acompanha-lo nas clínicas de Estomatologia.

A disciplina de Periodontia, pelos ensinamentos durante o período de estágio docente.

A Profª Drª Larissa Santana Rodriguez e Prof. Dr. Noé Vital Ribeiro Júnior, pela confiança e empréstimo da câmera fotográfica.

A todos os funcionários da Faculdade de Odontologia, fundamentais para o funcionamento da faculdade e execução do trabalho. Em especial a Andréa e Wal, funcionárias da clínica de Periodontia, e ao Marcinho, funcionário da Ortodontia, pelo auxílio oferecido.

A Universidade Federal de Alfenas e todos os professores, por toda estrutura e ensinamentos oferecidos durante os anos de graduação e pós-graduação. Sempre lembrarei com carinho dos anos passados nesta casa e de todas as oportunidades que me foram oferecidas.

A Universidade Federal de Uberlândia e aos professores Guilherme Oliveira, Priscilla Soares e Ana Paula Oliveira, pelo acolhimento e apoio durante a finalização do trabalho.

A empresa *N&W Dental Care* pelo fornecimento dos géis utilizados no estudo clínico.

O presente trabalho foi realizado com o apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Código de Financiamento 001 – e a Fundação de Amparo à Pesquisa do Estado de Minas Gerais – Brasil (FAPEMIG).

Minha gratidão a todos.

“A maior recompensa para o trabalho do homem não é o que se ganha, mas o que ele se torna com isso.”

John Ruskin, [18--]

RESUMO

O presente estudo tem como objetivo realizar uma revisão sistemática para avaliar a eficácia das diferentes abordagens terapêuticas para cicatrização do palato após a remoção de enxerto gengival. Ademais, pretende-se avaliar o efeito do gel com extrato de chá verde e ácido hialurônico na cicatrização do palato após a remoção de enxerto gengival por meio de um estudo clínico, controlado e randomizado. O projeto foi dividido em dois estudos. Para o estudo 1, buscas eletrônicas foram realizadas nas bases PubMed/MEDLINE, Embase, Web of Science, Scopus, LILACS e The Cochrane Library para publicações até setembro de 2022. As duplicatas foram removidas no software de gerenciamento de referências Endnote e a exclusão por título e resumo foi realizada no software online Rayyan. Após a seleção dos artigos pela leitura de texto completo, foi realizado a extração dos dados, análise da qualidade dos estudos incluídos e meta-análise em rede (NMA). No estudo 2, foram incluídos 42 participantes divididos em três grupos: (1) Grupo Coágulo (CO) (n=14): nenhum material foi colocado na área doadora, apenas o coágulo foi mantido em posição por meio de suturas; (2) Placebo (P) (n=14): área doadora no palato foi tratada utilizando o gel placebo aplicado pelo participante 3 vezes ao dia por 7 dias (N&W, Ribeirão Preto, São Paulo, Brasil); (3) Grupo Gel (G) (n=14): a área doadora no palato foi tratada utilizando o gel com extrato de chá verde e ácido hialurônico (Gel profissional Soft Tissue, N&W, Ribeirão Preto, São Paulo, Brasil) aplicado pelo participante 3 vezes ao dia por 7 dias. A área da ferida por medida clínica e imagens fotográficas, completa epitelização da ferida e cor da mucosa palatina foram avaliadas em todos os grupos após 3 dias, 1, 2 e 4 semanas. A percepção de dor do participante foi avaliada utilizando a escala visual analógica (VAS) e o consumo de analgésicos. Para o estudo 1, 70 estudos foram incluídos na revisão sistemática (análise qualitativa), sendo 14 destes submetidos a NMA (análise quantitativa). Todos os agentes de cicatrização de feridas avaliados promoveram melhor controle da dor e cicatrização de feridas em comparação com a sutura e esponjas hemostáticas isoladamente. Os resultados da NMA revelam que a fibrina rica em leucócitos e plaquetas (L-PRF) foi o agente mais eficaz na redução da dor pós-operatória em todos os períodos analisados (1, 3 e 7 dias). No estudo 2, não houve diferença estatisticamente significativa entre os grupos para nenhuma das variáveis analisadas em nenhum dos períodos de avaliação ($p>0.05$). Conclui-se na revisão que a PRF demonstrou superioridade no controle da dor pós-operatória no palato em relação aos tratamentos avaliados. Ademais, o gel com extrato de chá verde e ácido hialurônico não acelerou a cicatrização do palato após a remoção do enxerto gengival no presente estudo clínico.

Palavras-chave: Cicatrização; Autoenxerto; Palato.

ABSTRACT

The present study aims to perform a systematic review to assess the effectiveness of different therapeutic approaches for palate healing after gingival graft removal. Furthermore, it also intends to evaluate the effect of hyaluronic acid gel and green tea on palate healing after gingival graft removal through a randomized, controlled clinical trial. This project was divided into two studies. For study 1, electronic searches were performed in PubMed/MEDLINE, Embase, Web of Science, Scopus, LILACS and The Cochrane Library for publications through September 2022. Duplicates were removed in Endnote reference management software and exclusion by title and abstract was performed using the Rayyan online software. After selecting articles by reading the full text, data inheritance, analysis of the quality of included studies network meta-analysis (NMA). In study 2, 42 participants divided into three groups were included: (1) Clot Group (CO) (n=14): no material was placed in the donor area, only the clot was kept in position by means of sutures; (2) Placebo (P) (n=14): donor area on the palate was treated using the placebo gel applied by the participant 3 times a day for 7 days (N&W, Ribeirão Preto, São Paulo, Brazil); (3) Gel Group (G) (n=14): the donor area on the palate was treated using a gel with green tea extract and hyaluronic acid (Professional Soft Tissue Gel, N&W, Ribeirão Preto, São Paulo, Brazil) applied by participant 3 times a day for 7 days. Wound area by clinical measurement and photographic images, complete wound epithelization, and palatal mucosa color were assessed in all groups after 3 days, 1, 2, and 4 weeks. The pain visual analog scale (VAS) and analgesic consumption were used to assess the patient's perception of the treatment used. For study 1, 70 studies were included in the systematic review (qualitative analysis), 14 of which underwent NMA (quantitative analysis). All evaluated wound healing agents promoted better pain control and wound healing compared to suture and hemostatic sponges alone. The NMA results reveal that leukocyte and platelet-rich fibrin (L-PRF) was the most effective agent in reducing postoperative pain in all analyzed periods (1, 3 and 7 days). In study 2, there was no statistically significant difference between groups for any of the variable variables in the assessment periods. The review concludes that PRF demonstrated superiority in controlling postoperative pain in the palate compared to the evaluated treatments. Furthermore, the gel with green tea extract and hyaluronic acid did not accelerate healing of the palate after removal of the gingival graft in the present clinical study.

Keywords: Wound Healing; Autografting; Palate.

LISTA DE ABREVIATURAS E SIGLAS

AH - *HA*	Ácido Hialurônico - *Hyaluronic Acid*
AFIF – *WS-PI*	Área da Ferida por Imagem Fotográfica - *Wound Size by Photographic Image*
AFMC – WS-CM	Área da Ferida por Medida Clínica - *Wound Size by Clinical Measurement*
A-PRF	*Advanced- Platelet-Rich Fibrin*
CEF	Completa Epitelização da Ferida
CINEMA	*Confidence in Network Meta-Analysis*
CMP	Cor da Mucosa Palatina
CO	Coágulo - *Control*
CR	*Case Report*
CrI	Intervalo de Credibilidade - *Credibility Interval*
CS	*Case Series*
CWE	*Complete wound epithelialization*
DIC	Critérios de Informação de Desvio - *Deviation Information Criteria*
DMs - *MDs*	Diferenças médias - *Mean Differences*
ECR -*RCT*	Estudo clínico Randomizado - *Randomized clinical trial*
EGL - *FGG*	Enxerto Gengival livre - *Free gingival graft*
EHI	*Early Healing Index*
EHS	*Early Wound Healing Score*
ETC - CTG	Enxerto de Tecido Conjuntivo - *Connective Tissue Graft*
EMD	*Enamel matrix dentin*
F	*Female*
G	Gel
GRADE	*Grading of Recommendations Assessment, Development, and Evaluation*
HSDC	Hipersensibilidade Dentinária Cervical
HSI	*Healing Score Index*
ICP	Índice de Cura Precoce
ICs - *CIs*	Intervalos de Confiança - *Confidence Intervals*
IGF-1	Fator de Crescimento Semelhante à Insulina-1 - *Insulin-Like Growth Factor-1*

i-PRF	*Injectable- Platelet-Rich Fibrin*
IL	Interleucina - Interleukin
JAO	Jovânia Alves Oliveira
JCE	Junção Cemento-esmalte
KT	*Ketorolac Tromethamine*
LPS	*Lipopolysaccharide*
LTH	*Landry, Turnbull, and Howley*
M	*Male*
MCMC	Cadeias de Markov Monte Carlo - *Markov Monte Carlo Chains*
MIS	Marcela Iunes Silveira
MSS	*Modified Manchester Scar Scale*
NF-κB	Fator Nuclear Kappa β
NI	*Not informed*
NMA	Meta-análise em rede – *network meta-analysis*
NRS-101	*101-Point Numerical Rating Scale*
OR	*Odds Ratio*
P	Placebo
PDGF	Fator de Crescimento Derivado de Plaquetas - *Platelet-Derived Growth Factor*
PRF	Fibrina Rica em Plaquetas - *Platelet-Rich Fibrin*
PRP	*Platelet-rich plasma*
RANKL	Ligante do Receptor Ativador do Fator Nuclear Kappa β
RG	Recessão Gengival
SCP	Suzane Cristina Pigossi
SUCRA	Curva de classificação cumulativa - *Cumulative Classification Curve*
TCLE	Termo de Consentimento Livre e Esclarecido
TGF-β	Fator de Crescimento Transformador Beta - *Transforming Growth Factor Beta*
TNF- α	Fator de Necrose Tumoral α - *Tumor Necrosis Factor- α*
T-PRF	*Titanium-Prepared Platelet-Rich Fibrin*
UNIFAL	Universidade Federal de Alfenas
UFU	Universidade Federal de Uberlândia
VAS	Escala Visual Analógica - *Visual Analogue Scale*
VRS-4	*4-Point Verbal Rating Scale*

VEGF	Fator de Crescimento Endotelial Vascular - *Vascular Endothelial Growth Factor*
WBFS	*Wong and Baker Faces Scale*

SUMÁRIO

1 INTRODUÇÃO GERAL

A recessão gengival (RG) é caracterizada pela exposição da superfície radicular devido a migração apical da margem gengival em relação à junção cemento-esmalte, sendo considerada um dos problemas estéticos mais comuns encontrados no campo da Periodontia (KASSAB;COHEN, 2003; LOE;ANERUD;BOYSEN, 1992). As RG podem ser únicas ou múltiplas e são geralmente associadas as alterações anatômicas de tecido mole incluindo ausência/faixa estreita de gengiva queratinizada (GQ), presença de trauma oclusal e de escovação, alterações de posicionamento dentário, acúmulo de biofilme e perda de inserção devido a doença periodontal (HEASMAN *et al.*, 2015). Além do comprometimento estético, a RG pode estar associada a hipersensibilidade dentinária cervical (HSDC), dificuldade de higienização, cáries radiculares e lesões cervicais não cariosas (DAPRILE;GATTO;CHECCHI, 2007).

Nas últimas duas décadas, um interesse crescente tem sido demonstrado no desenvolvimento de técnicas cirúrgicas para reconstruir o tecido mole ao redor dos dentes e implantes. Esses procedimentos cirúrgicos no complexo mucogengival incluem aqueles realizados para prevenir ou corrigir defeitos anatômicos, de desenvolvimento, traumáticos ou induzidos por doenças que acometem a gengiva, mucosa alveolar e o tecido ósseo (WENNSTRÖM, 1996). Nesse contexto, destacam-se as diferentes técnicas de recobrimento radicular para o tratamento das recessões gengivais. O objetivo clínico dessas técnicas é a cobertura total da raiz, por meio do posicionamento da margem gengival levemente coronal à junção cemento-esmalte (JCE), sem a presença de bolsa residual e inflamação detectável (CAIRO *et al.*, 2009).

Para a realização do recobrimento radicular, o enxerto de tecido mole palatino pode ser obtido por meio do Enxerto Gengival Livre (EGL) ou do Enxerto de Tecido Conjuntivo (ETC) sozinho. O EGL é uma das abordagens mais antigas que faz o uso de tecidos autógenos, sendo considerada bem sedimentada e versátil. Essa terapia envolve a remoção completa de uma parte do tecido mole de um sítio doador original, e sua colocação em um leito receptor preparado (ZUCCHELLI *et al.*, 2010). Essa técnica é de fácil execução e pode ser utilizada mesmo na presença de uma fibromucosa palatina delgada, pois remove o epitélio de revestimento e a lâmina própria, onde há maior presença de tecido conjuntivo fibroso (BERTL *et al.*, 2015). Ademais, a obtenção do EGL pode ser realizada mais superficialmente, reduzindo as chances

de violar fibras nervosas e vasos sanguíneos, além de obter uma camada de tecido de alta qualidade da lâmina própria (ZUHR;BAUMER;HURZELER, 2014).

A região mais utilizada para remoção de enxertos de tecidos moles da cavidade oral é o palato duro (BERTL *et al.*, 2015). A fibromucosa palatina é caracterizada por um tecido conjuntivo denso (lâmina própria) coberto por um epitélio ortoqueratinizado (MULLER *et al.*, 2000). Uma camada de tecido adiposo e glandular (submucosa) de espessura variada está presente entre a fibromucosa palatina e o periósteo que cobre o osso palatino (HARRIS, 2003).

A espessura da fibromucosa palatina varia de indivíduo para indivíduo e, no mesmo indivíduo, de local para local do palato (MULLER *et al.*, 2000). Pode ser determinada clinicamente, no momento/após a anestesia, pela inserção da agulha ou de um alargador endodôntico perpendicular ao palato (JOLY *et al.*, 2007). A região mais espessa da mucosa palatina é, geralmente, do pré-molar ao canino, com média de 3mm, havendo uma diminuição na região do primeiro molar e aumento da espessura na região do segundo molar (ANURADHA *et al.*, 2013; BERTL *et al.*, 2015; SAID;ABU KHALID;FAROOK, 2020).

Após a remoção do EGL, a ferida cirúrgica da área doadora apresenta uma cicatrização por segunda intenção dentro de 2–4 semanas a depender da espessura e largura da ferida (FARNOUSH, 1978) e envolve diferentes fases fisiológicas. Nas primeiras 24 a 48 horas, ocorre a primeira fase, em que as células epiteliais se deslocam das bordas da ferida. Do 3º ao 5º dia após a lesão, ocorre a segunda fase da cicatrização da ferida, caracterizada pela formação de tecido de granulação e formação de novos capilares pelo brotamento de células endoteliais presentes nos vasos pré-existentes circundantes. Ao 7º dia, inicia-se a fase final da cicatrização da ferida, caracterizada pela remodelação dos tecidos recém-formados e alta síntese de colágeno. Além disso, o tecido de granulação se remodela gradualmente em tecido cicatricial por semanas e meses até que os tecidos restaurem sua resistência à tração a níveis quase normais (POLIMENI;XIROPAIDIS;WIKESJÖ, 2006). Ademais, a ferida palatina tem sido consistentemente associada ao maior desconforto para o paciente em decorrência da dor pós-operatória, sangramento e/ou retardo da cicatrização (DEL PIZZO *et al.*, 2002). Isso se deve aos traumas térmicos, químicos e/ou mecânicos no qual a ferida cirúrgica é exposta na área doadora (FARNOUSH, 1978).

Com o objetivo de obter uma cicatrização por primeira intenção e reduzir a morbidade pós-operatória, diferentes procedimentos alternativos para retirada do ETC foram descritos na literatura. As principais abordagens descritas são a técnica do alçapão (EDEL, 1974) e a técnica de incisão única (LORENZANA; ALLEN, 2000). Ambas as técnicas consistem na elevação do retalho de acesso de espessura parcial, retirada do ETC subepitelial e fechamento completo da

ferida palatina com o retalho de acesso. Entretanto, um estudo realizado por Zucchelli *et al.* (2010) demonstrou que o local doador do enxerto gengival colhido pela técnica do EGL, quando protegido, apresenta um desconforto pós-operatório semelhante ao local doador colhido pela técnica do alçapão.

Apesar das diferenças entre o tipo de cicatrização, em ambas as técnicas de remoção do enxerto, complicações potenciais podem ocorrer na área doadora incluindo necrose, infecção, dor, hemorragia excessiva, desconforto prolongado e em alguns casos, parestesia do local doador (DEL PIZZO *et al.*, 2002; ZUCCHELLI *et al.*, 2020).

Nesse contexto, a busca por abordagens terapêuticas que acelerem o reparo do leito doador é de extrema relevância clínica para redução do desconforto e complicações pós-operatórias. Diversas abordagens foram descritas na literatura, tais como o uso de laser de baixa potência (DIAS *et al.*, 2015; OZCELIK; HEIDARI *et al.*, 2017; SEYDAOGLU;HAYTAC, 2016), fibrina rica em plaquetas (PRF; do inglês *platelet rich fibrin*) (BAHAMMAM, 2018; FEMMINELLA *et al.*, 2016; KULKARNI *et al.*, 2014), esponjas de colágeno (STEIN *et al.*, 1985), cianoacrilato (FARNOUSH, 1978; STAVROPOULOU *et al.*, 2019; YILMAZ;KAYAALTI-YUKSEK;KARADUMAN, 2022) e ozônio (ISLER *et al.*, 2018; PATEL *et al.*, 2011).

Dentre os materiais, o adesivo tecidual de cianoacrilato tem sido utilizado para promover a cicatrização e minimizar as complicações pós-operatórias devido as suas características hemostáticas, bacteriostáticas e bactericidas (CASTRO-GASPAR *et al.*, 2021; OZCAN *et al.*, 2017; YILMAZ;KAYAALTI-YUKSEK;KARADUMAN, 2022). Castro-Gaspar *et al.* (2021) compararam, em um estudo clínico, controlado e randomizado, a eficácia do adesivo tecidual de cianoacrilato (grupo teste) com a sutura (grupo controle) na cicatrização da fibromucosa palatina. No grupo teste, houve uma diminuição significativa do tempo operatório, além da redução da dor e do sangramento nas primeiras 24 horas após a cirurgia. Por outro lado, Yilmaz;Kayaalti-Yuksek,Karaduman (2022) compararam o uso do cianoacrilato com a sutura e não encontraram diferença significativa entre os grupos para dor pós-operatória, sangramento e consumo de analgésicos. Já Ozcan *et al.* (2017) avaliaram o uso do cianoacrilato associado a PRF e obteve uma diminuição significativa na dor e do sangramento espontâneo nas primeiras 24 horas, além de melhores parâmetros de cicatrização das feridas e escores de alimentação normal nas duas primeiras semanas.

O uso da PRF na área doadora palatina tem demonstrado resultados promissores em termos de melhor cicatrização de feridas e redução do desconforto pós-operatório nos pacientes após a coleta o ETC (FEMMINELLA *et al.*, 2016; LEKTEMUR ALPAN; TORUMTAY CIN,

2020). Em um estudo clínico randomizado realizado por Femminella *et al.* (2016), o grupo em que foi utilizada a PRF na área doadora apresentou menor consumo de analgésico e menor queixa de desconforto, além de uma taxa de epitelização tecidual de 100% ao final da terceira semana de acompanhamento; por outro lado o grupo em que foi utilizada uma esponja de gelatina absorvível apresentou apenas 25% de pacientes com o tecido totalmente epitelizado ao final da terceira semana. Lektemur Alpan,Torumtay Cin (2020) também avaliaram o efeito do uso da PRF sobre a área doadora. Utilizaram-se métodos como escala visual analógica (VAS) para avaliação de dor e da coloração, consumo de analgésicos e índice de cura precoce (ICP) para comparação intergrupos. Os pacientes no grupo PRF relataram escores de dor significativamente mais baixos em todos os momentos. No 3º e 7º dias de pós-operatório, as pontuações do ICP foram mais baixas a favor do grupo PRF. Os valores da escala VAS de correspondência da cor do tecido foram menores no grupo controle no 7º e 14º dia, em comparação com o grupo PRF. A ingestão de analgésicos foi significativamente menor no grupo PRF no pós-operatório no primeiro e terceiro dia em comparação ao grupo controle. De modo semelhante, Bahammam (2018) realizou um ensaio clínico randomizado para avaliar o uso da membrana de PRF como bandagem palatina. O grupo PRF obteve melhor cicatrização da ferida na primeira semana com relação a contorno, textura e correspondência de cor, além de menores índices de dor e desconforto pós-operatório. Ademais, observou-se uma menor taxa de sangramento da ferida cirúrgica imediatamente após a aplicação da PRF.

Um outro método bastante utilizado com a finalidade de reparação da área doadora é a aplicação do laser de baixa potência, com base em seu efeito bioestimulador na cicatrização de feridas (DA SILVA NEVES *et al.*, 2016; DIAS *et al.*, 2015; USTAOGLU;ERCAN;TUNALI, 2017). Dias *et al.*, (2015) realizaram um estudo clínico randomizado para avaliar o efeito do laser Diodo na cicatrização da área doadora após a remoção do ETC. No grupo teste, o laser diodo (GaAlAs 600nm) foi aplicado na área doadora palatina imediatamente após a cirurgia e em dias alternados durante 7 dias. No grupo controle não foi realizada a aplicação do laser. O grupo em que foi aplicado o laser apresentou feridas menores após 14 e 45 dias. Nenhum paciente apresentou cicatriz na área operada e a análise colorimétrica revelou que não houve diferença estatisticamente significante entre os grupos. Os pacientes relataram desconforto leve a moderado, com baixo consumo de comprimidos analgésicos em ambos os grupos. Além disso, após 45 dias, o uso do laser não mostrou diferença no processo de reparo tecidual quando comparado ao grupo controle (sem aplicação de laser).

Ustaoglu;Ercan,Tunali (2017) também observaram que a epitelização completa da ferida foi maior no grupo em que foi utilizado o laser de baixa potência (teste) em comparação

ao grupo controle no 14º dia, além do sangramento, que foi menor no grupo teste durante os primeiros 2 dias. Padrões maiores de cicatrização foram observados no grupo teste em relação ao grupo controle em todas as visitas de acompanhamento. Por fim, as pontuações de correspondência de cores foram maiores no grupo teste em comparação ao grupo controle nas primeiras 3 visitas. Ainda, em 2016, Da Silva Neves e colaboradores realizaram um estudo clínico randomizado para comparar duas densidades do laser de baixa potência em relação a cicatrização de feridas e conforto pós-operatório. Os participantes foram divididos aleatoriamente em 3 grupos variando-se a dose de aplicação do laser. Os participantes receberam a dose de 60J/cm² (grupo 1) e 30J/cm² (grupo 2). No grupo 3 foi realizado uma simulação de aplicação do laser. A área remanescente da ferida foi significativamente menor aos 7 dias no grupo 1 com relação ao grupo 2 e 3. O desconforto pós-operatório foi leve e semelhante em todos os grupos. Com relação a correspondência de cor na área doadora, os grupos 1 e 2 apresentaram resultados significativamente melhores em comparação ao grupo 3 aos 14 dias, porém sem diferença entre eles (DA SILVA NEVES *et al.*, 2016).

O ozônio também tem sido cada vez mais utilizado como agente terapêutico por sua capacidade antimicrobiana e melhora na cicatrização de feridas. Isso ocorre devido a sua capacidade de promover o aumento da liberação de fatores de crescimento e ativar mecanismos antioxidantes locais (BOCCI, 2006; ISLER *et al.*, 2018; PATEL *et al.*, 2011). Em um estudo clínico, randomizado e controlado, Isler e colaboradores em 2018 avaliaram a eficácia do laser de baixa potência comparado a terapia tópica com ozônio na reepitelização das feridas palatinas. A epitelização da área doadora foi avaliada por meio de imagens digitais e pela aplicação do peróxido de hidrogênio a 3%. Os grupos laser e ozônio apresentaram taxas semelhantes de epitelização completa da ferida aos 14 dias. Porém, uma diferença significativa na epitelização foi observada entre o grupo ozônio e o grupo que não recebeu nenhuma intervenção (ISLER *et al.*, 2018). Outro estudo realizado por Patel *et al.* (2011) também avaliou o efeito terapêutico do óleo ozonizado em feridas palatinas. Observou-se uma redução significativa do tamanho da ferida e melhora da cicatrização epitelial no grupo que realizou a aplicação tópica de ozônio em comparação com o grupo controle.

Ainda com o objetivo de acelerar a cicatrização das áreas doadoras, o uso de fitoterápicos tem ganhado cada vez mais espaço e interesse da comunidade científica. Suas propriedades antioxidantes podem melhorar consideravelmente a cicatrização das feridas uma vez que inibem o estresse oxidativo reduzindo o processo inflamatório e acelerando o reparo tecidual. Dentro desse contexto, destaca-se a utilização de um composto a base do chá verde que demonstrou, em estudos pré-clínicos em modelos de periodontite experimental, uma

redução da perda óssea e da expressão de citocinas pró-inflamatórias [Interleucina 1β (IL-1 β), Fator de Necrose tumoral α (TNF- α)] (DE ALMEIDA *et al.*, 2019) e de marcadores de osteoclastogênese [ligante do receptor ativador do fator nuclear kappa β (RANKL)] (YOSHINAGA *et al.*, 2014).

Em um estudo *in vitro* Hagiu *et al.* (2020) avaliaram o efeito do extrato de chá verde em queratinócitos epiteliais gengivais tratados com LPS e observou-se que o uso do extrato nas concentrações de 2.5mg/ml, 5mg/ml e 10 mg/ml aumentaram significativamente em até 1.5 vezes a viabilidade celular frente a resposta inflamatória induzida. Observou-se uma diminuição da expressão gênica das citocinas pró-inflamatórias IL-1β, IL-6 e TNFα e uma significativa diminuição nos níveis de proteínas IL-1β, IL-6 e TNFα nos grupos tratados com extrato de chá verde. Ademais, foi aplicado o teste do arranhão para simular cicatrização de ferida e os grupos que fizeram uso do extrato de chá verde nas concentrações anteriormente relatadas obtiveram quase que total fechamento de ferida em 24h, enquanto que os grupos controles obtiveram somente 80% no mesmo intervalo de tempo.

Esse potencial anti-inflamatório também foi demonstrado em um estudo em animais em que o chá verde foi utilizado como terapia adjunta à raspagem e alisamento radicular em um modelo de periodontite experimental. Observou-se a redução da inflamação por meio de análise histológica e imunohistoquímica nos animais em que foi feito o uso do mesmo de forma tópica. O grupo extrato de chá verde também obteve menor padrão de imunomarcação das citocinas pro-inflamatórias IL-1ß e TNF-α e um padrão de marcação maior para IL-10 (anti-inflamatória) em comparação ao demais grupos controles (DE ALMEIDA *et al.*, 2019).

Para confirmar esses achados, Hrishi *et al.* (2016) realizou um estudo clínico que verificou a redução da inflamação e da perda de inserção clínica após o uso de um dentifrício a base de chá verde adjunto ao tratamento periodontal, o que foi associado ao seu efeito antioxidante. Outro estudo clínico, utilizou o enxaguatório bucal com extrato de chá verde em adolescentes com gengivite e também obteve uma melhoria nos índices de placa e sangramento gengival (JENABIAN *et al.*, 2012).

Além da utilização de fitoterápicos, o uso de substâncias bioativas, tais como o ácido hialurônico (AH), tem sido proposto com o objetivo de estimular o reparo combatendo o processo inflamatório. O AH é um componente do tecido conjuntivo com propriedades bacteriostáticas, anti-inflamatórias e antioxidantes , sendo encontrado nas fibras do ligamento periodontal e no tecido gengival (DAHIYA; KAMAL, 2013). Seu papel como agente na cicatrização de feridas e controle de inflamação tem sido amplamente utilizado e investigado em uma vasta gama de aplicações biomédicas, oftalmológicas, dermatológicas e ortopédicas

(DAHIYA; KAMAL, 2013). Em relação as suas aplicações em tratamentos odontológicos, uma revisão sistemática incluindo 20 estudos clínicos demonstrou que a administração tópica de AH traz benefícios tanto no reparo periodontal quanto no pós-operatório de cirurgias odontológicas (CASALE *et al.*, 2016).

Um estudo *in vitro* demonstrou que o AH foi capaz de reduzir a expressão de citocinas pró-inflamatórias em culturas de fibroblastos estimuladas por *Porphyromonas gingivalis* por meio da supressão das vias de sinalização MAPK e fator nuclear kappa β (NF-κB) (CHEN *et al.*, 2019). Também foi demonstrado potencial efeito antimicrobiano contra *Porphyromonas gingivalis* em um outro estudo in vitro de um gel a base da AH contendo transportador de oxigênio extracelular (M101) na busca de uma opção de otimização do tratamento periodontal (OZCELIK *et al.*, 2021). Ademais, estudos demonstraram que o AH estimulou a cicatrização e o processo de reparo durante o tratamento periodontal (SAHAYATA;BHAVSAR;BRAHMBHATT, 2014) e no tratamento de úlceras na cavidade oral (CASALE *et al.*, 2016). O uso do ácido hialurônico como agente químico presente em colutórios também demonstrou que esse produto diminui a inflamação em participantes portadores de gengivite no mesmo nível que a clorexidina (ABDULKAREEM *et al.*, 2020). Sugere-se ainda que, o uso do AH no tratamento periodontal, proporciona uma condição topográfica ideal na superfície da dentina radicular favorecendo a adesão das células do ligamento periodontal como foi observado em um estudo in vitro realizado em discos de dentina (MUELLER *et al.*, 2017).

Em um estudo clínico randomizado realizado por Cankaya *et al.* (2020) foi avaliado, utilizando fluxometria de laser Doppler (FLD), o efeito da aplicação do AH tópico sobre a vascularização do EGL nos sítios doadores e receptores durante o período inicial de cicatrização da ferida; além disso investigaram o efeito da aplicação do AH na mudança dimensional do EGL. Os valores da FLD do sítio receptor no grupo tratado com AH foram estatisticamente superiores aos do grupo controle nos dias 4 e 7; no entanto, nenhuma diferença foi encontrada para os dias 10, 14 e 30. Além disso, nenhuma diferença foi encontrada para os valores de FLD no sítio doador entre os grupos (com e sem AH) em todos os períodos examinados. A altura do enxerto medida no dia 30 foi estatisticamente maior no grupo tratado com AH em comparação ao grupo controle. A mudança percentual na espessura e altura do EGL foi estatisticamente menor no grupo tratado com AH em comparação ao grupo controle. Dessa forma, os autores concluíram que a aplicação do AH no leito receptor sob o EGL na primeira semana de cicatrização permite a formação de uma camada bem vascularizada, que atua como uma barreira contra as tensões do tecido, funcionando como um andaime entre o leito receptor e o

EGL, reduzindo assim a contração do enxerto, principalmente no sentido vertical. Este estudo mostrou ainda que o enxerto retirado do sítio doador tinha um valor de perfusão de sangue remanescente próprio.

De maneira semelhante, Yildirim *et al.* (2018) avaliaram os efeitos de duas concentrações diferentes de AH tópico (0,2% e 0,8%) no desconforto do paciente no pós-operatório e na cicatrização de feridas em áreas doadoras de palato após cirurgia de EGL. Os grupos testes experimentaram menos dor do que o grupo controle nos dias 3 e 7. A pontuação na escala VAS para sensação de queimação foi maior no grupo controle no dia 3 em comparação com os grupos em que foi utilizado o AH nas duas concentrações testadas. A epitelização completa foi observada no dia 21 em ambos os grupos teste, ao passo que foi alcançada no dia 42 no grupo controle. Os grupos testes mostraram maiores escores de correspondência de cores do que o grupo controle nos dias 21 e 42. Dessa forma, o estudo demonstrou que a aplicação tópica de HA promoveu um impacto positivo na dor pós-operatória e na sensação de queimação e acelerou a cicatrização das feridas palatinas em termos de epitelização e correspondência de cor. Ainda, Makvandi *et al.* (2020) demonstraram o potencial promissor na aceleração do reparo de uma formulação para uso tópico com a associação do AH e de agentes com propriedades antioxidantes (chá verde, framboesa e vitamina E) através de um ensaio *in vitro* de cicatrização de ferida utilizando fibroblastos.

Diante do exposto, reforça-se que, apesar da diversidade de materiais disponíveis, a literatura ainda é conflitante e incerta em relação a eficácia das diferentes abordagens terapêuticas propostas para o reparo da área doadora no palato e diminuição do desconforto pós-operatório do paciente após o reparo do enxerto gengival. Além disso, apesar das propriedades de estímulo cicatricial apresentadas pelos compostos derivados do chá verde e AH, o uso combinado destes materiais, na forma de gel, para acelerar a cicatrização do sítio doador e redução do desconforto e complicações pós-operatórias, após a remoção do enxerto gengival, não foram avaliados até o momento.

2 OBJETIVO GERAL

O objetivo do presente estudo é avaliar a eficácia das abordagens terapêuticas para cicatrização do palato após a remoção de enxerto gengival.

2.1 OBJETIVOS ESPECÍFICOS

a) Avaliar a eficácia das abordagens terapêuticas para cicatrização do palato após a remoção de enxerto gengival por meio de uma revisão sistemática;

b) Avaliar o efeito do gel com extrato de chá verde e ácido hialurônico na cicatrização do palato após a remoção de enxerto gengival por meio de um estudo clínico, controlado e randomizado.

3 ARTIGO 1

Wound healing agents for palatal donor area: a network meta-analysis[1]

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[1] Artigo científico elaborado e submetido de acordo com as normas do periódico internacional Clinical Oral Implants Research.

ABSTRACT

Background: The aim of this systematic review and network meta-analysis (NMA) was to assess the efficacy of different wound healing agents for palatal donor area management after soft tissue graft harvesting. **Methods**: The review protocol was registered in PROSPERO (CRD42023398675). Electronic searches in six databases were conducted for publications up to September 2022. Studies with data from patients undergoing therapeutic approaches using agents for palatal healing after gingival graft harvesting were included. Data about postoperative pain, wound healing and postoperative complications reported for each agent were extracted. A Bayesian random effects network meta-analysis (NMA) was conducted for postoperative pain levels (evaluated using visual analogic scale) and wound healing (complete epithelialization evaluation using hydrogen peroxide test). **Results**: Seventy publications were included in the systematic review (qualitative analysis), with 14 of these subjected to NMA (quantitative analysis). The summarized results from the qualitative (systematic review) and quantitative (NMA) analysis showed that all wound healing agents evaluated promoted better pain control and wound healing compared to spontaneous healing (suture) and hemostatic sponges alone. The NMA outcomes reveal that leucocyte- and platelet-rich fibrin (L-PRF) was the most effective agent in reducing postoperative pain in all analyzed periods (1, 3, and 7 days). Moreover, the PRF seems to accelerate wound healing and reduce postoperative complications palatal necrosis and bleeding) compared to other agents. **Conclusion**: In conclusion, the L-PRF was the most effective agent in reducing postoperative pain, accelerating wound healing and reducing postoperative complications after harvesting soft tissue graft from palatal area.

Keywords: Wound healing; Palate; Pain; Transplants.

1 INTRODUCTION

Autogenous connective tissue graft, including subepithelial connective tissue graft (CTG) and free gingival graft (FGG), are recognized as the gold standard treatment for root coverage and soft tissue augmentation around teeth and dental implants (Zuhr, Baumer, & Hurzeler, 2014). With an autogenous nature, these soft tissue grafts ensure superior and predictable results in comparison to synthetic or allogenic grafts due to their biocompatibility and long-term stability (Kulkarni, Thomas, Varghese, & Bhat, 2014).

The palatal masticatory mucosa is the most preferred donor area to obtain a soft tissue graft because of its ideal tissue thickness and wide keratinized tissue removal (Almeida, Esper, Sbrana, Ribeiro, & Kaizer, 2009). The palatal wound healing after graft removal occurs within 2-4 weeks (Wang, Bunyaratavej, Labadie, Shyr, & MacNeil, 2001) and can be divided into four organized and consecutive time-dependent phases, including coagulation/hemostasis, inflammation, formation, and remodeling (S. B. Dias et al., 2015) First, the blood clot is formed mainly by the platelet cells and then, the would cleaning is promoted by monocytes and neutrophils in the inflammatory phase. In the formation phase, a granulation tissue is formed and the endothelial, fibroblasts and epithelial cells are responsible for the capillary formation, connective tissue formation, and re-epithelialization, respectively. The process ends with the remodeling of newly formed tissues and high collagen synthesis in the remodeling phase (Alasqah, Alrashidi, Alshammari, Alshehri, & Gufran, 2022; A. A. A. Hassan, Akl, & Adel-Khattab, 2020). This phase occurs for weeks and months until the tissues restore their tensile strength to nearly normal levels (Almeida et al., 2009).

Commonly, morbidity and patient discomfort can be expected in the palate donor area after soft tissue graft harvesting. For FGG, the palatal donor sites heal with secondary intention and require a longer healing duration with patient discomfort and pain, even when small size grafts are obtained (Bahammam, 2018; Namadmalian Esfahani, Khorsand, & Mohseni Salehimonfared, 2021). Similarly, higher levels of pain can be also expected in CTG harvesting techniques due to the risk of necrosis or dehiscence of the primary flap (Tavelli et al., 2018). These complications occur when the sutures fail to secure the flap over the wound or in the presence of a thin primary flap (Zucchelli et al., 2010). In addition to postoperative pain, the soft tissue graft harvest in the hard palate was also associated with the occurrence of donor site bleeding, necrosis, burning, sensation loss, and delayed wound healing (Del Pizzo, Modica, Bethaz, Priotto, & Romagnoli, 2002). These complications difficult for the patient speak and aliments consumption during the post-operative phase which may negatively affect patients' quality of life (Alasqah et al., 2022).

As most complications in soft tissue grafting are observed at the donor site, the appropriate management of this area is essential to avoid side effects and reduce patient discomfort (Wessel & Tatakis, 2008). In this context, several hemostatic and wound healing agents have been proposed for palatal management to accelerate healing and reduce the prolonged bleeding and pain caused by the palatal wound (Castro-Gaspar et al., 2021; Miguel, Mathias-Santamaria, Rossato, Ferraz, Rangel, et al., 2021). Variable success has been reported for palatal wound treatment using collagen membrane (Basma et al., 2022; Thoma et al., 2016), cyanoacrylate adhesives (Castro-Gaspar et al., 2021; Stavropoulou, Atout, Brownlee, Schroth, & Kelekis-Cholakis, 2019), platelet-rich fibrin (PRF) (Femminella et al., 2016; Patarapongsanti, haya, Sirinirund, Khongkhunthian, & Khongkhunthian, 2019) photobiomodulation therapy (Almeida et al., 2009; G. Ustaoglu, Ercan, & Tunali, 2017), hyaluronic acid gel (Khalil, Habashneh, Alomari, & Alzoubi, 2022; Yıldırım, Ozener, Doğan, & Kuru, 2018) and others (Alasqah et al., 2022; Kim, Tramontina, Papalexiou, & Luczyszyn, 2010; Tasdemir, Alkan, & Albayrak, 2016).

Although previously systematic reviews evaluating the healing effects of PRF (Meza-Mauricio et al., 2021), cyanoacrylate adhesives (Escobar et al., 2021; Verissimo, Ribeiro, Martins, Gurgel, & Lins, 2021) and low level laser therapy (Al-Shibani, 2019) on surgical wounds were made, there is still no clear evidence to guide clinicians into the best clinical practice for palate donor area management. Network meta-analysis is an interesting tool used to make recommendations regarding clinical and cost-effectiveness, assisting with the development of treatment guidelines (Nikolakopoulou et al., 2020). Therefore, this systematic review and network meta-analysis aimed to assess the efficacy of different wound healing agents for palatal donor area management after soft tissue graft harvesting.

2 MATERIAL AND METHODS

2.1 Protocol and registration

The present systematic review with network meta-analysis was guided by the Preferred Reporting Items for Systematic Reviews Involving a Network Meta-analysis (PRISMA NMA) statement and a protocol was registered in PROSPERO (ID: CRD42023398675).

2.2 Focused question

The focused question was elaborated by PVO acronym (Population, Variable and Outcome): “In patients subjected to gingival graft harvesting (P), which agent (V) is more effective in palatal wound healing acceleration and postoperative discomfort reduction (O)?

2.3 Eligibility criteria

The inclusion criteria were original research articles such as case reports, case series and clinical trials in which data from patients undergoing therapeutic approaches using agents for palatal healing after gingival grafts harvesting are presented. Pre-clinical studies (*in vitro* and *in vivo* studies), review articles, conference proceedings, protocol articles, letters to the editor, book chapters or studies not published in English language were excluded.

2.4 Literature search

Detailed search strategies were conducted on the PubMed/MEDLINE, Embase, Web of Science, Scopus, LILACS and The Cochrane Library databases for publications up to September 2022. The search strategies were created using the Medical Subject Headings (MeSH) and Embase Subject Headings (Emtree). Boolean operators (AND and OR) combined the descriptors and improved the search strategy through different combinations, respecting each database syntax rules (Supplementary Table S1). Search restrictions, including language and publication period, were not made.

Table S1 – Strategies for database search

Database	Search Strategy (September, 2022)
PubMed/ MEDLINE	**#1** ("Gingival recession"[All Fields] OR "Recession defect"[All Fields] OR "Recession-type defect"[All Fields] OR "Root coverage"[All Fields] OR "Periodontal surgery"[All Fields])
	#2 ("Palate"[All Fields] OR "Palatal area"[All Fields] OR "Palatal graft"[All Fields] OR "Free gingival graft"[All Fields] OR "Connective tissue graft"[All Fields] OR "Gingival graft"[All Fields] OR "Palatal donor site"[All Fields] OR "Soft tissue graft"[All Fields] OR "Palatal wound"[All Fields])
	#3 (“Palatal healing”[All Fields] OR “Palatal repair”[All Fields] OR “Palatal pain”[All Fields] OR “Wound heal”[All Fields] OR “Wound healing”[All Fields] OR “Wound closure”[All Fields] OR “Wound closure techniques”[All Fields] OR (“pain”[MeSH Terms] OR “pain”[All Fields]) OR (“healed”[All Fields] OR “Wound healing”[MeSH Terms] OR (“wound”[All Fields] AND “healing”[All Fields]) OR “Wound healing”[All Fields] OR “healing”[All Fields] OR “healings”[All Fields] OR “heals”[All Fields]) OR “Postoperative complications”[All Fields] OR “Morbidity”[All Fields] OR (“discomfort”[All Fields] OR “discomforting”[All Fields] OR “discomforts”[All Fields]) OR (“epithelializa”[All Fields] OR “epithelializat”[All Fields] OR “epithelialize”[All Fields] OR “epithelialized”[All Fields] OR “epithelializes”[All Fields] OR “epithelializing”[All Fields] OR “Re-Epithelialization”[MeSH Terms] OR “Re-Epithelialization”[All Fields] OR “epithelialization”[All Fields] OR “epithelialization”[All Fields]) OR “Re-Epithelialization”[All Fields] OR “Wound Epithelialization”[All Fields] OR “epithelialization wound”[All Fields] OR “Analgesia”[All Fields] OR “Bleeding”[All Fields] OR “Hemostasis”[All Fields] OR “Hemostases”[All Fields] OR “Hemostatics”[All Fields] OR “Hemorrhage”[All Fields])
	#1 AND #2 AND #3

Embase	**#1** ('gingival recession' OR 'recession defect' OR 'recession-type defect' OR 'root coverage' OR 'periodontal surgery')
	#2 (palate OR (palatal AND area) OR (palatal AND graft) OR graft OR autografting OR (free AND gingival AND graft) OR (connective AND tissue AND graft) OR (gingival AND graft) OR (palatal AND donor AND site) OR (soft AND tissue AND graft) OR (palatal AND wound))
	#3 (palatal AND healing OR (palatal AND repair) OR (palatal AND pain) OR (wound AND heal) OR (wound AND healing) OR (wound AND closure) OR (wound AND closure AND techniques) OR pain OR healing OR (postoperative AND complications) OR morbidity OR discomfort OR epithelialization OR 're epithelialization' OR (wound AND epithelialization) OR (epithelialization, AND wound) OR analgesia OR bleeding OR hemostases OR hemostatics OR hemorrhage)
	#1 AND #2 AND #3
Web of Science	**#1** ((((ALL=(“Gingival recession”)) OR ALL=("Recession defect")) OR ALL=("Recession-type defect")) OR ALL=("Root coverage")) OR ALL=("Periodontal surgery")
	#2 ((((((((((ALL=(“Palate”)) OR ALL=("Palatal área")) OR ALL=("Palatal graft")) OR ALL=(Graft)) OR ALL=(“Autografting”)) OR ALL=("Free gingival graft")) OR ALL=("Connective tissue graft")) OR ALL=("Gingival graft")) OR ALL=("Palatal donor site")) OR ALL=("Soft tissue graft")) OR ALL=("Palatal wound")
	#3 ((((((((((((((((((((ALL=("Palatal healing")) OR ALL=("Palatal repair")) OR ALL=("Palatal pain")) OR ALL=("Wound heal")) OR ALL=(“Wound healing”))) OR ALL=("Wound closure")) OR ALL=("Wound closure techniques")) OR ALL=(Pain)) OR ALL=(Healing)) OR ALL=(“Postoperative complications”)) OR ALL=(“Morbidity”)) OR ALL=(Discomfort)) OR ALL=(Epithelialization)) OR ALL=("Re-Epithelialization")) OR ALL=("Wound Epithelialization")) OR ALL=("Epithelialization, Wound")) OR ALL=("Analgesia")) OR ALL=("Bleeding")) OR ALL=("Hemostasis")) OR ALL=("Hemostases")) OR ALL=("Hemostatics")) OR ALL=("Hemorrhage")
	#1 AND #2 AND #3
Scopus	**#1** (ALL ("Gingival recession" OR "Recession defect" OR "Recession-type defect" OR "Root coverage" OR "Periodontal surgery")
	#2 ALL ("Palatal graft" OR "Free gingival graft" OR "Connective tissue graft" OR "Gingival graft" OR "Palatal donor site" OR "Soft tissue graft" OR "Palatal wound")
	#3 ALL ("Wound healing" OR "Wound closure" OR "Wound closure techniques" OR pain OR "Postoperative complications" OR epithelialization OR "Re-Epithelialization" OR "Wound Epithelialization" OR "Epithelialization, Wound" OR "Bleeding" OR "Hemostasis" OR "Hemostases" OR "Hemostatics" OR "Hemorrhage"))
	#1 AND #2 AND #3
LILACS	**#1** (“Gingival recession” OR "Recession defect" OR "Recession-type defect" OR "Root coverage" OR "Periodontal surgery")
	#2 (“Palate” OR "Palatal area" OR "Palatal graft" OR Graft OR “Autografting” OR "Free gingival graft" OR "Connective tissue graft" OR "Gingival graft" OR "Palatal donor site" OR "Soft tissue graft" OR "Palatal wound")
	#3 ("Palatal healing" OR "Palatal repair" OR "Palatal pain" OR "Wound heal" OR “Wound healing” OR "Wound closure" OR "Wound closure techniques" OR Pain OR Healing OR “Postoperative complications” OR “Morbidity” OR Discomfort OR Epithelialization OR "Re-Epithelialization" OR "Wound Epithelialization" OR "Epithelialization, Wound" OR "Analgesia" OR "Bleeding" OR "Hemostasis" OR "Hemostases" OR "Hemostatics" OR "Hemorrhage")
	#1 AND #2 AND #3
The Cochrane Library	**#1** “Gingival recession” OR "Recession defect" OR "Recession-type defect" OR "Root coverage" OR "Periodontal surgery" in All Text
	#2 “Palate” OR "Palatal area" OR "Palatal graft" OR Graft OR “Autografting” OR "Free gingival graft" OR "Connective tissue graft" OR "Gingival graft" OR "Palatal donor site" OR "Soft tissue graft" OR "Palatal wound" in All Text
	#3 "Palatal healing" OR "Palatal repair" OR "Palatal pain" OR "Wound heal" OR “Wound healing” OR "Wound closure" OR "Wound closure techniques" OR Pain OR Healing OR “Postoperative complications” OR “Morbidity” OR Discomfort OR Epithelialization OR "Re-Epithelialization" OR "Wound Epithelialization" OR "Epithelialization, Wound" OR "Analgesia" OR "Bleeding" OR "Hemostasis" OR "Hemostases" OR "Hemostatics" OR "Hemorrhage" in All Text
	#1 AND #2 AND #3

The publications found in all electronic databases was transferred to the EndNote Program™ X9 version (Thomson Reuters, New York, NY, USA, 2018) to remove duplicate

references. Then the results were exported to Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar) (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016) for selection by titles and abstracts. The reference lists of the identified articles were also hand-searched for additional studies.

2.5 Data selection and extraction

Two investigators (J.A.O. and M.I.S.) made the initial search for the evaluation of titles and abstracts independently using the previous eligibility criteria. Irrelevant studies were excluded, and the full text of the articles included based on title and abstract were independently read and evaluated according to selection criteria (J.A.O. and M.I.S.). Disagreements between reviewers were resolved by discussion including a third investigator (S.C.P.), for the final decision. The articles excluded in the full-text analysis were listed separately, and the reasons for exclusion were specified.

Two investigators (J.A.O. and M.I.S.) independently read all studies and extracted the following data for the qualitative analysis: (a) study type; (b) patients number and gender; (c) mean age and standard deviation of patients of each group; (d) smoking habits; (e) type of gingival graft removal technique; (f) wound healing agents type (study groups); (g) number of treated palatal wound; (h) palatal stent application; (i) postoperative follow-up; (j) postoperative pain; (k) palatal wound healing and (l) postoperative complications occurrence.

2.6 Quality assessment

Two reviewers (J.A.O. and M.I.S.) separately assessed the individual quality of each included study. Any disagreement was discussed with a third author (S.C.P.). The methodological quality of case reports and case series were assessed using the evaluation framework suggested by Murad, Sultan, Haffar, and Bazerbachi (2018) based on the selection, ascertainment, causality and reporting domains. Questions 4 to 6 of domain causality were not applied in this study because are destined to cases of adverse drug events. In addition, the risk of bias in the randomized clinical trials (RCT) was assessed using RoB 2.0 tool (Sterne et al., 2019).

2.7 Methods for results synthesis

2.7.1 Pairwise Meta-analysis

A meta-analysis with direct comparisons between interventions was performed using Review Manager software (version 5.4, Copenhagen, Denmark, 2020). For postoperative pain assessment, estimated effects between interventions were expressed as mean differences (MDs) with 95% confidence intervals (CIs) using a fixed effects model. The agent's effectiveness in palatal wound healing was estimated using odds ratios (OR) in a Mantel-Haenszel fixed effects model. The heterogeneity between studies was evaluated using Chi-square tests according to the applied model (fixed or random), which was considered low for values ≤ 25%, moderate for values between 25% and 50% and high for values > 50% (Higgins, Thompson, Deeks, & Altman, 2003).

2.7.2 Network Meta-analysis (NMA)

Subsequently, a Bayesian random effects network meta-analysis (NMA) was conducted using the 'gemtc' package of the RStudio software (version 4.0.4, Boston, United States, 2020). Statistical simulations using Markov Monte Carlo Chains (MCMC) were created to calculate MDs between interventions, with a 95% Bayesian Credibility Interval (CrI). Number of chains ('n.chain'), discarded simulations ('n.adapt'), total number of simulations ('n.iter') and simulation extraction interval ('thin') were adapted to the number of studies included and interactions between interventions in the generated model. In addition, Brooks-Gelman-Rubin consistency analysis methods and deviation information criteria (DIC), as well as the generation of density graphs from Trace plots and Node-splitting were used to evaluate the convergence and fit of the model (S. Dias, Welton, Caldwell, & Ades, 2010).

The combination of direct and indirect evidence comparisons by the NMA provided the probability of choosing and ranking among the best treatments and the MD among the evaluated interventions. In addition, a League table, with comparisons between interventions and the estimates of surface values under the cumulative classification curve (SUCRA) were used to interpret the results (Cipriani et al., 2009).

2.8 Certainty of evidence

Reporting bias analysis using funnel plots was performed using Review Manager 5.4 software. Certainty of evidence of the results generated by the NMA was evaluated using the CINeMA tool (Confidence in Network Meta-Analysis) originally framed in GRADE (Grading

of Recommendations, Assessment, Development and Evaluation) (Nikolakopoulou et al., 2020; Papakonstantinou, Nikolakopoulou, Higgins, Egger, & Salanti, 2020).

3 RESULTS

3.1 Study selection

The electronic search in the databases found 6612 results, being 4296 unique citations. A total of 104 publications (87 publications obtained from the database search and 17 publications obtained through other search methods) were evaluated for full-text reading, of which 33 were subsequently excluded based on the inclusion criteria (Supplementary materials; Table S2) and 70 included in the systematic review (qualitative analysis). Of these 70 publications, only 14 had enough data to compose the meta-analysis (Figure 1).

Table S2 - Articles excluded with the reasons after evaluating the full text.

Author/Year	Exclusion reasons
Agroya et al. (2021)	No therapeutic approaches for palatal healing reported.
Alawad, Othman, Hsaian, and Alsabek (2022)	No therapeutic approaches for palatal healing reported.
Almeida et al. (2009)	No therapeutic approaches for palatal healing reported.
Aroca, Keglevich, Barbieri, Gera, and Etienne (2009)	No therapeutic approaches for palatal healing reported.
Arunachalam, Sudhakar, Janarthanam, and Das (2014)	No therapeutic approaches for palatal healing reported.
Bahammam (2018)	No therapeutic approaches for palatal healing reported.
Chiu, Chou, Kuo, Liang, and Chiu (2020)	No therapeutic approaches for palatal healing reported.
Abubekir, Şeydanur, Mustafa, and Mustafa (2015)	No therapeutic approaches for palatal healing reported.
Danaci et al. (2022)	Full text not found.
Farnoush (1978)	Review
Fekrazad, Chiniforush, and Kalhori (2019)	Palatal graft removal using laser.
B. et al. (2015)	No therapeutic approaches for palatal healing reported.
Fickl et al. (2014)	No therapeutic approaches for palatal healing reported.
Fourel (1982)	Full text not found.
Griffin, Cheung, Zavras, and Damoulis (2006)	No therapeutic approaches for palatal healing reported.
Harris (1997)	No therapeutic approaches for palatal healing reported.
Jahnke, Sandifer, Gher, Gray, and Richardson (1993)	No therapeutic approaches for palatal healing reported.
Kim et al. (2010)	Only hemostasis was evaluated.
Maino et al. (2018)	No therapeutic approaches for palatal healing reported.
Ozcelik, Seydaoglu, and Haytac (2016)	Palatal graft removal using laser.
Pandit, Khasa, Gugnani, Malik, and Bali (2016)	No therapeutic approaches for palatal healing reported.
Pedlar (1985)	No therapeutic approaches for palatal healing reported.
Popova, Mlachkova, and Emilov (2008)	No therapeutic approaches for palatal healing reported.
Santamaria et al. (2017)	No therapeutic approaches for palatal healing reported.
Subrahmanyam (2015)	Skin graft
Tirone, Salzano, Panuello, Pozzatti, and Rodi (2021)	No therapeutic approaches for palatal healing reported.
G. Ustaoglu et al. (2017)	No therapeutic approaches for palatal healing reported.
Verma et al. (2019)	No therapeutic approaches for palatal healing reported.
Wiench et al. (2016)	Full text not found
Wirthlin, Vernino, and Hancock (1980)	No therapeutic approaches for palatal healing reported.
Yaghobee et al. (2021)	No therapeutic approaches for palatal healing reported.
Yildiz and Gunpinar (2019)	No therapeutic approaches for palatal healing reported.
Zukorlic and Jakoba (2011)	Full text not found

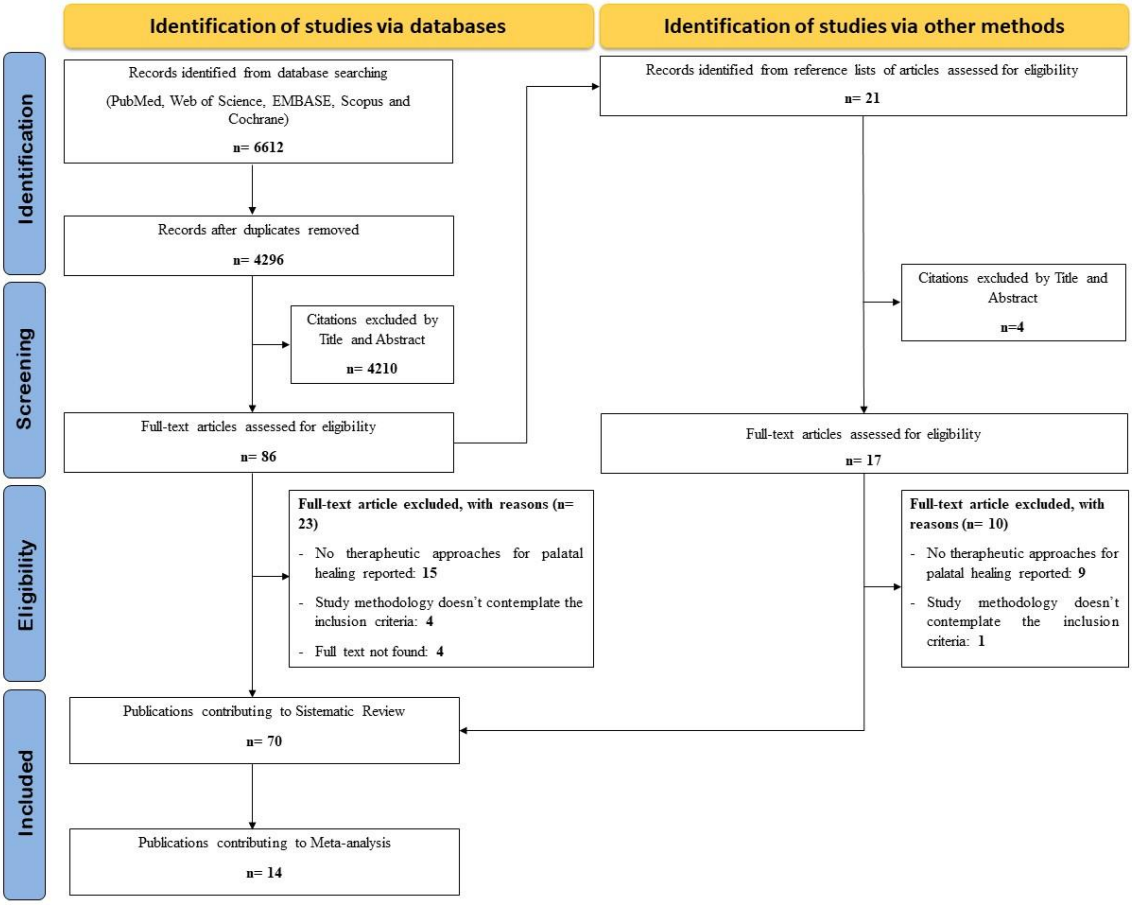

Figure 1: Flow chart of the search strategy of the study

3.2 Characteristics of eligible studies

Considering the 70 articles included in the systematic review, 56 were RCT, 10 case series and 4 case reports. A total of 1963 patients (992 female, 622 male) and 2120 palatal wounds were included. The age of the patients ranged from 16 to 81 years. Fifty-three studies did not include smoking patients, 11 did not report this information, and 6 included smoking patients. Sixty-three studies used the FGG and 8 studies used the CTG to obtain the soft tissue graft from the palatal area (Table S3).

The most frequently wound healing agents for palatal donor area management evaluated in the eligible studies were PRF (17 studies), collagen hemostatic sponge (16 studies), periodontal dressing (14 studies) and laser therapy (11 studies). In addition to these agents, studies frequently described the use of cyanoacrylate adhesives (6 studies), collagen membrane/matrix/plug (4 studies), ozone (5 studies) and hyaluronic acid gel associated with periodontal dressing (4 studies). Moreover, the use of other agents alone or in association was also described including PRF associated with cyanoacrylate (1 study), human amniotic membrane (2 studies), oxidized regenerated cellulose absorbable hemostat (2 studies), chitosan

gel (2 studies), gelatin hemostatic sponge associated with cyanoacrylate (2 studies), PRP (2 study), autologous fibrin glue (1 study), collagen matrix associated with cyanoacrylate (1 study), collagen hemostatic sponge associated with periodontal dressing (1 study), collagen hemostatic sponge associated with hyaluronic acid gel and periodontal dressing (1 study), hyaluronic acid gel associated with gelatin hemostatic sponge (1 study), gel containing enamel matrix derivatives (Straumann® Emdogain®) (1 study), flurbiprofen spray (1 study), herbal extract (1 study), electrotherapy (1 study), bromelain capsule (1 study), erythropoetin gel (1 study), propylene mesh (1 study), adhesive film with ketorolac tromethamine (1 study), medihoney dressing (1 study), hemostatic paste (1 study), wet exposed burn ointment gel (MEBO) (1 study), simvastatin gel (1 study), simvastatin gel associated with chitosan (1 study), aloe vera-chitosan gel (1 study), synthetic extracellular matrix (1 study), non-thermal atmospheric pressure plasma (1 study), latex membrane (1 study), and topical phenytoin (1 study) (Table 1 and S3).

Regarding the outcomes assessed in the eligible studies (Table 1 and S3), *56 studies evaluated postoperative pain* [using visual analogic scale (VAS; 50 studies), 101-numerical rating scale (NRS-10; 3 studies), four-point verbal rating scale (VRS-4; 2 studies), functional pain scale (FPS; 1 study), Wong and Baker faces scale (WBFS; 1 study) and 4 studies not informed the method of pain evaluation], *27 studies evaluated analgesics consumption*, *34 studies evaluated wound healing* [visually (15 studies) or using VAS for color (6 studies), landry index (7 studies), early healing index (EHI; 5 studies), manchester scar scale (MSS, 2 studies), scar and tissue colorimetry (2 studies), likert scale (1 study) and/or modified EHI (1 study)], *33 studies evaluated epithelialization* ([using hydrogen peroxide test (23 studies), visually (7 studies), disclosure solution (2 studies) and/or toluidine blue (2 studies)] and *20 studies evaluated wound area reduction* (using donor site measurements). For post-operative complications, the presence of bleeding was reported by 29 studies, while 5 studies reported the occurrence of palatal necrosis.

3.3 Individual results of eligible studies

3.3.1 Postoperative pain

3.3.1.1 PRF

Lower pain scores (Bahammam, 2018; Femminella et al., 2016; A. A. A. Hassan et al., 2020; Işler et al., 2019; Kulkarni et al., 2014; Lektemur Alpan & Torumtay Cin, 2020; Ozcan et al., 2017; Shakir, Bhasale, Pailwan, & Patil, 2015) and analgesic consumption (Bahammam, 2018; Femminella et al., 2016; Lektemur Alpan & Torumtay Cin, 2020) were reported in the

palatal donor area covered with PRF in comparison to spontaneous healing (Lektemur Alpan & Torumtay Cin, 2020; Shakir et al., 2015), non-eugenol pack (Bahammam, 2018; Kulkarni et al., 2014), collagen hemostatic sponge (Femminella et al., 2016; A. A. A. Hassan et al., 2020), hyaluronic acid gel (A. A. A. Hassan et al., 2020), cyanoacrylate adhesive (Ozcan et al., 2017) and topical gaseous ozone (Işler et al., 2019). One case series (with 3 patients per group) showed superior results for collagen hemostatic sponge in comparison to PRF in terms of pain duration and analgesic consumption (Belkhede, Salaria, & Aggarwal, 2019). No differences between PRF and collagen hemostatic sponge was observed for pain levels in Sharma, Kumar, Puri, Bansal, and Khatri (2019) study. The advanced-PRF (A-PRF) showed lower pain levels in comparison to collagen hemostatic sponge in one study (Sousa et al., 2020). The injectable-PRF (i-PRF) showed superior results for pain control in comparison to spontaneous healing but not in comparison to autologous fibrin glue (Kızıltoprak & Uslu, 2020).

3.3.1.2 Collagen agents

From the studies reporting the use of collagen matrix/membrane/plug in pain control, the collagen plug alone promoted higher pain levels and analgesic consumption in comparison to collagen plug associated with cyanoacrylate adhesive, PRF and palatal stent (Basma et al., 2022). A case series (3 patients) evaluating the use of collagen membranes associated with palatal stent showed that all patients reported overall positive treatment experiences with minimal (2 patients) to moderate (1 patient) palatal discomfort (Berridge, Johnson, Cheng, Swenson, & Miller, 2019). For collagen hemostatic sponge outcomes, similar pain levels were observed in comparison to spontaneous healing in one study (Işler et al., 2019). On the other hand, Tavelli et al. (2018) reported better pain control with collagen hemostatic sponge in comparison to spontaneous healing, however, better results was obtained when collagen hemostatic sponge was associated with cyanoacrylate adhesive (Tavelli et al., 2018; Tavelli et al., 2019). Saroff, Chasens, Eisen, and Levey (1982) reported no differences in pain levels between collagen hemostatic sponge and periodontal dressing in a case series including 10 patients per group. Contradictory, Shanmugam, Kumar, Arun, Arun, and Karthik (2010) showed superior results in pain control for collagen hemostatic sponge in comparison to periodontal dressing in a RCT including 16 patients per group. Khalil et al. (2022) observed that collagen hemostatic sponge promoted better pain control when associated with hyaluronic acid gel than with periodontal dressing. In comparison to PRF, less pain levels were obtained for PRF in comparison to collagen hemostatic sponge in three studies (Femminella et al., 2016; A. A. A. Hassan et al., 2020; Sousa et al., 2020), however, collagen hemostatic sponge promoted more less levels of pain in comparison to PRF in one case series (Belkhede et al.,

2019). Schinini, Sales, Gomez, Romanelli, and Chambrone (2021) showed that sutured and non-sutured sites treated with collagen hemostatic sponge display similar pain control. Inferior results in pain control were obtained with collagen hemostatic sponge in comparison to Alvogyl in one study (Ehab, Abouldahab, Hassan, & Fawzy El-Sayed, 2020). Similar pain levels were obtained with collagen hemostatic sponge and oxidized regenerated cellulose in one study (Rossmann & Rees, 1999).

3.3.1.3 Laser therapy

Four studies (Bitencourt et al., 2022; Isler, Uraz, et al., 2018; Lafzi et al., 2019; Lavu et al., 2022) reported lower pain scores (Isler, Uraz, et al., 2018; Lafzi et al., 2019; Lavu et al., 2022) and analgesic consumption (Bitencourt et al., 2022) with the use of diode laser in palatal donor area in comparison to spontaneous healing. Laser modulation using LED also promoted less pain in comparison to spontaneous healing (Vieira, Lopes, DeMarco, de Melo Filho, & Jardini, 2010). However, no differences in pain levels between diode laser and spontaneous healing (da Silva Neves et al., 2016; S. B. Dias et al., 2015; Işler et al., 2019), palatal stent (Morshedzadeh, Aslroosta, & Vafaei, 2022), topical gaseous ozone (Isler, Uraz, et al., 2018; Işler et al., 2019), collagen membrane (Işler et al., 2019) and PRF (Işler et al., 2019) were reported in five studies (da Silva Neves et al., 2016; S. B. Dias et al., 2015; Isler, Uraz, et al., 2018; Işler et al., 2019; Morshedzadeh et al., 2022). One study described greater VAS pain score after 3 days of post-operative in diode laser group in comparison to spontaneous healing (Heidari et al., 2017).

3.3.1.4 Cyanoacrylate adhesive

The most included studies not reported differences between cyanoacrylate adhesive and spontaneous healing for pain levels (Castro-Gaspar et al., 2021; Stavropoulou et al., 2019; Yilmaz, Kayaalti-Yuksek, & Karaduman, 2022) and analgesic consumption (Stavropoulou et al., 2019; Yilmaz et al., 2022). In one study lower pain was found using cyanoacrylate adhesive in comparison to spontaneous healing, however, the lowest drug consumption was reported when cyanoacrylate adhesive was associated with a collagen hemostatic sponge (Tavelli et al., 2018). Tavelli et al. (2019) also reported lower pain levels and analgesic consumption in cyanoacrylate adhesive associated with collagen hemostatic sponge in comparison to collagen hemostatic sponge alone. In Basma et al. (2022), cyanoacrylate adhesive associated with collagen plug showed superior results in the pain reduction in comparison to collagen plug alone but not in comparison to palatal stent. When associated with PRF, cyanoacrylate adhesive resulted in more pain control in comparison to palatal stent in one study (Ozcan et al., 2017).

3.3.1.5 Ozone therapy

Topical gaseous ozone promoted less pain in comparison to spontaneous healing in Isler, Uraz, et al. (2018) study, however, Işler et al. (2019) showed no differences between both groups. Topical gaseous ozone associated with palatal stent promoted better pain control (less pain and analgesic consumption) in comparison to palatal stent alone (Tasdemir et al., 2016).

3.3.1.6 Hyaluronic acid gel

Hyaluronic acid gel associated with periodontal dressing promoted better pain control in comparison to periodontal dressing in two studies (A. Hassan, Ahmed, Ghalwash, & Elarab, 2021; Yıldırım et al., 2018). Hyaluronic acid gel associated with periodontal dressing and collagen hemostatic sponge also promoted less pain levels in comparison to periodontal dressing and collagen hemostatic sponge (Khalil et al., 2022). In addition, hyaluronic acid gel associated with collagen hemostatic sponge showed less pain levels than gelatin hemostatic sponge alone (A. A. A. Hassan et al., 2020).

3.3.1.7 Other agents

The other wound healing agents also described in the literature that promoted less pain levels in comparison to control group were adhesive film with ketorolac tromethamine (Al-Hezaimi et al., 2011), medihoney dressing material (Alasqah et al., 2022), topical phenytoin (Doshi, McAuley, & Tatakis, 2021), Alvogyl (Ehab et al., 2020), flurbiprofen oral spray (Isler, Eraydin, Akkale, & Ozdemir, 2018), human amniotic membrane dressing (Kadkhoda, Tavakoli, Chokami Rafiei, Zolfaghari, & Akbari, 2020), medicinal plants extract (Keceli, Aylikci, Koseoglu, & Dolgun, 2015), simvastatin and chitosan gel (Madi & Kassem, 2018), human amniotic membrane (Martelloni, Montagner, Trojan, & Abate, 2019), electrotherapy treatment (Miguel, Mathias-Santamaria, Rossato, Ferraz, Figueiredo-Neto, et al., 2021), oxidized regenerated cellulose (Rossmann & Rees, 1999), bromelain (Soheilifar et al., 2015) and propylene mesh (Yussif, Wagih, & Selim, 2021). On the other hand, no differences in pain levels were observed for enamel matrix protein derivative (Miguel, Mathias-Santamaria, Rossato, Ferraz, Rangel, et al., 2021), non-thermal atmospheric pressure plasma (Pekbagriyanik, Dadas, & Enhos, 2021), aloe vera-chitosan dressing (Sankar, Gujjari, & Kulkarni, 2021) and latex membrane (Spin, de Oliveira, Spin-Neto, Herculano, & Marcantonio, 2017) in comparison to control group.

3.3.2 Wound healing

3.3.2.1 PRF

Most of included studies evaluating palatal donor sites covered with PRF membranes in comparison to spontaneous healing (Lektemur Alpan & Torumtay Cin, 2020; Reddy et al., 2015; Shakir et al., 2015), non-eugenol pack (Aravindaksha, Batra, Sood, Kumar, & Gupta, 2014; Bahammam, 2018; Kulkarni et al., 2014), collagen hemostatic sponge (Femminella et al., 2016; A. A. A. Hassan et al., 2020; Sharma et al., 2019), cyanoacrylate adhesive (Ozcan et al., 2017) and hyaluronic acid gel (A. A. A. Hassan et al., 2020) reported considerably faster healing with PRF membranes. Only one case series (with 3 patients per group) showed superior results for collagen hemostatic sponge in comparison to PRF (Belkhede et al., 2019). Two studies reported better healing with palatal donor sites treated with titanium-prepared platelet-rich fibrin (T-PRF) in comparison to collagen hemostatic sponge (Koca-Ünsal et al., 2022) and acrylic stent (Gülbahar Ustaoglu, Ercan, & Tunali, 2016). In addition, two studies also showed superior healing in palatal donor sites covered with A-PRF. The injectable-PRF (i-PRF) showed superior results for wound healing in comparison to spontaneous healing but not in comparison to autologous fibrin glue (Kızıltoprak & Uslu, 2020).

3.3.2.2 Collagen agents

Only two studies evaluated the healing pattern promoted by collagen matrix and superior results for collagen matrix in comparison to a soft protective splint were observed (Thoma et al., 2016; Thoma, Sancho-Puchades, Ettlin, Hammerle, & Jung, 2012). For collagen hemostatic sponge outcomes, Saroff et al. (1982) reported no differences in wound repair promoted by collagen hemostatic sponge in comparison to periodontal dressing. On the other hand, Shanmugam et al. (2010) showed superior results in wound repair for collagen hemostatic sponge versus periodontal dressing. In comparison to PRF, better wound healing were obtained for PRF in comparison to collagen hemostatic sponge in four studies (Femminella et al., 2016; A. A. A. Hassan et al., 2020; Koca-Ünsal et al., 2022; Sousa et al., 2020), however, collagen hemostatic sponge promoted superior repair in comparison to PRF in one case series (Belkhede et al., 2019). Schinini et al. (2021) showed that sutured and non-sutured sites treated with collagen hemostatic sponge display similar early wound healing outcomes. Better wound healing was observed with collagen hemostatic sponge in comparison to spontaneous healing (Tavelli et al., 2018), however, better results was obtained when collagen hemostatic sponge was associated with cyanoacrylate adhesive (Tavelli et al., 2018; Tavelli et al., 2019). Inferior results in wound repair were obtained with collagen hemostatic sponge in comparison to Alvogyl and oxidized regenerated cellulose (Ehab et al., 2020; Rossmann & Rees, 1999).

3.3.2.3 Laser therapy

Seven studies (Bitencourt et al., 2022; da Silva Neves et al., 2016; S. B. Dias et al., 2015; Heidari et al., 2017; Lafzi et al., 2019; Lavu et al., 2022; Morshedzadeh et al., 2022) reported superior wound healing with the use of diode laser in comparison to spontaneous healing (Bitencourt et al., 2022; da Silva Neves et al., 2016; S. B. Dias et al., 2015; Heidari et al., 2017; Lafzi et al., 2019; Lavu et al., 2022) and palatal stent (Morshedzadeh et al., 2022). Laser modulation using LED also promoted higher wound healing in comparison to spontaneous healing (Vieira et al., 2010). Only one study (Isler, Uraz, et al., 2018) showed no differences between diode laser application and spontaneous healing or topical gaseous ozone.

3.3.2.5 Cyanoacrylate adhesive

Two studies (Castro-Gaspar et al., 2021; Yilmaz et al., 2022) reported no differences in wound repair between cyanoacrylate adhesive and spontaneous healing and only one study reported superior results for cyanoacrylate adhesive (Tavelli et al., 2018).

3.3.2.6 Ozone therapy

An improvement in wound repair was reported with topical gaseous ozone alone (Isler, Uraz, et al., 2018) and ozonated oil associated with palatal stent (Patel et al., 2012; Patel, Kumar, Kumar, Gd, & Patel, 2011) in comparison to spontaneous healing.

3.3.2.6 Hyaluronic acid gel

Hyaluronic acid gel associated with periodontal dressing promoted better wound repair in comparison to periodontal dressing only in one study (Yıldırım et al., 2018). In A. Hassan et al. (2021) no differences between both treatments were observed for wound repair. Moreover, hyaluronic acid gel associated with collagen hemostatic sponge showed similar wound repair in comparison to collagen hemostatic sponge alone (A. A. A. Hassan et al., 2020). For vascularization analysis, no differences were found between hyaluronic acid gel associated with periodontal dressing and palatal stent in comparison to periodontal dressing with palatal stent (Çankaya, Gürbüz, Bakirarar, & Kurtiş, 2020).

3.3.2.7 Other agents

The other wound healing agents also described in the literature that improved wound repair in comparison to control group were medihoney dressing material (Alasqah et al., 2022), alvogyl (Septodont, Niederkassel, Germany) (Ehab et al., 2020), human amniotic membrane dressing (Kadkhoda et al., 2020), medicinal plants extract (Keceli et al., 2015), simvastatin (10 mg/mL)/chitosan gel (Madi & Kassem, 2018), human amniotic membrane (Martelloni et al., 2019), glycagen dressing (Synthetic Extracellular Matrix) (Martin et al., 1995), electrotherapy treatment (Miguel, Mathias-Santamaria, Rossato, Ferraz, Figueiredo-Neto, et al., 2021), non-

thermal atmospheric pressure plasma (Pekbagriyanik et al., 2021), oxidized regenerated cellulose (Rossmann & Rees, 1999), aloe vera-chitosan dressing (Sankar et al., 2021), erythropoietin gel (Yaghobee et al., 2021) and propylene mesh (Yussif et al., 2021). No differences in pain levels were observed for topical phenytoin (Doshi et al., 2021), enamel matrix protein derivative (Miguel, Mathias-Santamaria, Rossato, Ferraz, Rangel, et al., 2021), bromelain (Soheilifar et al., 2015) and latex membrane (Spin et al., 2017). Only one study evaluating flurbiprofen oral spray in palatal donor area after FGG harvesting reported wound repair delay in comparison to placebo sprays (Isler, Eraydin, et al., 2018).

3.3.3 Post-operative complications

3.3.3.1 PRF

Five studies reported post-operative complications outcomes (Işler et al., 2019; Kızıltoprak & Uslu, 2020; Lektemur Alpan & Torumtay Cin, 2020; Sousa et al., 2020; Gülbahar Ustaoglu et al., 2016) being palatal necrosis more frequency in spontaneous healing (Işler et al., 2019; Lektemur Alpan & Torumtay Cin, 2020) and collagen hemostatic sponge (Sousa et al., 2020) in comparison to PRF. Post-operative bleeding was also more frequency in spontaneous healing in comparison to PRF (Kızıltoprak & Uslu, 2020; Gülbahar Ustaoglu et al., 2016).

3.3.3.2 Collagen agents

Only one study reported a partial necrosis in one patient (sample of 10 patients) treated with collagen hemostatic sponge (Işler et al., 2019). Stein, Salkin, Freedman, and Glushko (1985) in a case series (20 patients) observed that palatal donor area treated with collagen hemostatic sponge associated with periodontal dressing healed normally with no evidence of infection, tissue reaction or other adverse effects. Rossmann and Rees (1999) reported bleeding episodes during the first 7 days after surgery for patients treated with palatal stent and oxidized regenerated cellulose, while no sites treated with collagen hemostatic sponge had an adverse event.

3.3.3.3 Laser therapy

Three studies reported post-operative complications outcomes (Bitencourt et al., 2022; Isler, Uraz, et al., 2018; Morshedzadeh et al., 2022). Bitencourt et al. (2022) observed less swelling and bleeding for diode laser in comparison to spontaneous healing. However, Morshedzadeh et al. (2022) observed more bleeding in diode laser group than in palatal stent group.

3.3.3.4 Cyanoacrylate adhesive

Only one study reported the post-operative complications outcomes for cyanoacrylate adhesive (Castro-Gaspar et al., 2021). More frequency of spontaneous bleeding in the donor area during the first 24h was observed in the groups treated with cyanoacrylate adhesive in comparison to suture (spontaneous healing).

3.3.3.5 Other agents

No post-operative complications were reported in the included studies for ozone therapy, hyaluronic acid gel and other agents.

Table S3 - Characteristics of the studies and participants included in the systematic review according to the PICO strategy (population, intervention, comparison and outcome).

Author (Year)	Study type	Number of patients	Age	Number of male (M) and female (F)	Graft removal technique	Palatal wound treatment	Evaluation period	Outcomes for pain, wound healing and post-operative complications	
Al-Hezaimi et al. (2011)	RCT	68 (34 per group)	18 to 64 years	M: 31 F: 37	FGG	Control group: Adhesive film without ketorolac tromethamine (KT) Test group: Adhesive film with KT	1-5, 24 and 48h	Pain (VAS)	The test group reported a significant reduction of pain intensity during the first 2 and 5 hours after surgery. After the KT adhesive film was applied in the control group, pain intensity was reduced to a non-significant level by the third hour after surgery. No adverse reaction was observed.
Alasqah et al. (2022)	RCT	20 (10 per group)	35 years	M: 10 F:10	FGG	Control group: Spontaneous healing Test Group: Medihoney dressing material	1-7, 15 and 30 days	Pain (VAS) and healing (Donor site measurements)	A significant difference in the patient's proportion showing the donor site healing percentage was found to be 56% for test group versus 44% for the control group (p=0.001) in the first week. At 4-week, the donor site healing percentage was found to be 86% (in width) and 91% (in length) for test group versus 14% (in width) and 9% (in length) for control group (p=0.001). The control group experienced significantly higher pain and discomfort compared to test group.
Aravindaksha et al. (2014)	CS	5 (Control group: 1; Test group: 4)	NI	NI	FGG	Control Group: Non-eugenol pack Test Group: PRF (3000 rpm for 10 min)	12/13, 18/19, 24/ 25 and 30/31 days	Healing (Hydrogen peroxide test)	Palatal donor sites covered with PRF membranes demonstrated considerably faster healing compared to control sites.

Bahammam (2018)	RCT	24 (12 per group)	Control: 28.5 ± 3.7 years Test group: 27.8 ± 4.3 years	M: 14 F: 10	FGG	Control Group: Non-eugenol pack (Coe-pak TM). Test Group: PRF (3000 rpm for 10 min) + Non-eugenol pack	1-7, 15, 21, 30 days and 2 months	Pain (VAS, NRS-101 and VRS-4), color, contour and texture (Likert scales), bleeding and analgesic consumption	Lower pain scores were observed for test group and the pain levels returned to baseline levels earlier, compared to the control group. In the Likert scale, higher scores were observed for control group at all times compared to the test group, indicating poorer color, contour, and texture match. Higher analgesic consumption was also observed for control group compared to test group.
Basma et al. (2022)	RCT	72 (18 per group)	Control group: 57.6 ± 18.4 years Test group 1: 55.4 ± 14.8 years Test group 2: 64.2 ± 9.9 years Test group 3: 52.0 ± 18.9 years	M: 27 F:45	FGG	Control Group: Collagen plug (Cytoplast RTMPLUG, Collagen Matrix, Inc., Oakland, New Jersey) + sutures Test Group 1: Collagen plug with cyano-acrylate (PeriAcryl, Glustitch Inc., Delta, BC, Canada) Test Group 2: PRF (3000 rpm for 10 min) + sutures Test Group 3: palatal stent (PS) only	1-14 days	Pain (VAS), bleeding and analgesic consumption	All test groups indicated significant lower pain perception, analgesic consumption, and higher willingness for retreatment in comparison to control group. No statistically significant differences among test groups were observed. There were no statistically significant differences in amount of day-by-day swelling, bleeding, and activity tolerance among four groups. Compared to other groups, the PS had the lowest overall pain scores (over the 14-day period).
Belkhede et al. (2019)	CS	6 (3 per group)	NI	NI	FGG	Control Group: Gelatin Sponge (GS) Test Group: PRF (3000 rpm for 10 min)	1- 4 weeks	Postoperative discomfort (NRS), bleeding, analgesic consumption, CWE (hydrogen peroxide test)	GS group patients reported less postoperative discomfort in terms of pain duration, analgesic consumption, and better CWE in two patients and in the third patient at 2nd-and 3rd-week postoperatively in comparison to PRF group where CWE occurred at the 3rd week.

Berridge et al. (2019)	CS	3	53, 54 and 29 years	M: 1 F: 2	FGG	Collagen membranes + palatal stent	7, 14 and 30 days	Pain	Two patients reported minimal donor site discomfort at any time point. One patient with large bilateral donor sites reported moderate palatal discomfort limited to the first postoperative week. All patients reported overall positive treatment experiences.
Bitencourt et al. (2022)	RTC	44 (22 per group)	21-30 years: 15 patients 31-30 years: 13 patients >41: 16 patients	M: 11 F: 33	FGG	Control Group: Spontaneous healing Test Group: Diode laser (808nm, 50/60, 100 mW, 3J, 30 sec immediately after surgery, 24 and 48 h)	6, 24, 48, 72 hours, 7, 14 and 28 days	Pain (VAS), bleeding, analgesic consumption, and wound closure (with two tone disclosing dye solution and donor site measurements)	No adverse effects were reported in the study. Postoperative analgesic requirement was significantly higher in the control group. Test group reported significant less swelling and bleeding, mainly in the first 48 h. Test group presented a significantly higher palatal wound closure at 7 days compared to placebo group (33.41 vs. 21.20 respectively).
Çankaya et al. (2020)	RTC	40 (20 per group)	45 years Control group: 34.7 ± 6.1 years Test group: 35.4 ± 5.23 years	M: 13 F: 27	FGG	Control Group: Periodontal dressing (COE-PAK, GC America) + palatal stent Test Group: HA + periodontal dressing (COE-PAK, GC America) + palatal stent	4, 7, 10, 14 and 30 days	Vascularization	No differences were found for the laser Doppler flowmetry values of the palatal site between the HA and control groups at all examined time points.
Castro-Gaspar et al. (2021)	RTC	24 (Control Group: 14; Test Group: 10)	NI	M: 12 F: 12	FGG	Control Group: Spontaneous healing Test Group: Cyanoacrylate tissue adhesive (Periacryl®90, GluStitch Inc., Delta, Canada)	1-7, 14, 21 days and 2 months	Pain (VAS), bleeding, healing time (visually) and inflammation (VRS)	Spontaneous bleeding in the donor area during the first 24 h was observed in 11.1% of the tissue adhesive cyanoacrylate group versus 88.9% of the suture group—a significant difference. No significant between-group difference was observed in postoperative pain, inflammation, or degree of healing over time.

da Silva Neves et al. (2016)	RCT	51 (Control group: 15 Test group 1: 18 Test group 2: 18)	Control group: 40.01 ± 7.6 years Test group 1: 43.2 ± 9.8 years Test group 2: 47 ± 9.3 years	M: 23 F: 28	CTG	Control Group: Spontaneous healing Test Group 1: Diodo laser (660 nm, 30mW, 60 J/cm2, immediately after surgery and 48, 96, 144, 192, 240, 288 hours) Test Group 2: Diodo laser (660 nm, 30mW, 30 J/cm2, immediately after surgery and 48, 96, 144, 192, 240, 288 hours)	7, 14, 30, 45, 60 and 90 days	Pain (VAS after air spray), analgesic consumption, wound area (donor site measurements), scar and tissue colorimetry	Test Group 1 presented statistically significant smaller wounds at day 7. None of the patients presented scars in the operated area, and all the patients reported mild discomfort, with low consumption of analgesic pills.
S. B. Dias et al. (2015)	RCT	32 (16 per group)	Control group: 41.68 ± 9.2 Test group: 42.06 ± 10.2	M: 15 F: 17	CTG	Control Group: Spontaneous healing Test Group: Diodo laser (660 nm, 30mW, 15 J/cm2, 20 sec, immediately after surgery and 48, 96, 144, 192, 240, 288, 336 hours)	7, 14, 45, 60 and 90 days	Pain (VAS after air spray), analgesic consumption, wound area (donor site measurements), scar and tissue colorimetry	The test group presented statistically significant smaller wounds at days 14 and 45. None of the patients presented a scar at the operated area, and no differences in colorimetry analysis was observed between groups. Patients reported mild to moderate discomfort, with low analgesic pills consumption.
Doshi et al. (2021)	RCT (split-mouth design)	20	23-31 years 25.8±2.1 years	M: 16 F: 4	FGG Biopsies (diameter 4 and 6 mm; depth 1.5 mm)	Control Group: Carrier alone (placebo) Test Group: Topical phenytoin	1, 5, 14 and 21 days	Pain (VAS and FPS), analgesic consumption, healing (HSI), wound area (donor site measurements and CWE (hydrogen peroxide test)	30% of participants reported statistically significant more pain on control side than the test side at day 1. Time and treatment had a significant effect on HSI score. There was no difference between control and test groups in CWE and wound area.

Ehab et al. (2020)	RCT	36 (18 per group)	Control group: 34.1 ± 6.3 Test group: 31.3 ± 9.5	M: 12 F: 24	FGG	Control Group: GS (Cutanplast Standard, Mascia Brunelli S.p.a, Milano, Italy). Test Group: Alvogyl (Septodont, Niederkassel, Germany)	1-14 days, 3, 4 and 5 weeks	Pain (VAS), bleeding, analgesic consumption and CWE (hydrogen peroxide test)	Although significantly higher VAS pain scores were reported in the control as compared with the test group up to 12 days post-surgically, with higher analgesics consumption, a multivariate regression analysis demonstrated no statistically significant effect of any factor, including dressing type on VAS pain scores. At 4 weeks, 22.2% of patients in the test group versus 11.1% in the control group demonstrated CWE.
Femminella et al. (2016)	RCT	40 (20 per group)	18 - 47 years 32.4 ± 5.0 years	M: 15 F: 25	FGG	Control group: GS Test group: PRF membrane (3000 rpm for 10 min)	1- 4 weeks	Pain (VAS), bleeding, analgesic consumption and CWE (hydrogen peroxide test)	The test group showed a significantly faster CWE at the end of week 2, whereas at the end of week 3, all palatal wounds in the test patients epithelialized completely. Similarly, test patients reported significantly less discomfort and took a significantly lower dose of analgesics.
A. A. A. Hassan et al. (2020)	RCT	30 (10 per group)	Control group: 34.90 ±8.18 Test group 1: 30.90 ±7.53 Test group 2: 35.10 ±7.09	M:10 F: 20	FGG	Control group: GS Test group 1: PRF membrane (3000 rpm for 10 min) Test group 2: HA plus GS	1, 3, 7, 14, 21 and 30 days	Pain (VAS), bleeding (VAS), healing (Landry) and wound area (donor site measurements)	VAS pain scores were smaller in PRF group in comparison to other groups. PRF group also showed the highest value of healing index during all the follow up intervals.
A. Hassan et al. (2021)	RCT	30 (10 per group)	24 to 49 years Control group: 34.20 ± 2.19 years Test group 1: 40.60 ± 2.02 years Test group 2:	M: 4 F: 26	FGG	Control group: Periodontal pack (Pericem cement quengco, Non-Eugenol, Italy) Test group 1: Moist Exposed Burn Ointment (MEBO; Julphar®, Ras Al Khaimah,	3, 7, 14, 21, 42 days	Pain (VAS), analgesic consumption, color (VAS) and wound area (donor site measurements)	MEBO showed statistically significant less VAS score compared to the other two groups, while HA showed statistically significant less VAS score compared to the control group. Both MEBO and HA showed statistically significant less total analgesic consumption. No statistically

			37.80 ± 2.65 years			United Arab Emirates) + periodontal pack Test group 2: 0.2% HA (Gengigel®, Ricerfarma S.r.l., Milano, Italy) + periodontal pack			significant difference was observed between groups for wound size. MEBO showed statistically significant higher VAS for color match.
Heidari et al. (2017)	RCT (split-mouth design)	12	24 to 55 years 40.2 ± 9.2 years	M: 4 F: 8	FGG	Control group: Spontaneous healing Test group: Diode laser (660 nm, 200 mW, continuous mode, time of irradiation: 32 s, energy density: 4 J/cm2, spot size: 0.5 cm immediately after FGG surgery, and 1,2,4 and 7 days)	1, 2, 7, 14, 21, 30 and 45 days	Pain (VAS), analgesic consumption and CWE (hydrogen peroxide test)	At 14 and 21 days, the number of donor sites with CWE was greater in laser group compared to the control group. After 21 days, all donor sites in the test group were CWE, while at the same time, only eight donor sites in the control group showed CWE. The VAS pain score did not show statistically significant between two groups, except for the first 3h after procedure when laser group showed greater VAS pain score.
Isler, Uraz, et al. (2018)	RCT	36 (12 per group)	38.97 ±11.93 years Control group: 41.25 ±10.91 years Test group 1: 38.41 ±14.66 years Test group 2: 37.25 ±10.48 years	M: 12 F: 24	FGG	Control Group: Spontaneous healing Test Group 1: Diode laser (970 ±15 nm, 2 W, 35 J/cm2, 30 sec, immediately after surgery and 1, 3 and 7 days). Test Group 2: Ozone therapy (2100 ppm, 80% oxygen, 30 sec, immediately after surgery and 1, 3 and 7 days)	3, 7, 14 and 30 days	Pain and discomfort (VAS), analgesic consumption, wound area (donor site measurements) and CWE (hydrogen peroxide test)	At day 14, statistically significant smaller wounds were observed with digital image analysis in the ozone group in comparison to the control group. However, intergroup comparison of the remaining wound area did not reveal any significant differences. The mean VAS sores was significantly higher in the control group compared with the laser and ozone group at day 7.
Isler, Eraydin, et al. (2018)	RCT	48 (12 per group)	41.1 ± 10.8 years CTG Control group: 40.9 ± 6.69 Test group:	M: 21 F: 27	CTG and FGG	Control group: Placebo sprays Test group: Flurbiprofen oral spray (0.075 g of flurbiprofen, Sanovel Pharmaceuticals, Istanbul, Turkey)	1, 3, 7, 14, 21, 28, 42 e 56 days	Pain and discomfort (VAS), bleeding, analgesic consumption, color (VAS),	The prevalence of CWE was significantly higher in the control-FGG group than flurbiprofen-FGG group at 21 days postoperatively, while there was no significant alteration for both flurbiprofen-CTG and control-CTG groups at any follow-up periods. In

			38.9 ± 10.8 FGG Control group: 42.4 ± 14.6 Test group: 43.28 ± 9.34					healing (Landry) and CWE (hydrogen peroxide test)	flurbiprofen-FGG group, significant improvements were observed for postoperative pain, patients' discomfort and burning sensation at 14 days postoperatively.
Işler et al. (2019)	RCT	60 (10 per group)	18 - 65 years 39.5 ±12.7 Control group: 40.0 ±15.7 Test group 1: 40.4 ±16 Test group 2: 39.6 ±6.2 Test group 3: 37.0 ±11.3 Test group 4: 40.3 ±11.3 Test group 5: 39.7 ±15.8	M: 16 F: 44	FGG	Control group: Spontaneous healing Test group 1: PRF (3000 rpm for 10 min) Test group 2: Essix retainer (Clear Advantages Series, Ortho Technology, Florida, United States). Test group 3: Topical gaseous ozone (80% oxygen power, 2100 ppm 30 sec immediately after surgery, 1, 3, and 7 days) Test group 4: Diode laser (970 ± 15 nm, 5.25 J/cm2, 2W immediately after surgery, 1, 3, and 7 days) Test group 5: Collagen fleece (Bego Collagen Fleece, Bremen, Germany)	1-7 days and 14 days	Pain (VAS) and necrosis	The statistically significant difference was observed between PRF and ozone groups for the mean VAS values regarding postoperative pain only on day 5. Although there was a tendency towards a lower VAS value in the PRF group compared to other groups for all study follow-up periods, all inter-group comparisons did not show any statistical significance on the other postoperative days. The presence of partial necrosis was observed in one patient from control group and one patient from collagen fleece group.
Kadkhoda et al. (2020)	RCT	27 (Control group: 12; Test group: 15)	54 (18–70) years	M:14 F:13	FGG	Control Group: Spontaneous healing Test group: Human amniotic membrane dressing	7,14 and 21 days	Pain (VAS), analgesic consumption and color (VAS)	The mean color match scores were higher in the test group than the control group at 14 ($p<0.01$) and 21 days after surgery ($p=0.02$). The difference in tissue texture ($p=0.01$) and inflammation ($p=0.02$) between the two groups was only significant on day 14 ($p<0.05$). The pattern of pain relief was better in the test group compared with the control group, especially in first days, although the differences were not

									significant in terms of the number of analgesics taken or the pain score.
Keceli et al. (2015)	RCT	33 (Control group: 16; Test group: 17)	30.82 ±8.72 years Control group: 28.44 ± 9.07 Test group: 33.06 ± 8.02	M: 5 F: 28	FGG	Control group: Palatal stent Test group: Medicinal plants extract (Ankaferd Blood Stopper®, Ankaferd Health Products Ltda., Istanbul, Turkey) + palatal stent	1-7, 15, 30 days, 2, 3 and 6 months	Pain (VAS), bleeding, color and epithelization (hydrogen peroxide test)	In the test group, primary bleeding was shorter and fewer individuals showed secondary bleeding during the first 3 days. During the 6 days, pain scores were higher in the control group. Later, no inter-group difference was observed. Epithelization was relatively faster and color match was slightly better in the test group.
Keskiner, Lutfioğlu, Aydogdu, Saygun, and Serdar (2016)	RCT	30 (15 per group)	Control group: 23.90 ±4.40 years Test group: 25.20 ±5.30 years	M:15 F:15	FGG	Control group: Palatal stent Test group: Nd:YAG laser (1064nm, 250mW, 1.6 J/cm2, 10 sec, immediate postoperative, 24, 48, 72 and 96 hours) + palatal stent	7 and 12 days	TGF-β1, PDGF-BB, and IL-8 levels by ELISA	Increases in TGF-β1, PDGF-BB, and IL-8 levels in palatal wound fluid suggest that photobiomodulation may accelerate wound healing by stimulating production of selected mediators.
Khalil et al. (2022)	RCT	21 (Control group: 10; Test group: 11)	Control group: 23.90 ± 4.40 years Test group: 32 ± 2 years	M: 6 F:15	FGG	Control group: Collagen hemostatic sponge + periodontal dressing (Septo-pack gingival dressing, Septodont, Saint Maur-des-fosses, France). Test group: Collagen hemostatic sponge + HA (HYADENT BG) + periodontal dressing	1-14 days	Pain (VAS)	Pain scores in donor sites were statistically significant higher in control group in comparison to test group until day 7.
Kızıltoprak and Uslu (2020)	RCT	36 (12 per group)	18 to 53 years Control group: 32.08 ± 9.46 Test group 1: 28.92 ± 9.66	M: 9 F: 27	FGG	Control group: Spontaneous healing Test group 1: i-PRF (2300 rpm for 3 min)	3, 7, 14 days and 1 and 3 months	Pain (VAS), bleeding, analgesic consumption, epithelization	Epithelialization was higher in the test groups on the 14th day in comparison to control group. MSS scores at the 14th day and 1st month were lower in the test group 2 than in the control and

			Test group 2: 33.25 ± 10.97			Test group 2: Autologous fibrin glue (2700 rpm for 2 min)		(hydrogen peroxide test), wound healing (LTH index), color, contour, and distortion of the wound (MSS) and wound area (donor site measurements	test group 1. In the test group 2, LTH index levels at the 3rd, 7th, and 14th days and 1 month were higher than in control and test group 1. VAS scores of the test group 2 were lower than in the control and test group 1 at the 7th day. Bleeding was lower in the test groups in comparison to the control group.
Koca-Ünsal et al. (2022)	RCT	10 (5 per group)	Control group: 30 years Test group: 42 years	M: 1 F: 9	FGG	Control Group: GS (Clinisponge, Yücel Medical, Istanbul, Turkey) Test group: T-PRF (3000 rpm for 10 min)	2, 4, 7 and 14 days	Vascularization	The test group showed increased vascularity which suggested a better healing of the soft tissue.
Kulkarni et al. (2014)	CS	18 (Control group: 8; Test group: 10)	42 (16-56) years	Control group: NI Test group: M: 5/ F: 5	FGG	Control Group: Non-eugenol pack Test group: PRF membrane (3000 rpm for 10 min) + Suture + non-eugenol pack	7, 14 and 21 days	Pain (WBFS) and epithelization (visually for wound closure)	Complete wound closure was observed for test group after 14 days and these patients reported lesser post-operative morbidity in comparison to control group patients.
Lafzi et al. (2019)	CS (split-mouth)	12 (12 per group)	45.9 (41-53) years	M: 6 F: 6	FGG	Control group: Spontaneous healing Test group: Diode laser (808 nm, 50mW, 15J/cm2, 30 sec, immediately after surgery, 48, 96 and 144 hours)	3, 24 hours, 7, 14 and 21 days	Pain (VAS) and wound area (donor site measurements)	The test group presented significantly better shade matching and wound healing on days 7, 14 and 21. Twenty-four hours after surgery, the pain was significantly lower in the test group compared to the control group.
Lavu et al. (2022)	RCT	33 (Control group: 19; Test group: 14)	Control group: 31.68 ± 6.20 Test group: 31.21 ± 8.15	M: 20 F: 13	CTG	Control group: Spontaneous healing Test Group: Diode laser (660 nm, 50mw, 17.5 J/cm2, 25 sec, on day of surgery, 3, 7 e 10 days)	3, 7, 10 and 14 days	Pain (VAS) and wound healing (EHS)	The control group shows significant higher VAS score than the test group. The VAS score decreases faster in the test group than in the control group. A higher mean of EHS scores in the test group at all time points was observed as compared to the control group.

Lektemur Alpan and Torumtay Cin (2020)	RCT	40 (20 per group)	Control group: 30.89 ± 6.92 Test group: 30.6 ± 6.45	M: 19 F: 21	CTG	Control Group: Spontaneous healing Test Group: PRF membrane (2800 rpm for 12 min)	Baseline, 1, 3, 7, 10, 14 and 30 days	Pain (VAS), bleeding, necrosis, analgesic consumption, wound healing (EHI) and color (VAS)	The patients in the test group reported significantly lower pain scores at all-time points. Postoperative 3rd and 7th day, EHI scores were lower in the favor of the test group. VAS score values of tissue color match were lower in the control group at 7th and 14th day, compared with the test group. Analgesic intake was significantly lower in the test group in comparison to control group at 1st and 3rd day. Two subjects showed flap necrosis in the control group.
Madi and Kassem (2018)	RCT	40 (10 per group)	25 - 40 years	NI	FGG	Test Group 1: Simvastatin suspension (10mg/mL; 50mg of simvastatin in 5mL of purified water). Test Group 2: Simvastatin (10 mg/mL)/chitosan gel [(2.5%); 50mg simvastatin in 1mL 1% acetic acid + 4mL chitosan gel] Test Group 3: Chitosan gel (2.5%; 125mg chitosan flakes in 5mL 1% acetic acid) Test Group 4: Petroleum gel (negative control)	1, 3, 5, 7 and 14 days	Pain (VAS), analgesic consumption and wound healing	Statistically significant reduction in wound-healing scores was observed after 3 and 7 days for group 2 compared to other groups. A significant reduction was also observed in VAS score for group 2 compared to other groups at day 1, 3, 5 and 7.
Martelloni et al. (2019)	CS	1	38 years	F: 1	FGG	Human amniotic membrane (HAM)	7, 30 days, 2, 4, 6, 8 months.	Pain, analgesic consumption, closure of the wound and epithelization (visually)	One week after the HAM application, the wound was healed and 1 month later the donor area was completely re-epithelialized. In addition, there was no pain in the days following the procedure and no painkillers were taken.

Martin et al. (1995)	CS	11 (Control group: 1; Test group: 10)	NI	M: 5 F: 6	FGG	Control group: Periodontal dressing (Coe pack). Test group: Synthetic Extracellular Matrix (Glycagen, Bioetica, Lyon, France)	7 days	Tissue reconstruction	The patients who had received a Glycagen dressing had clearly healed wounds on day 7 when the protective dressing is removed. This aspect differed greatly from the usual picture seen on day 7 for patients receiving classical dressings such as Coe Pack.
Miguel, Mathias-Santamaria, Rossato, Ferraz, Figueiredo-Neto, et al. (2021)	RCT	53 (Control group: 27; Test Group: 26)	Control group: 44.6 ± 10.1 years Test group: 44.4 ± 11.1 years	M: 19 F: 34	FGG	Control Group: Spontaneous healing Test Group: Electrotherapy treatment (100 μA, 9 kHz, 120 sec, once a day for 5 consecutive days)	3, 7, 14, 21, 30, 45 and 90 days.	Pain (VAS), analgesic consumption, epithelization (disclosure solution) and wound area (donor site measurements)	The test group achieved earlier wound closure and epithelialization at 7 and 14 days after harvest when compared with the control group. Painful symptomatology was reported less frequently in the test group than in the control group at 3-day follow-up. Analgesic consumption was generally low.
Miguel, Mathias-Santamaria, Rossato, Ferraz, Rangel, et al. (2021)	RCT	44 (22 per group)	Control group: 44.31 ± 11.51 years Test group: 48.27 ± 12.42 years	M: 17 F: 27	FGG	Control Group: Spontaneous healing Test group: Enamel matrix protein derivative (0.3 ml—Emdogain®; Straumann Holding AG—Basel Switzerland)	3, 7, 14, 21, 30, 45 and 90 days.	Pain (VAS), analgesic consumption, epithelization (disclosure solution), healing (EHI) and wound area (donor site measurements)	Test and control groups achieved wound closure and re-epithelialization 30 days postoperatively, without inter-group differences. Similarly, number of analgesics did not present significant inter-group differences. The VAS (pain) did not show any significant intra-or inter-group differences during the 7 postoperative days.
Morshedzadeh et al. (2022)	RCT (split-mouth)	14	29 to 65 years 44 ± 10.3 years	M: 4 F:10	FGG	Control Group: Palatal acrylic resin stent Test group: Diodo laser (940 nm, 0.21 W, 0.075 W/cm2, 30 sec, immediately after surgery, 48, 96, 144, 192, 240, 288, 336, 384, 432 hours) + Palatal acrylic resin stent	0-11, 14, 28 and 60 days.	Pain and discomfort (VAS), bleeding, color, epithelization (hydrogen peroxide test) and remaining wound area (donor site measurements)	Remaining Wound Area was significantly smaller in the test than in the control group on the days 7 and 14 after the surgery. Bleeding was higher in the test group than in the control group on the day of surgery. Pain, discomfort, epithelization and color match scores had no significant difference between test and control group.

Ozcan et al. (2017)	RCT	125 (Control group: 41; Test groups: 42)	21 to 48 years Control group: 37.61 ± 6.64 Test group 1: 34.55 ± 7.64 Test group 2: 37.11 ± 4	NI	FGG	Control group: Palatal stent Test Group 1: PRF (2700 rpm for 12 min) + Butyl-cyanoacrylate (PeriAcryl, GluStitch). Test Group 2: Butyl-cyanoacrylate (PeriAcryl, GluStitch)	1-7, 14, 21, 28, 35 and 42 days	Pain (VAS), bleeding and epithelization (hydrogen peroxide test)	Statistically significant differences were found for bleeding, pain and epithelialization in favor of the test group 1.
Patarapongsanti et al. (2019)	RCT (split-mouth)	18	45 - 78 years 60.00 ± 8.45 years	M: 7 F:11	FGG	Control Group: Oxidized regenerated cellulose (Surgicel, Ethicon; Johnson & Johnson, USA) + absorbable suture Test group: PRF (3000 rpm for 10 min) + absorbable suture	1, 3, 7 days, 3 and 4 weeks	Pain (VAS), CWE (hydrogen peroxide test) and wound area (donor site measurements)	Similar wound size reduction at 1 week (test: 36.87%, control: 38.78%) was found. At 2 weeks, most of the sites in test group (88.89%) showed CWE, whereas 66.67% of the control group had CWE. Pain was more prevalent in the control group (27.77%) than in the test group (11.1%) on day 1.
Patel et al. (2011)	RCT	18 (Control group: 10; Test group: 8)	28.13 ± 6.38 years	M: 8 F: 10	FGG	Control group: 2 mL of non-ozonated oil per day + palatal stent Test group: 2 mL ozonated oil per day (14 lg of ozone per mL) + palatal stent	24 hours, 5, 7, 14, 21, 28 days and 3 months	Wound area (donor site measurements) and cytological analysis	Planimetrical results showed a significant improvement in wound size on days 5, 7, 14, 21, and 28 in the test group compared to the control group. Cytological results showed a significant improvement in epithelial healing on days 7, 14, and 21, and the second and third months, postoperatively, after the application of ozonated oil compared to control oil.
Patel et al. (2012)	RCT	20 (10 per group)	28.13 ± 6.38 years	M: 8 F: 12	FGG	Control group: 2 mL of non-ozonated oil per day + palatal stent Test group: 2 mL ozonated oil per day (14 lg of ozone per mL) + palatal stent	24 hours, 3, 7, 14 and 21 days and 2, 3, 8 and 18 months.	Cytological analysis	Cytological results showed that there was a significant improvement in epithelial healing by the 7th, 14th and 21st day and 2, 3 and 8 months postoperatively in the ozone group compared to the control group.
Pekbagriyanik et al. (2021)	RCT	36 (18 per group)	Control group: 40.6 ± 9.604 Test group: 40.5 ± 10.072	M: 31 F: 5	FGG	Control Group: Palatal stent Test Group: Non-thermal atmospheric pressure plasma (PlasmaOne,	1-7, 15, 21, 28, 35, 42, 49, 56 days	Pain (VAS), bleeding, analgesic consumption, color,	At week 2, the number of patients with complete epithelization was greater in the test group compared to the control group. Additionally, color match in donor site was better in the test group

						plasma Medical Systems GmbH, Germany, mode 3 for 2 min)		epithelization (hydrogen peroxide test)	than in the control group during the first five follow-up assessments. No significant difference was found between the two groups regarding bleeding, pain level, drug use, and alteration of sensation.
Rath, Zheng, Fern, es, and Priyadarshini (2022)	CR	1	22 years	F:1	FGG	A-PRF (1500 rpm for 14 min) + palatal stent	1-8 days, 2 weeks, 6 months and 1 year	Pain (NRS-101 and VRS-4), color, epithelization, and healing (visually)	In terms of healing, the use of A-PRF membrane appears to accelerate healing at the donor site, thereby reducing postoperative complications.
Reddy et al. (2015)	CS	2 (1 per group)	25 years	M: 1 F: 1	FGG	Control Group: Spontaneous healing Test Group: PRF (3000 rpm for 10 min)	12/13, 18/19, 24/25, 29/30 and 30/31 days	Epithelization/ healing (hydrogen peroxide test and Landry)	PRF membrane demonstrated considerably faster healing and higher healing score compared to site not covered by PRF membrane.
Rossmann and Rees (1999)	RCT	26 patients (Control group: 8; Test groups: 9) 30 sites (10 per group)	Control Group: 40 years Test group 1: 40 years Test group 2: 46.4 years	NI	FGG	Control Group: Surgical stent Test group 1: Oxidized regenerated cellulose (Surgicel fibrillar absorbable hemostat, Johnson & Johnson Medical, Arlington, TX) + surgical stent Test Group 2: GS (Gelfoam absorbable gelatin sponge, Upjohn Co., Kalamazoo, MI.) + surgical stent	2/3, 7, 14 and 21 days	Pain (VAS), bleeding, analgesic consumption, color and epithelization (visually)	The median time to hemostasis was significantly shorter when a hemostatic agent was applied to the palatal wounds compared to control. Pain assessment showed no differences across treatment groups. However, by 21 days, only the test group 1 had complete healing with all sites rated as normal to rapid healing, compared to the test group 2 where 40% of the sites were rated as slow healing. Adverse events, primarily bleeding episodes during the first 7 days after surgery, were found in 40% of the test group 1 and control group, while no sites in the test group 2 had an adverse event.

Samani, Saberi, Tabatabaei, and Moghadam (2017)	RCT (split-mouth)	10	20 - 45 years	NI	FGG	Control Group: Spontaneous healing Test Group: PRP (4000 rpm for 8 min)	2, 4, 7, 10 and 14 days	Pain (VAS), healing (LTH index), wound area (donor site measurements) color, contour, and distortion of the wound (MSS)	Significant differences between the study groups and across different time intervals were seen in favor of the test group for pain, wound closure, epithelization, color and contour.
Sankar et al. (2021)	RCT (pilot study)	20 (10 per group)	39.14 ± 6.66 years	M: 15 F: 5	FGG	Control Group: Chitosan dressing alone (5g of commercially purchased chitosan to 100 mL of water) + palatal stent Test Group: Aloe vera-chitosan dressing (Commercially available Aloe vera gel at a ratio of 1:2 v/v) + palatal stent.	7, 14, 21 days and 1 month.	Pain (VAS) and healing (Landry)	There was a statistical significance in wound healing in test group when compared to control group from 14-21st day postoperative. However, no statistical significance for pain values was observed between groups.
Saroff et al. (1982)	CS	20 (10 per group)	21 - 65 years	M: 10 F: 10	FGG	Control Group: Periodontal dressing (Coe Pak, Coe Laboratories, Chicago, IL). Test Group: Microcrystalline collagen hemostat (Avitene, Avicon, Inc., Fort Worth, TX)	2, 7 and 28 days	Pain (Wolff and Jarvik scale), bleeding, epithelization (toluidine blue)	Ten minutes after the grafts were removed, the mean volume of blood absorbed by the sampling technique was 0.96 ml in the treated wounds versus 1.85 ml in the control. However, no differences in the healing and pain analysis were observed between control and test group.
Schinini et al. (2021)	RCT	36 (18 per group)	31.9 (21 to 49) years Control group: 33.2 (24–49) years Test group: 30.6 (21–46) years	M: 7 F: 29	CTG	Control Group: Collagen hemostatic sponge (Hemospon, Technew Comind, Rio de Janeiro, Brazil) Test Group: Collagen hemostatic sponge (Hemospon, Technew	7, 14 and 30 days	Pain (VAS), bleeding and healing (EHI)	Eight subjects from suture group and 10 from no suture group showed complete wound closure at day 14 and at 30 days, complete closure was observed in 35 out of 36 patients. Sutured and non-sutured sites display similar early wound healing outcomes and patient-reported outcomes.

						Comind, Rio de Janeiro, Brazil) + suture			
Shakir et al. (2015)	CR	2 (1 per group)	NI	NI	FGG	Control group: Spontaneous healing Test Group: PRF (3000 rpm for 10 min)	2, 7, 12, 18, 24 and 30 days	Pain (VAS) and epithelization (hydrogen peroxide test)	Patient with PRF palatal dressing showed complete wound closure by 18 days and reported lesser post-operative morbidity than the patient in whom PRF was not used.
Shanmugam et al. (2010)	RCT	32 (16 per group)	25−50 years	NI	FGG	Control Group: Non-eugenol-based dressing (Coe-pak®, GC America Inc., USA). Test Group: Collagen hemostatic sponge (Colla Cote®, Zimmer Dental CA, USA)	2, 7, 14 and 42 days	Pain and color (VAS), consistency and histological examination	The color, consistency, pain and burning sensation parameters showed significant improvement in the test group when compared to control group. Histologically, there was a greater evidence of collagen formation and turn over in the test group than control group.
Sharma et al. (2019)	RCT	20 (10 per group)	M: 36.2 (20-52) years F: 30.33 (18-48) years	M: 5 F: 15	FGG	Control group: Collagen hemostatic sponge (CollaCote®, Zimmer dental) + palatal stent Test Group: PRF (3000 rpm for 10 min) + palatal stent	7, 8, 12, 13, 18, 19, 24, 25 and 30 days	Pain, bleeding, epithelization (hydrogen peroxide test and toluidine blue), wound area (donor site measurements)	Intragroup comparisons showed significant improvement in wound healing parameters in both groups, but the PRF group healed slightly better initially. No statistically significant difference was found on intergroup comparison with respect to depth, hemorrhage, pain, epithelialization, and size.
Soheilifar et al. (2015)	RCT	26 (13 per group)	Control Group: 27.83 ± 8.67 Teste Group: 28.23 ± 7.991	M: 9 F: 17	FGG	Control Group: Placebo (same packaging as bromelain once a day for 10 days). Test Group: Bromelain (500 mg once a day for 10 days)	7, 10 and 14 days	Pain (VAS), bleeding, analgesic consumption, and epithelization (hydrogen peroxide test)	Bromelain caused a significant reduction in pain at the donor site (2.605±0.509) compared to the placebo (4.885±0.519). The number of donor sites with complete epithelialization was higher in the test group compared to the control group, but this difference was not statistically significant. The two groups were the same regarding postoperative bleeding.

Sousa et al. (2020)	RCT	25 (Control group: 11; Test group: 14)	19-65 years 36.4 ± 14.9 years	M: 9 F: 16	FGG	Control Group: Collagen hemostatic sponge (Technew, Rio de Janeiro, Brazil) Test Group: A-PRF (1500 rpm for 8 min)	2, 7, 14, 30 and 90 days	Pain (VAS), necrosis, epithelization (visually) and wound area (donor site measurements)	A-PRF group had higher palatal wound reduction than the control group, at 7, 14, and 30 days of follow-up. The highest difference between the groups was attained at 30 days (91.5% for A-PRF versus 59.0% control group). At 14 days, a significant difference in the proportion of patients showing total epithelization was found: 64.3% for A-PRF versus 9.1% for the control group. The control group experienced higher pain level and discomfort until the 14th day. On the seventh day, one patient in the control group exhibited necrosis of donor site margins.
Spin et al. (2017)	RCT	24 (Control group: 14; Test group: 10)	45 (30-70) years Control group: 45.3 ± 12.2 years Test group: 45.7 ± 12.0 years	M: 6 F: 18	FGG	Control Group: Acrylic plate and surgical cement (Pericem, Technew, Rio de Janeiro, RJ, Brazil). Test Group: Latex membrane (developed exclusively to the study) + Acrylic plate and surgical cement (Pericem, Technew, Rio de Janeiro, RJ, Brazil).	3, 7, 15 and 30 days	Pain (VAS), bleeding, epithelization (hydrogen peroxide test) and wound area (donor site measurements)	At 15 days, control group patients presented a fully healed wound, while mean wound closure was 98.6% in the latex group. As for bleeding, at 7 days it was positive for 21.4% of the patients in the control group, while it was already negative for all patients in the latex group. Regarding reported pain, VAS values were larger in the control group, although with no statistical significance.
Stavropoulou et al. (2019)	RCT	35 (Control group: 18; Test group: 17)	23 to 81 years Control group: 58.5 ± 13.52 years Test group: 53.18 ± 20.2 years	M: 10 F: 25	CTG	Control group: Polytetrafluoroethylene sutures Test Group: Cyanoacrylate (PeriAcryl 90 High Viscosity, GluStitch, Delta, BC)	7 days	Pain (VAS), bleeding, necrosis and analgesic consumption and modified early wound healing index	The discomfort median value was 1.49 in the suture group and 1.86 in the cyanoacrylate. Postoperative bleeding was reported from two patients and abnormal inflammation was recorded only for one patient from the cyanoacrylate group. No statistically significant differences were found between the two methods in reported pain level and analgesic intake.

Stein et al. (1985)	CS	20	NI	NI	FGG	Collagen hemostatic sponge (Collastat) + coe-pack	7 and 30 days	Bleeding and healing (visually)	The highly porous sponges conformed to the wound, absorbed fluid, and produced consistently reliable hemostasis with no secondary bleeding. Healing proceeded normally with no evidence of infection, tissue reaction or other adverse effects.
Tasdemir et al. (2016)	RCT	30 (15 per group)	34.6 (22 – 49) years Control group: 34.6 ± 7.9 Test Group: 34.6 ± 7.9	M: 15 F: 15	FGG	Control group: Prefabricated plastic stent Test group: Ozone immediately after surgery and at days 1 and 3 postsurgery + Prefabricated plastic stent	1, 2, 3, 6, 8, 10, and 13 days	Pain (VAS) and analgesic consumption	Increase in blood perfusion units in the test group was significantly higher than control group at 1, 2-, 3-, 6- and 8-days post-surgery. Significant differences occurred between test and control groups in terms of VAS values during the first week post-surgery for donor sites. The analgesic consumption was significantly lower in the test group.
Tavelli et al. (2018)	RCT	50 (10 per group)	26 – 73 50.02 ± 11.36 Control Group: 46.4 ± 14.4 Test Group 1: 45.3 ± 11.5 Test Group 2: 5.2 ± 1.1 Test Group 3: 52.8 ± 7.1 Test Group 4: 4.9 ± 0.7	M:17 F: 33	FGG	Control Group: 5-0 nonresorbable monofilament suture (Seralon, Serag Wiessner). Test Group 1: Adhesive agent (PeriAcryl 90 HV, Glustitch) Test Group 2: Hemostatic agent (Spongostan,Ethicon) Test Group 3: Periodontal dressing (Peripac, Dentsply DeTrey) Test Group 4: Hemostatic agent combined with an adhesive agent (Spongostan + PeriAcryl)	1, 2, 3, 4, 5, 6, 7, 10, and 14 days	Pain (VAS) analgesic consumption and healing (visually)	Lower pain was found in all test groups compared to the control group. The test group 4 had very low pain throughout the 14 days. The lowest healing scores at day 10 were associated with the control group (6.8 VAS points) in contrast to the four test groups (8.2 to 9.0 VAS points). Fifty percent of study participants who did not receive any palatal protection reported taking additional doses of pain-relief medication. The lowest drug consumption was reported for the test group 4.

Tavelli et al. (2019)	RCT	44 (22 per group)	32 - 73 51.7 ± 11 Control group: 52.6 ± 9.3 Test group: 50.86 ± 12.55	M: 15 F: 29	FGG	Control group: GS (Spongostan; Ethicon, Somerville, USA). Test group: GS plus adhesive (PeriAcryl 90 HV; Glustitch, Delta, Canada)	1, 2, 3, 4, 5, 6, 7, 10, and 14 days	Pain (VAS) and analgesic consumption	Statistically significant differences in pain perception were found between test and control groups in each of the studied days. Analgesic consumption was lower in the test group. Graft width < 14 mm was found to be associated with lower discomfort.
Thoma et al. (2012)	RCT (split-mouth design)	15	NI	NI	FGG Biopsies (diameter 6 mm; depth 3 mm)	Control group: Soft Protective Splint Test group: Xenogeneic collagen matrix (6 mm x 3 mm; Mucograft®; Geistlich Pharma AG, Wolhusen, Switzerland) + Soft Protective Splint	4, 8, 15 and 29 days	Wound area (donor site measurements), color and epithelization (visually)	The defect area decreased over time for both treatments. Reepithelization was completed in all subjects by day 15. The defect area was significantly smaller for test (19.3 ± 3.4 mm^2) compared with control (21.3 ± 3.3 mm^2) at day 4, and at day 8 (test: 11.7 ± 2.5 mm^2; control: 13.6 ± 2.9 mm^2. The colour match was more favourable for test group at day 4, 8 and 29. Somatosensory measurements revealed slightly lower wound sensitivity at day 4 for test compared with control.
Thoma et al. (2016)	RCT (split-mouth design)	20	NI	NI	FGG Biopsies (diameter 6 mm; depth 3 mm)	Control group: Soft Protective Splint Test group: Xenogeneic collagen matrix (6 mm x 3 mm; Mucograft®; Geistlich Pharma AG, Wolhusen, Switzerland) + Soft Protective Splint	4, 8, 15 and 29 days	Cytological analysis	At day 4, wound bed keratinization amounted to 12.4 ± 7.5% (control) and 18.0 ± 10.2% (test). This increased up to day 8 (19.7 ± 25.5% control; 29.1 ± 8.0% test) and reached complete keratinization at day 15 in both groups. An increase in the amount of granulation tissue (32–88% control; 14–41% test) was observed from day 4 to day 8. Angiogenesis was first detected at 8 days. At day 29, the amount of connective tissue in all compartments reached values similar to the native tissue at baseline.

Tomar, Singh, Jain, Kaushik, and Dureja (2016)	CR	1	31 years	M: 1	FGG	PRF membrane (3000 rpm for 10 min) + interrupted sutures using 4-0 silk	15 and 30 days	Healing (visually) and discomfort	Uneventful healing was observed at PRF site by 15 days followed by 1 month. The considerably less healing time required by PRF membrane site resulted in less postoperative discomfort to the patient.
Gülbahar Ustaoglu et al. (2016)	RCT	34 (Control group: 18 Test group: 16)	NI	NI	FGG	Control group: Acrylic stent Test group: T-PRF + Acrylic stent	3, 7, 14, 21, 30 days and 6 months	Pain (VAS), bleeding, analgesic consumption, color (VAS) and CWE (hydrogen peroxide test)	Color match scores of the test group were significantly higher than those of the control group at 7 and 14 days. CWE was observed at a higher frequency in the test group than in the control group on day 14. Post-operative bleeding prevalence was lower in the test group than in the control group for the first 2 days.
Vieira et al. (2010)	CS	10	42 years 32-58 years	M: 01 F: 09	FGG	Control group: Spontaneous healing Test group: Laser (LED, 5W, 650 nm, and 8 J/cm2 at 0 h, 48 h and 72 h after surgery).	1, 2, 3, 4, 5, 6, 7, 14 and 21 days	Pain (VAS) and epithelization (hydrogen peroxide test)	Statistically significant differences in pain level were found between the control and test groups on days 1 and 2 after surgery. The wound healing analysis showed that 80% of the irradiated patients and 40% of patients in the control group were healed 14 days after surgery.
Yaghobee et al. (2021)	RCT (split-mouth design)	12	30 - 53 years 44.58 ± 7.5 years	M: 3 F: 9	FGG	Control group: 2 mL of the gel alone (after the procedure and 2 days later). Test group: 1 mL erythropoietin gel at a concentration of 4,000 IU mL-1 (after the procedure and 2 days later)	2, 7, 14, 21, and 28 days	Epithelization (hydrogen peroxide test), color, texture, and contour (visually)	The test group showed significantly better keratinization only on day 21. Comparison of clinical healing based on direct examination revealed significantly better healing in the test group on day 28. Furthermore, inflammation in the test group was lower than in the control group on the same day.
Yen, Griffin, Cheung, and Chen (2007)	RCT (split-mouth design)	20	30-70 years	M: 7 F: 13	CTG	Control group: 5-0 bioabsorbable polyglactin suture + non eugenol periodontal dressing Test group: Platelet	1, 2, 4, and 6 weeks	Pain (VAS), necrosis, color, texture, and contour (visually)	The test group not showed accelerate donor site clinical healing. No significant statistical differences in complication occurrence and perceived pain levels were found between control

						concentrate + 5-0 bioabsorbable polyglactin suture + non eugenol periodontal dressing			and test sites. Biopsy samples revealed that during healing, test sites contained lower concentrations of inflammatory cells, more type I mature collagen, and less type III immature collagen than control sites.
Yıldırım et al. (2018)	RCT	36 (12 per group)	21 - 62 years 32.58 ± 7.81 years	M: 9 F: 27	FGG	Control group: Periodontal dressing (Peripac, DENTSPLY DeTrey GmbH, Konstanz, Germany). Test group 1: 0.2% HA gel (Gengigel, Ricerfarma SRL, Milano, Italy) + periodontal dressing Test group 2: 0.8% HA gel (Gengigel Prof, Ricerfarma SRL) + periodontal dressing	3, 7, 14, 21, and 42 days	Pain (VAS), bleeding, color, CWE (visually)	Test groups experienced less pain than the control group on days 3 and 7. Mean VAS score for burning sensation was higher in the control group on day 3 compared with test groups 1 and 2. CWE in all patients was achieved on day 21 in both test groups, whereas it was achieved on day 42 in the control group. The test groups showed higher color match scores than the control group on days 21 and 42.
Yilmaz et al. (2022)	RCT	27 (Control group: 14 Test group: 13)	38.48 ± 10.04 years	M: 5 F: 22	FGG	Control group: Spontaneous healing Test group: Cyanoacrylate (Indermil, Connexicon Medical)	1, 2, 3 e 4 weeks	Pain (VAS), analgesic consumption and epithelization (hydrogen peroxide test)	The epithelization, color harmony, post-operative pain scores and the number of painkillers were similar in both groups.
Yussif et al. (2021)	RCT	24 (12 per group)	Control group: 27.67 ± 5.55 Test group: 27.75 ± 4.96	M: 11 F: 13	FGG	Control group: Custom-made acrylic palatal stent Test group: Propylene mesh (©Ethicon US, LLC. 2019)	2, 4, 6, 8, 14 and 30 days	Pain, bleeding (VAS) and healing index	The polypropylene mesh was more effective at reducing bleeding (2.4 ± 1.075) and pain (1.600 ± 0.516) in comparison to the custom-made acrylic stent (bleeding 5.8 ± 1.22 and pain 7.100 ± 0.316). The decline in amount of bleeding amount and its duration achieved by the propylene mesh was statistically significant. There was no statistically significant difference in patient satisfaction and the duration of

									healing process between the 2 groups. However, the healing profile of the test group was statistically significant when compared with the control group.

M: Male; F: Female; RCT: Randomized clinical trial; CS: Case series; CR: Case Reports; FGG: Free gingival graft; KT: ketorolac tromethamine; CTG: Subepithelial connective tissue graft; PRF: Platelet-Rich Fibrin; T-PRF: Titanium-prepared, platelet-rich fibrin; i-PRF: injectable platelet-rich fibrin; A-PRF: Advanced-platelet-rich fibrin; PRP: Platelet-rich plasma; HA: Hyaluronic acid; CHE: Collagen Hemostatic Sponge; CWE: Complete re-epithelialization of the palatal wound; VAS: Visual Analogue Scale; NRS-101: 101-point numerical rating scale; VRS-4: 4-point verbal rating scale; WBFS: Wong and Baker Faces Scale; EHS: Early Wound Healing score; EHI: Early Healing index; LTH: Landry, Turnbull, and Howley; MSS: Modified Manchester scar scale NI: Not informed.

Table 1 - Main results of the qualitative analysis (systematic review)

Outcomes	Variables/value	Number of studies
Sites number	2120	70
Palatal Wound Treatment	PRF	17
	Collagen hemostatic sponge	16
	Periodontal dressing	14
	Laser	11
	Cyanoacrylate	6
	Collagen matrix/membrane/plug	4
	Ozone	5
	HA + periodontal dressing	4
	PRF + periodontal dressing	2
	Human amniotic membrane	2
	Oxidized regenerated cellulose	2
	Hemostatic Sponge	2
	Hemostatic Sponge + cyanoacrylate	2
	Chitosan gel	2
	Other types of treatments mentioned only once	26
Wound area reduction	Yes	20
	Not informed	50
Epithelization	Yes	33
	Not informed	37
Wound area healing	Yes	34
	Not informed	36
Bleeding	Yes	29
	No	17
	Not informed	24
Necrosis	Yes	5
	No	25
	Not informed	40
Pain	Yes	56
	Not informed	14
Analgesic consumption	Yes	27
	Not informed	43

PRF: Platelet-Rich Fibrin; HA: Hyaluronic acid.

3.4 Quality assessment

All included case reports and case series were classified as high quality (Table S4). For the RCTs, 29 studies obtained a low risk of bias, 20 studies showed some concerns, and 7 studies obtained a high risk of bias (Figure 2). Most of the included studies showed the high risk of bias in domain 2 (deviations from the intended interventions) due the to absence of blinding the people responsible for participants' assigned intervention during the trial.

Table S4 - Quality assessment of included studies classified as case series and case reports.

First Author	Year	Case Report/Case Series	Selection		Ascertainment				Causality								Reporting		Quality Assessment
			Question 1		Question 2		Question 3		Question 4		Question 5		Question 6		Question 7		Question 8		
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
Aravindaksha	2014	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High
Belkhede	2019	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X			X	High
Berridge	2019	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High
Kulkarni	2014	Case Series		X	X		X		NA	NA	NA	NA	NA	NA	X		X		High
Lafzi	2019	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High
Martelloni	2019	Case Report	X		X			X	NA	NA	NA	NA	NA	NA	X		X		High
Martin	1995	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High
Rath	2022	Case Report	X		X		X		NA	NA	NA	NA	NA	NA		X	X		High
Reddy	2015	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High
Saroff	1982	Case Series		X	X		X		NA	NA	NA	NA	NA	NA	X		X		High
Shakir	2015	Case Report	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High
Stein	1985	Case Series		X	X		X		NA	NA	NA	NA	NA	NA	X		X		High
Tomar	2016	Case Report	X		X			X	NA	NA	NA	NA	NA	NA	X		X		High
Vieira	2010	Case Series	X		X		X		NA	NA	NA	NA	NA	NA	X		X		High

NA: Not applied; Questions: Question 1: Did the patient(s) represent the whole case(s) of the medical center?; Question 2: Was the exposure adequately ascertained?; Question 3: Was the outcome adequately ascertained? Question 4: Were other alternative causes that may explain the observation ruled out?; Question 5: Was there a challenge/rechallenge phenomenon?; Question 6: Was there a dose–response effect?; Question 7: Was follow-up long enough for outcomes to occur?; Question 8: Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?; *High: 0 to 1 categorized with “NO”; Moderate: 2 to 3 categorized with “NO”; Low: 3 to 4 categorized with “NO”.

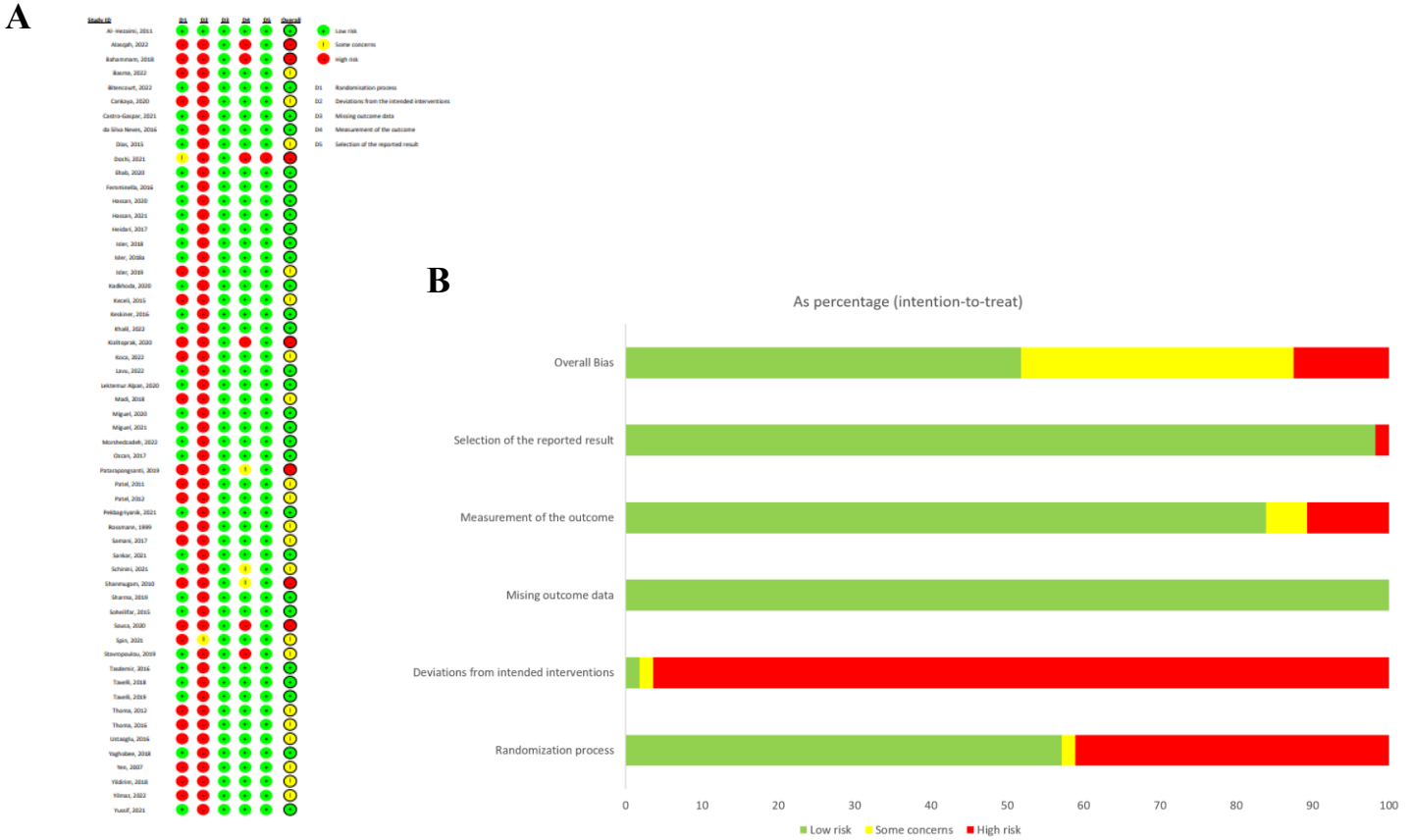

Figure 2: Risk of bias using RoB2 tool of randomized controlled trial studies included in this review. A: Review authors' judgments about each risk of bias item for the included studies; B: Review authors' judgments about each item of the risk of bias presented as percentages across all the studies included.

3. 5 Results synthesis

Twelve RTCs (Bitencourt et al., 2022; Castro-Gaspar et al., 2021; Femminella et al., 2016; A. A. A. Hassan et al., 2020; Işler et al., 2019; Miguel, Mathias-Santamaria, Rossato, Ferraz, Figueiredo-Neto, et al., 2021; Miguel, Mathias-Santamaria, Rossato, Ferraz, Rangel, et al., 2021; Morshedzadeh et al., 2022; Patarapongsanti et al., 2019; Pekbagriyanik et al., 2021; Shanmugam et al., 2010; Yilmaz et al., 2022),were included in the quantitative analysis for pain assessment (using VAS) at 1, 3 and 7 days of post-operative. A direct comparison between leucocyte and platelet-rich fibrin (L-PRF) and hemostatic sponge with the other interventions linked in the evidence network was not possible for palatal wound healing analysis, consequently, only nine RCTs (Femminella et al., 2016; Heidari et al., 2017; Isler, Uraz, et al., 2018; Miguel, Mathias-Santamaria, Rossato, Ferraz, Figueiredo-Neto, et al., 2021; Miguel, Mathias-Santamaria, Rossato, Ferraz, Rangel, et al., 2021; Morshedzadeh et al., 2022; Papakonstantinou et al., 2020; Pekbagriyanik et al., 2021; Yilmaz et al., 2022), were included for the palatal wound complete epithelialization evaluation (using hydrogen peroxide test) after 14- and 21-day.

3.5.1 Direct meta-analysis

For pain assessment at 1, 3 and 7 days postoperative, the direct comparison between the agents demonstrated that the use of L-PRF was more efficient in reducing postoperative pain in comparison to the hemostatic sponge at 1 day (MD: 2.18; 95% CI: 1.50 – 2.86; $P < 0.00001$) (Supplementary Figure S1). At day 3, L-PRF was superior in pain control in comparison hemostatic sponge (MD: 0.46; 95% CI: 0.12 – 0.80; $P = 0.008$) and ozone therapy (MD: 0.89; 95% CI: 0.15 – 1.63; $P = 0.02$) (Supplementary Figure S2). At 7 days, L-PRF also showed less pain levels in comparison to the suture (MD: 1.5; 95% CI: 0.11 – 2.89; $P = 0.03$) and hemostatic sponge (MD: 2.25; 95% CI: 1.56 – 2.94; $P < 0.00001$) (Supplementary Figure S3). Furthermore, periodontal dressing resulted in higher postoperative pain levels compared to the hemostatic sponge at 7 days (MD: 0.83; 95% CI: 0.26 – 1.40; $P = 0.004$) (Supplementary Figure S3). No differences were obtained between other agents at 1, 3 and 7 days ($P > 0.05$) (Supplementary Figure S1-S3).

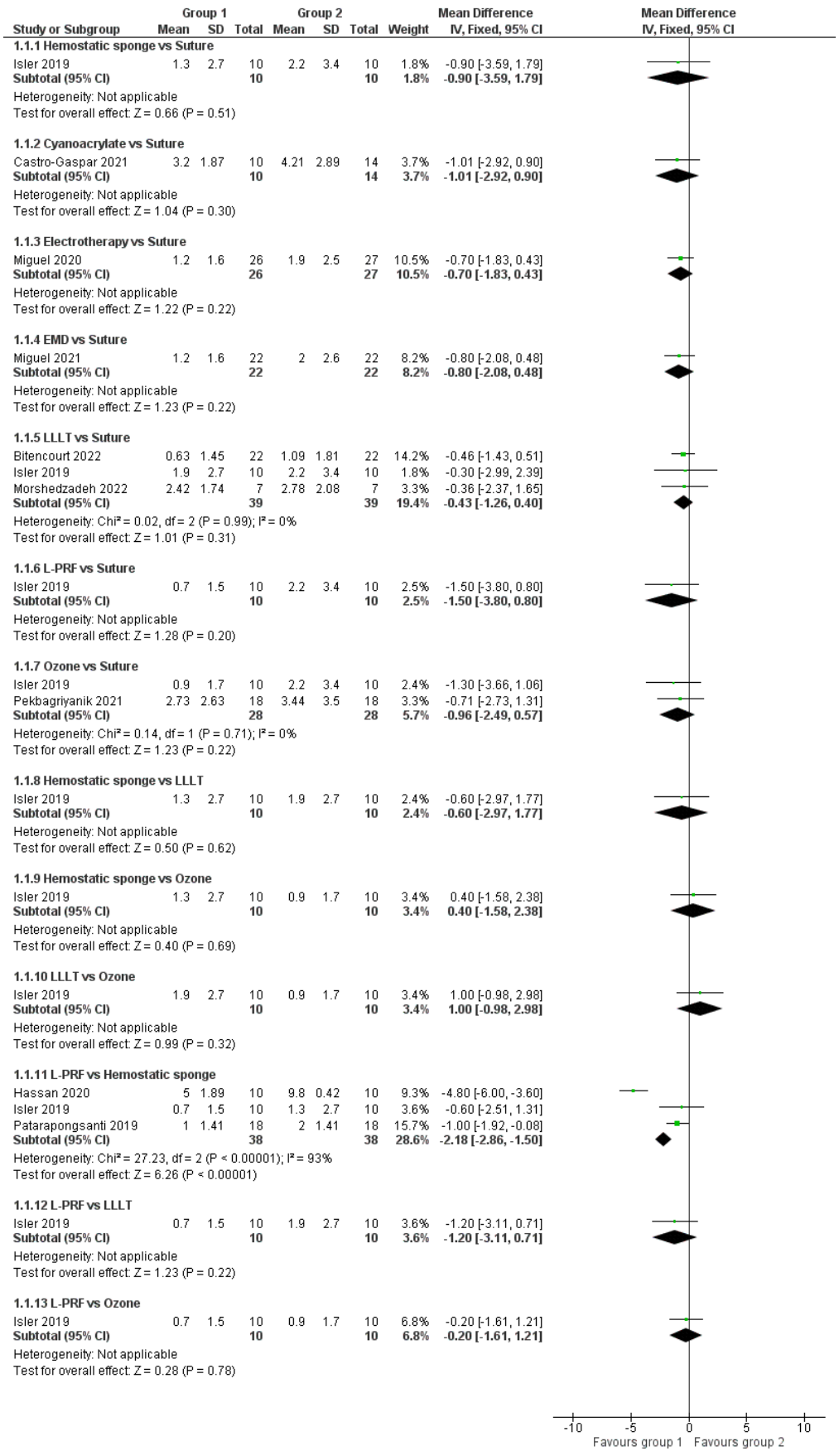

Figure S1: Direct pairwise comparison (CI 95%) between different wound healing agents in terms of pain control at 1 day.

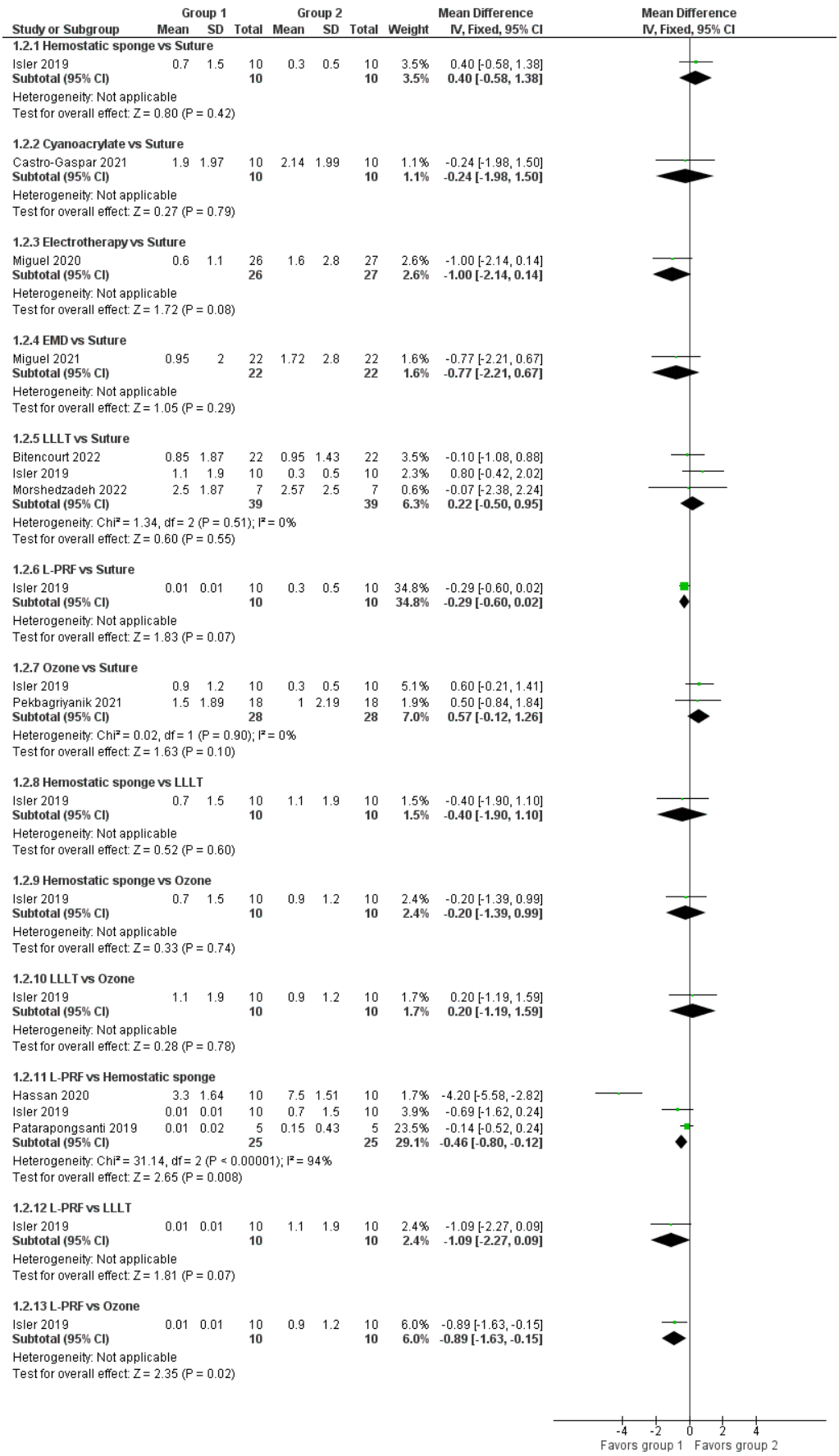

Figure S2: Direct pairwise comparison (CI 95%) between different wound healing agents in terms of pain control at 3 days.

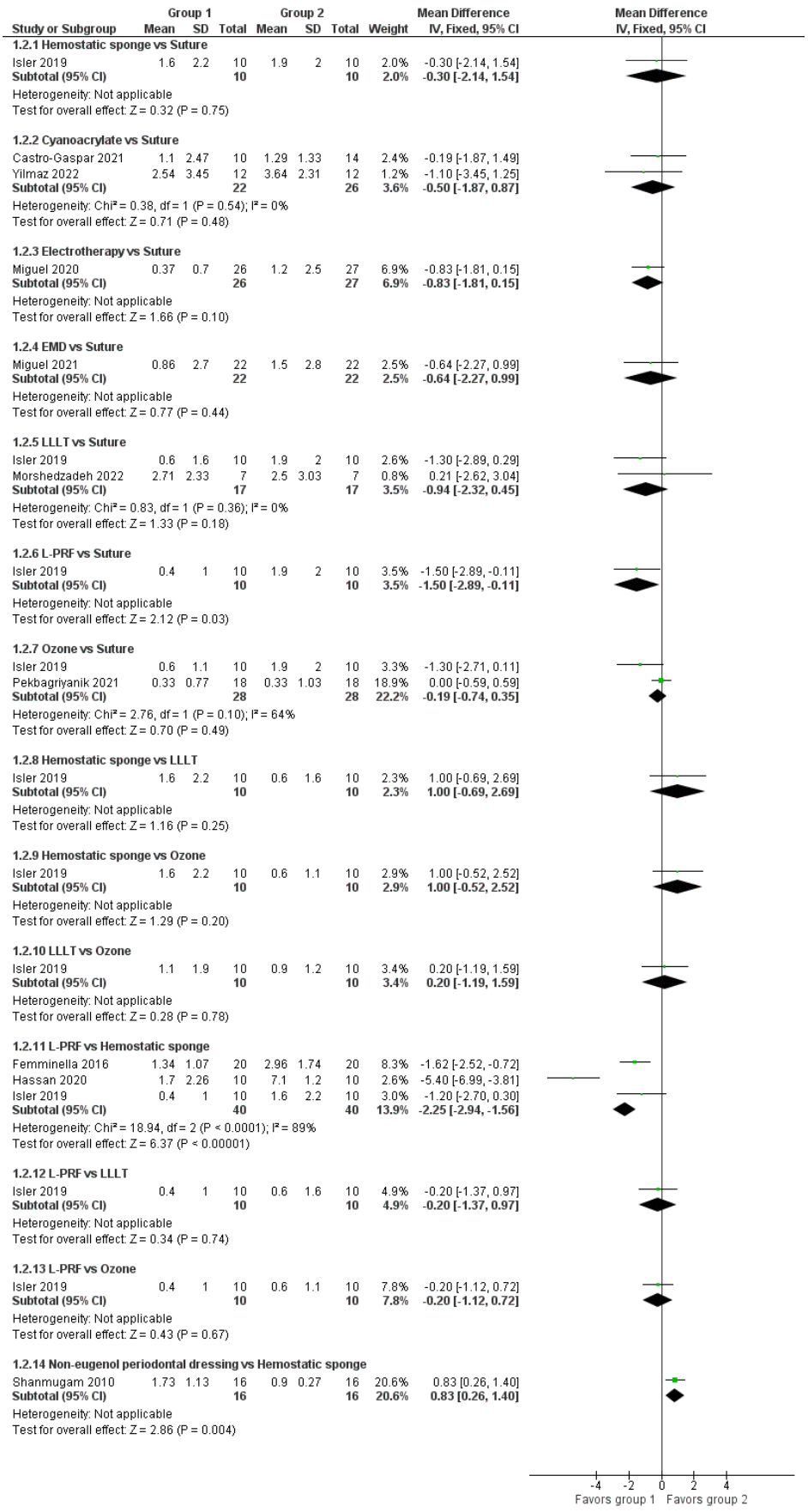

Figure S3: Direct pairwise comparison (CI 95%) between different wound healing agents in terms of pain control at 7 days.

Regarding palatal wound healing, L-PRF promoted superior results in comparison to the hemostatic sponge at 14 (OR: 0.23; 95% CI: 0.07 – 0.78; P = 0.02) and 21 days (OR: 0.04; 95% CI: 0.00 – 0.27; P = 0.001) (Supplementary Figure S4 and S5). In addition, better wound repair was obtained with laser (OR: 0.14; 95% CI: 0.03 – 0.68; P = 0.01) and ozone therapy (OR: 0.09; 95% CI: 0.01 – 0.52; P = 0.007) in comparison to suture at 14 days (Supplementary Figure S4). No differences were obtained between other agents at 14 and 21 days (P > 0.05) (Supplementary Figure S4 and S5).

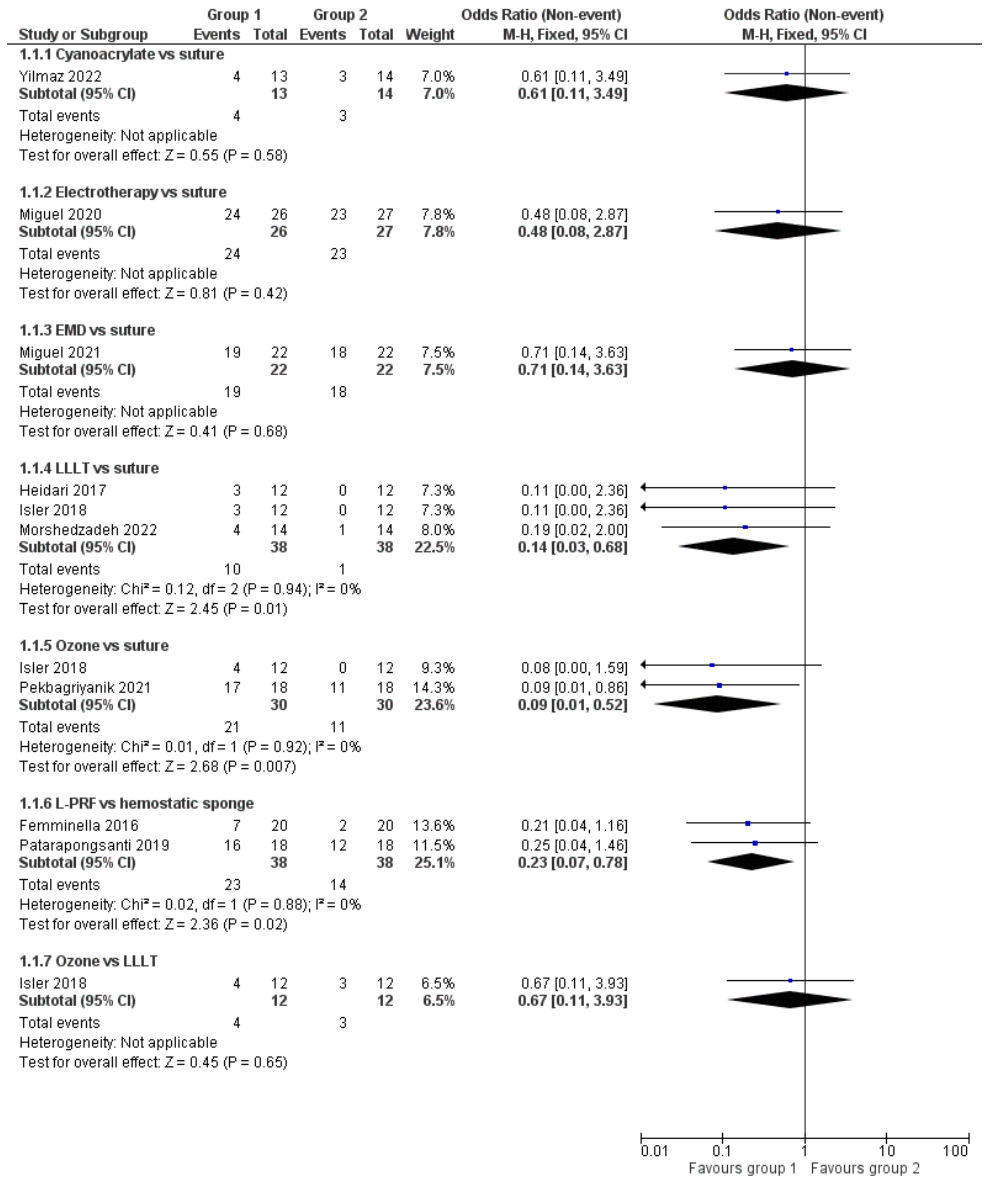

Figure S4: Direct pairwise comparison (CI 95%) between different wound healing agents in terms of wound healing at 14 days.

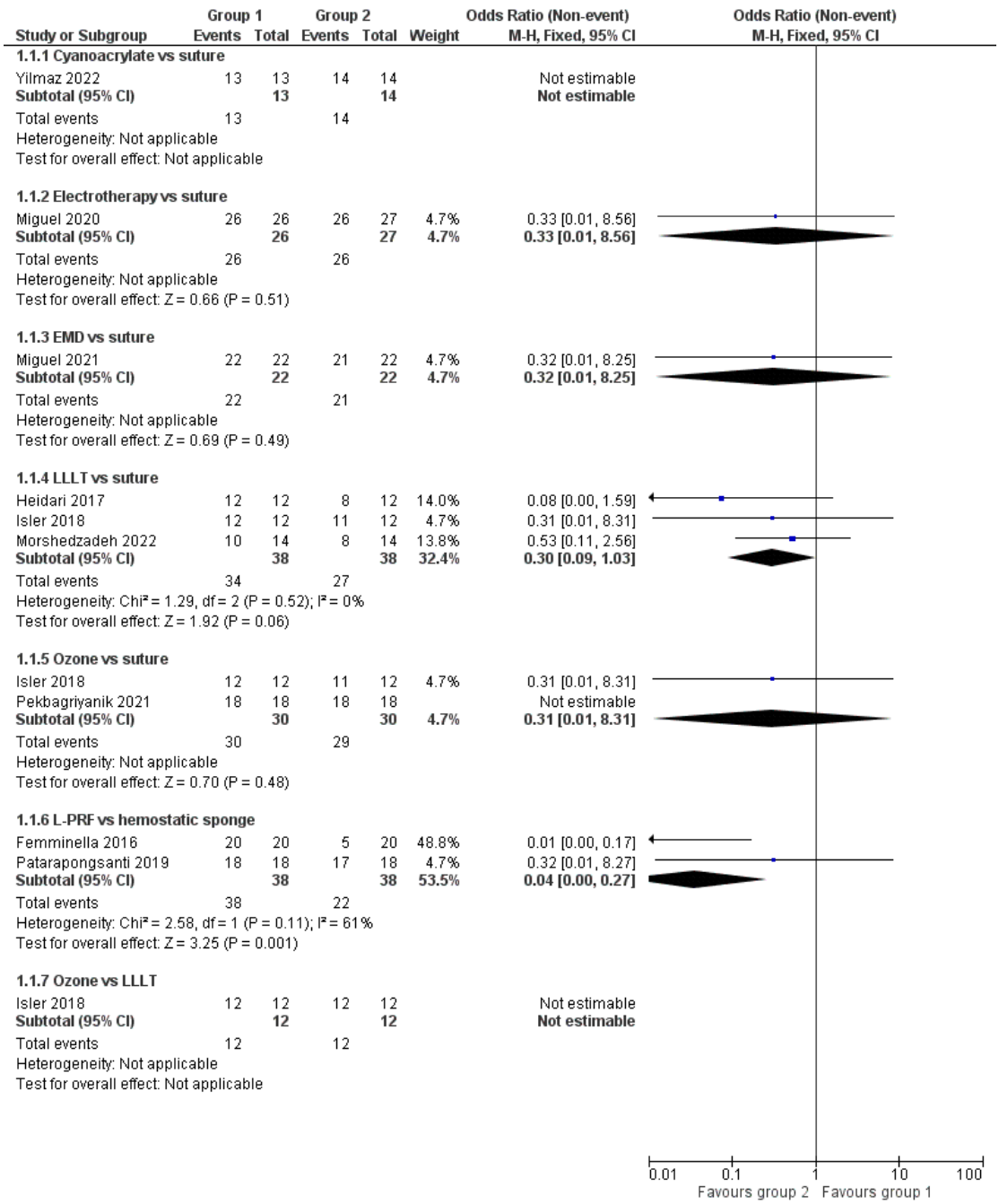

Figure S5: Direct pairwise comparison (CI 95%) between different wound healing agents in terms of wound healing at 21 days.

3.5.2 Network meta-analysis (NMA)

The network meta-analysis plots of direct evidence for pain assessment (using VAS) at 1, 3, and 7 days and wound healing (using hydrogen peroxide test) at 14 and 21 days were shown in Figure 3 and Figure S6 (supplementary materials), respectively.

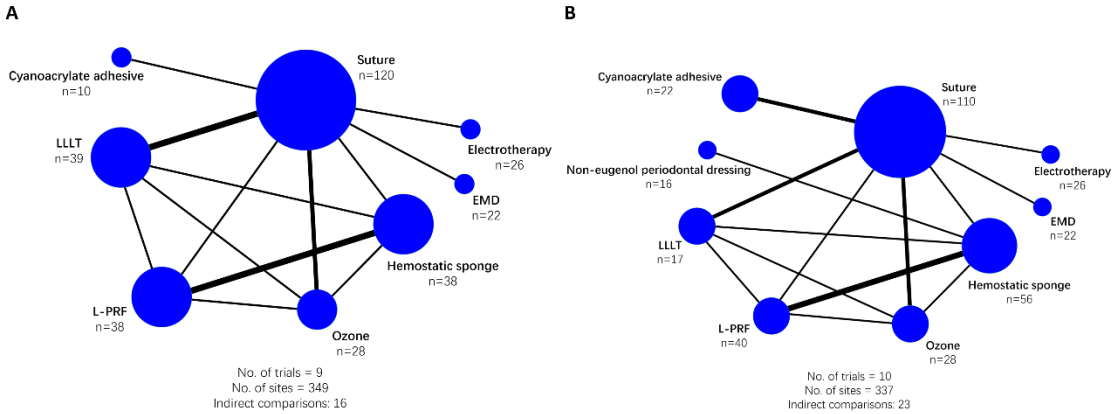

Figure 3: Network meta-analysis plots for pain assessment (using VAS) at 1, 3 (A) and 7 days (B). The plot size corresponds to the sample size contribution of each intervention EMD: Enamel matrix dentin; LLLT: Low level laser therapy; L-PRF: Leucocyte and platelet-rich fibrin.

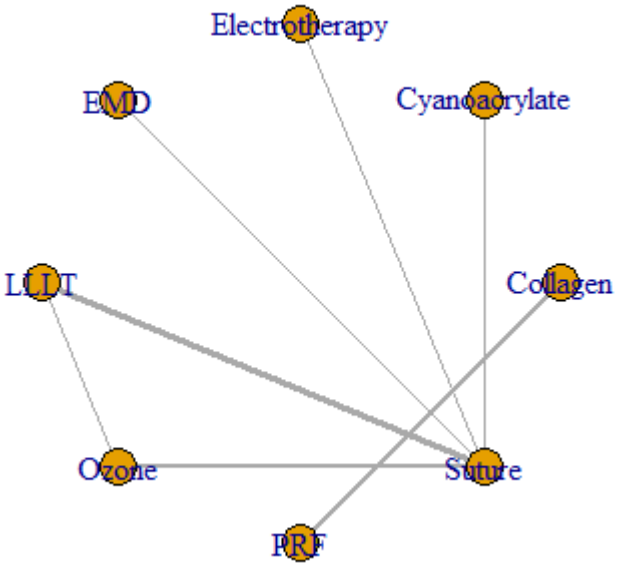

Figure S6: Network meta-analysis plots for palatal wound healing (using hydrogen peroxide test) at 14 and 21 days.

The NMA results for pain assessment on 1 day (Table 2) showed that L-PRF promoted better results for pain control in comparison to all evaluated agents (i.e. suture, ozone therapy, laser therapy, enamel matrix protein derivative gel (EMD), electrotherapy, cyanoacrylate adhesive and hemostatic sponge). In addition, all agents were superior to the hemostatic sponge, except the suture (Table 2). Ozone therapy was superior to laser therapy and electrotherapy. On the other hand, laser therapy promoted higher pain levels in comparison to EMD, electrotherapy and cyanoacrylate adhesive (Table 2). At 3 days, L-PRF was superior to ozone therapy, laser therapy, cyanoacrylate adhesive and hemostatic sponge (Table 2). All agents were superior to hemostatic

sponge, except ozone therapy (Table 2). EMD and electrotherapy was superior to cyanoacrylate adhesive (Table 2). Ozone therapy and laser therapy showed inferior results in comparison to EMD, electrotherapy and cyanoacrylate adhesive (Table 2). At 7 days, L-PRF promoted superior results in comparison to all agents (Table 2) and all agents were superior to hemostatic sponge and periodontal dressing (Table 2).

For palatal wound healing, the NMA results (Supplementary Table S5) showed that all agents (i.e. ozone therapy, laser therapy, EMD, electrotherapy and cyanoacrylate adhesive) promoted better repair in comparison to suture at 14 days. Ozone therapy was superior to all agents evaluated in this period (Supplementary Table S5). Laser therapy was superior to EMD, electrotherapy and cyanoacrylate adhesive (Supplementary Table S5). The electrotherapy was superior to enamel matrix protein derivative gel and cyanoacrylate adhesive (Supplementary Table S5). At 21 days, cyanoacrylate adhesive promoted less wound repair in comparison to all agents evaluated (Supplementary Table S5). Ozone therapy, EMD and electrotherapy was superior to suture and laser therapy (Supplementary Table S5).

Table 2: League table with postoperative pain results from NMA at 1, 3 and 7 days. Wound healing agents were ordered in alphabetical order. Negative (-) values favor treatments in the column compared to the left row. Values in bold represent statistically significant results ($P < 0.05$).

1 day							
HS	**-1.138 (-6.952,4.892)**	**-0.8344 (-6.44, 5.005)**	**-0.9212 (-6.59, 4.92)**	**-0.4528 (-4.18, 3.432)**	**-1.182 (-4.919, 2.765)**	**-2.203 (-4.738, 0.4011)**	-0.1213 (-3.75, 3.664)
	Cyanoacrylate	0.3016 (-6.057, 6.688)	0.2069 (-6.194, 6.619)	**0.6786 (-4.644, 5.981)**	-0.04632 (-5.661, 5.538)	**-1.064 (-7, 4.748)**	**1.009 (-3.617, 5.638)**
		Electrotherapy	-0.1007 (-6.35, 6.169)	**0.3735 (-4.726, 5.456)**	**-0.3573 (-5.76, 5.05)**	**-1.37 (-7.124, 4.268)**	**0.7043 (-3.672, 5.07)**
			EMD	**0.4659 (-4.667, 5.607)**	-0.2599 (-5.68, 5.166)	**-1.273 (-7.064, 4.386)**	**0.8001 (-3.627, 5.224)**
				LLLT	**-0.7328 (-4.26, 2.826)**	**-1.748 (-5.528, 1.925)**	0.3314 (-2.268, 2.94)
					Ozone	**-1.014 (-4.87, 2.692)**	**1.062 (-2.086, 4.221)**
						PRF	**2.076 (-1.491, 5.767)**
							Suture
3 days							
HS	**-0.8498 (-6.08, 4.426)**	**-1.617 (-6.749, 3.563)**	**-1.385 (-6.585, 3.835)**	**-0.3692 (-3.70, 2.997)**	-0.193 (-3.596, 3.224)	**-1.494 (-3.919, 0.7386)**	**-0.6144 (-3.77, 2.572)**
	Cyanoacrylate	**-0.7674 (-6.59, 5.075)**	**-0.539 (-6.432, 5.35)**	**0.479 (-4.339, 5.286)**	**0.6565 (-4.372, 5.671)**	**-0.6465 (-5.97, 4.466)**	0.236 (-3.962, 4.423)
		Electrotherapy	0.2256 (-5.581, 6.044)	**1.242 (-3.461, 5.932)**	**1.42 (-3.495, 6.305)**	0.1205 (-5.12, 5.139)	**0.9993 (-3.055, 5.052)**
			EMD	**1.013 (-3.736, 5.778)**	**1.193 (-3.774, 6.143)**	-0.1123 (-5.39, 4.982)	**0.7687 (-3.358, 4.905)**
				LLLT	0.178 (-3.009, 3.349)	**-1.124 (-4.529, 2.074)**	-0.2443 (-2.60, 2.132)
					Ozone	**-1.3 (-4.758, 1.96)**	**-0.4206 (-3.15, 2.338)**
						PRF	**0.8782 (-2.125, 4.109)**
							Suture
7 days							
HS	**-1.702 (-6.684, 3.333)**	**0.8296 (-3.575, 5.241)**	**-1.944 (-7.682, 3.903)**	**-1.758 (-7.604, 4.21)**	**-1.613 (-5.421, 2.378)**	**-1.586 (-5.355, 2.259)**	**-2.645 (-5.329, -0.08086)**	**-1.113 (-4.758, 2.637)**
	Cyanoacrylate	**2.533 (-4.144, 9.198)**	-0.2399 (-5.797, 5.379)	-0.04863 (-5.738, 5.698)	0.09745 (-4.527, 4.865)	0.126 (-4.416, 4.681)	**-0.9402 (-5.987, 3.943)**	**0.5953 (-2.746, 3.979)**
		Dressing material	**-2.779 (-9.965, 4.544)**	**-2.586 (-9.895, 4.827)**	**-2.441 (-8.235, 3.524)**	**-2.414 (-8.188, 3.435)**	**-3.469 (-8.675, 1.595)**	**-1.945 (-7.654, 3.853)**
			Electrotherapy	0.1889 (-6.236, 6.619)	**0.327 (-5.166, 5.933)**	**0.3598 (-5.055, 5.749)**	**-0.6951 (-6.578, 4.925)**	**0.8307 (-3.636, 5.294)**
				EMD	0.1434 (-5.489, 5.832)	0.1724 (-5.388, 5.673)	**-0.8873 (-6.904, 4.851)**	**0.6433 (-3.986, 5.241)**
					LLLT	0.02984 (-3.764, 3.7)	**-1.029 (-5.034, 2.651)**	**0.4993 (-2.812, 3.726)**
						Ozone	**-1.056 (-4.911, 2.591)**	**0.4689 (-2.566, 3.561)**
							PRF	**1.53 (-2.005, 5.298)**
								Suture

HS: Hemostatic sponge; EMD: Enamel matrix dentin; LLLT: Low level laser therapy; PRF: Platelet-rich fibrin.

Table S5: League table with wound healing results from NMA at 14 (yellow) and 21 (blue) days. Wound healing agents were ordered in alphabetical order. Negative values (-) in yellow favor the left row over the column. Positive values (+) in blue favor the column over the row on the right). Values in bold represent statistically significant results (P < 0.05).

Cyanoacrylate	**0.3093 (-4.385, 5.073)**	-0.1636 (-4.765, 4.465)	**2.417 (-1.376, 7.018)**	**2.736 (-1.183, 7.374)**	**-0.54 (-3.851, 2.703)**
-31.93 (-106.7, 26.48)	**Electrotherapy**	**-0.4797 (-5.193, 4.199)**	**2.082 (-1.806, 6.793)**	**2.421 (-1.681, 7.168)**	**-0.8433 (-4.277, 2.476)**
-32.52 (-106.4, 25.8)	-0.2608 (-45.97, 46.34)	**EMD**	**2.564 (-1.173, 7.233)**	**2.899 (-1.038, 7.588)**	**-0.3803 (-3.641, 2.867)**
-13.22 (-79.68, 38.3)	**15.73 (-2.997, 57.27)**	**15.79 (-2.853, 58.19)**	**LLLT**	**0.3354 (-2.52, 3.014)**	**-2.943 (-6.057, -0.748)**
-28.38 (-100.2, 28.96)	3.399 (-41.35, 48.55)	3.496 (-40.03, 49.16)	**-11.71 (-51.14, 3.87)**	**Ozone**	**-3.263 (-6.501, -0.8946)**
-10.97 (-77.22, 40.58)	**17.98 (-0.319, 59.49)**	**18.05 (-0.183, 60.35)**	2.117 (-0.2351, 5.743)	**13.95 (-1.192, 53.53)**	**Suture**

EMD: Enamel matrix dentin; LLLT: Low level laser therapy.

Furthermore, the effectiveness ranking in reducing postoperative pain for each agent was presented using SUCRA (Table 3). The results showed that L-PRF was the most effective agent in reducing postoperative pain between the groups in all periods (1 day: 79.12%; 3 days: 70.31% and 7 days: 77.83%). Moreover, the ranking between treatments was defined as L-PRF > Ozone therapy > Cyanoacrylate adhesive > EMD > Electrotherapy > Laser therapy > Suture > Hemostatic sponge for 1 day; L-PRF > Electrotherapy > EMD > Cyanoacrylate adhesive > Suture > Laser therapy > Ozone therapy > Hemostatic sponge for 3 days and L-PRF > Electrotherapy > EMD > Cyanoacrylate adhesive > Laser therapy > Ozone therapy > Suture > Hemostatic sponge > Periodontal dressing for 7 days.

Table 3: Wound healing agents effectiveness ranking for pain assessment at 1, 3 and 7 days.

1 day							
PRF	**Ozone**	**Cyanoacrylate**	**EMD**	**Electrotherapy**	**LLLT**	**Suture**	**HS**
79.12%	58.62%	55.54%	52.01%	50.23%	41.56%	31.65%	31.23%
3 days							
PRF	**Electrotherapy**	**EMD**	**Cyanoacrylate**	**Suture**	**LLLT**	**Ozone**	**HS**
70.31%	66.74%	62.02%	51.28%	45.98%	39.22%	34.82%	29.60%

7 days								
PRF	**Electrotherapy**	**EMD**	**Cyanoacrylate**	**LLLT**	**Ozone**	**Suture**	**HS**	**Dressing material**
77.83%	61%	57.3146%	57.3144%	55.78%	55.41%	42.87%	24.27%	18.17%

PRF: Platelet-rich fibrin; EMD: Enamel matrix dentin; LLLT: Low level laser therapy; HS: Hemostatic sponge.

Regarding the palatal wound healing, EMD, electrotherapy and ozone therapy were the most effective agents in wound healing at 14 days (Supplementary Table S6). For 21 days, ozone and laser therapies promoted the better wound healing in comparison to others (Supplementary Table S6). The ranking established for this variable at 14 days was defined as: EMD > Electrotherapy > Ozone therapy > Laser therapy > Cyanoacrylate adhesive > Suture (Supplementary Table S6). At 21 days, the treatment ranking was defined as: Ozone > Laser therapy > Electrotherapy > Cyanoacrylate adhesive > EMD > Suture (Supplementary Table S6).

Table S6: Wound healing agents effectiveness ranking for wound healing at 14 and 21 days.

14 days					
EMD	**Electrotherapy**	**Ozone**	**LLLT**	**Cyanoacrylate**	**Suture**
0.7664187	0.7619947	0.7036707	0.3846040	0.2234467	0.1598653
21 days					
Ozone	**LLLT**	**Electrotherapy**	**Cyanoacrylate**	**EMD**	**Suture**
0.873140	0.815752	0.426388	0.358152	0.324732	0.201836

EMD: Enamel matrix dentin; LLLT: Low level laser therapy.

3.5.3 Reporting bias

Funnel plots for pain assessment indicated the presence of potential reporting bias in a study comparing PRF and hemostatic sponge at 1 and 3 days (A. A. A. Hassan et al., 2020). At 7 days, two studies comparing PRF and hemostatic sponge (Femminella et al., 2016; A. A. A. Hassan et al., 2020) and one study comparing hemostatic sponge to periodontal dressing (Shanmugam et al., 2010) showed potential publication bias. The study bias was due to greater MD in the study in comparison to estimated MD difference between the other studies (Supplementary Figure S7).

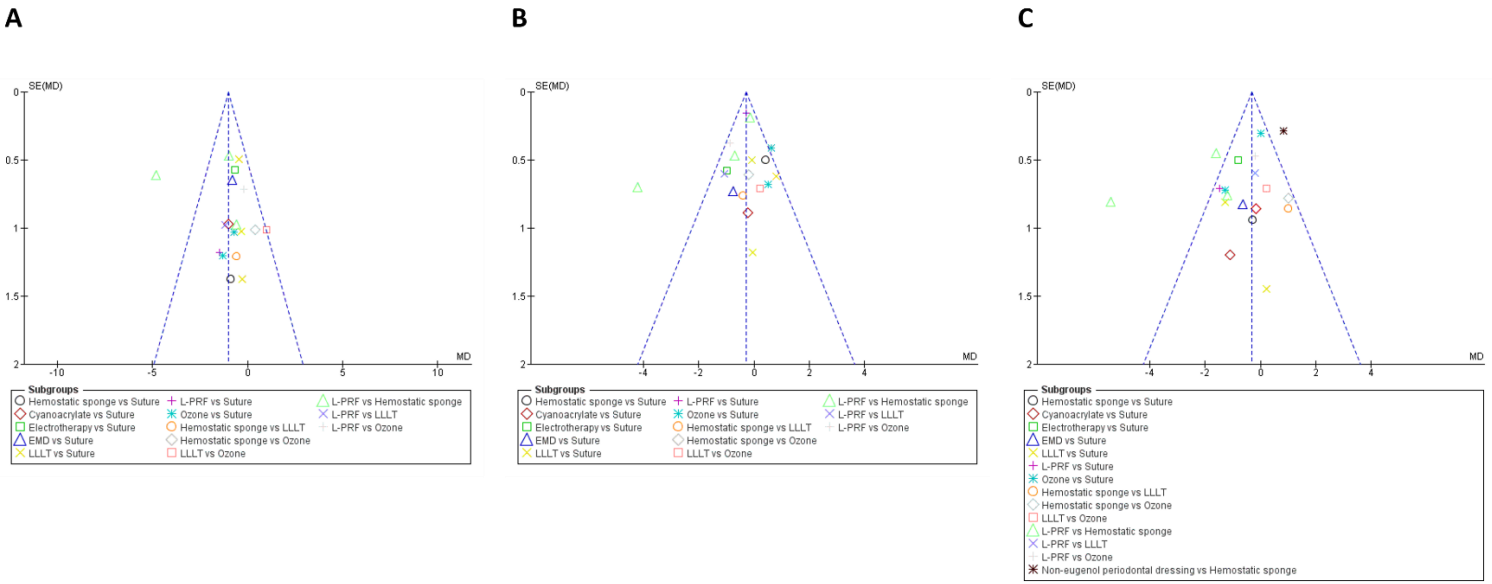

Figure S7: Funnel plots for publication bias analysis at 1 (A), 3 (B) and 7 days (C). The center line of the graph represents the null hypothesis and the side lines represent the confidence interval of the pooled estimates of the studies.

3.5.4 Certainty of evidence

Low or very low levels of confidence were obtained to the results of pain assessment from this NMA after CINeMA application. The results generated by CINeMA for the comparisons including the three wound healing agents with the highest SUCRA value (for each period) and the control group (suture) are shown in Figure 4. The reasons for downgrading the certainty of evidence included the major concerts obtained in all comparison in the “imprecision” domain. In addition, most of comparisons showed “some concerns” for “reporting bias” and “within-study bias” domains.

Comparison (No. of studies)	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
1 day							
Mixed evidence							
Cyanoacrylate:Suture (1)							**Low**
Ozone:PRF (1)							**Very low**
Ozone:Suture (2)							**Very low**
PRF:Suture (1)							**Very low**
Indirect evidence							
Cyanoacrylate:Ozone							**Very low**
Cyanoacrylate:PRF							**Very low**
3 days							
Mixed evidence							
EMD:Suture (1)							**Low**
Electrotherapy:Suture (1)							**Low**
PRF:Suture (1)							**Very low**
Indirect evidence							
Electrotherapy:EMD							**Very low**
EMD:PRF							**Low**
Electrotherapy:PRF							**Very low**
7 days							
Mixed evidence							
EMD:Suture (1)							**Low**
Electrotherapy:Suture (1)							**Very low**
PRF:Suture (1)							**Very low**
Indirect evidence							
Electrotherapy:EMD							**Low**
EMD:PRF							**Low**
Electrotherapy:PRF							**Very low**

Figure 4: Certainty of evidence generated using CINeMA approach. PRF: Platelet-rich fibrin; EMD: Enamel matrix dentin.

DISCUSSION

Pain expectation associated with the donor area is the main reason for lower patient agreement to undergo peri-implant and periodontal procedures with soft tissue grafts (Beaudette, Fritz, Sullivan, Piccini, & Ward, 2018). Therefore, the choice of the most effective wound healing agent needs to be done by the clinicians to ensure adequate protection of the palatal wound and a more comfortable postoperative, with less pain experience. Based on that, this systematic review was made to assess the efficacy of wound healing agents available for palatal donor area management after soft tissue graft harvesting. In addition, an NMA was designed to determine the best therapeutic approach for postoperative pain reduction (evaluated using VAS) and wound healing acceleration (complete epithelialization evaluation using hydrogen peroxide test) after soft tissue graft harvesting.

Overall, the summarized results from the qualitative (systematic review) and quantitative (NMA) analysis showed that all wound healing agents evaluated promoted better pain control and wound healing compared to spontaneous healing (suture) and hemostatic sponges alone. The NMA outcomes reveal that L-PRF was the most effective agent in reducing postoperative pain in all analyzed periods (1, 3, and 7 days). Moreover, considering the systematic review results, the PRF seems to accelerate wound healing and reduce postoperative complications occurrence (palatal necrosis and bleeding) in comparison to other agents.

The PRF is a second-generation platelet concentrate obtained from autologous blood using an economical, easy, and simplified process, without biochemical blood handling (Choukroun et al., 2006). It's composed of a three-dimensional fibrin network that retained high levels of potent growth factors [i.e., platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), fibroblast-derived growth factors, vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1)], living cells and matrix proteins (i.e., thrombospondin-1, fibronectin, vitronectin, heparin and hyaluronic acid) which promotes angiogenesis and healing processes (Del Corso et al., 2012; Dohan Ehrenfest, de Peppo, Doglioli, & Sammartino, 2009). A slow sustained growth factors release from PRF was reported for up to 28 days, suggesting that the wound healing process can be stimulated by PRF until the complete palatal area epithelialization (Dohan et al., 2006). Moreover, the PRF fibrin network also acts as a scaffold for endothelial cell migration, which is necessary for angiogenesis and

vascularization (Gamal, Abdel Ghaffar, & Alghezwy, 2016). Finally, PRF increases fibroblasts and keratinocytes proliferation resulting in accelerated early wound healing (Houde, 1982).

It could be hypothesized that the PRF use as a palatal bandage provides mechanical occlusion which protects the damaged structures exposed by surgery, giving more comfortable and hemostasis during the postoperative period (Femminella et al., 2016). Also, the leukocytes present in the PRF fibrin network have anti-nociceptive effects by the release of anti-inflammatory cytokines (IL-13, IL-4, and IL-10), chemokines, and opioid peptides (metenkephalin, dynorphin-A, and β-endorphin) (Dohan Ehrenfest et al., 2014). In addition, mediators such as histamine, dopamine, and serotonin are also released from platelets dense granules, contributing to pain reduction in the donor area after graft harvesting (Kızıltoprak & Uslu, 2020). Therefore, the outcomes reported in this review are supported by the PRF's modulator's role in many aspects of wound healing, including primary hemostasis, immunoinflammatory response, chemotaxis, angiogenesis, and cell proliferation (Choukroun et al., 2006; Dohan et al., 2006). However, it is important to emphasize that the PRF technique success significantly depends on an adequate blood collection and centrifugation protocol (Bahammam, 2018).

Another frequently approach reported in the studies included in this review was the low level laser therapy. Better wound healing was observed with laser therapy compared to spontaneous healing (qualitative analysis and NMA). This result can be explained by the potential of laser therapy in stimulates collagen synthesis and cell proliferation (Conlan, Rapley, & Cobb, 1996), which probably accelerates the inflammatory process and increases wound healing (de Farias Gabriel et al., 2019). Laser therapy also increase the levels of growth factors, extracellular matrix-remodeling proteins, adenosine triphosphate synthesis, fibroblastic proliferation, and angiogenesis in a dose-dependent manner (de Medeiros et al., 2017; G. Ustaoglu et al., 2017). In addition to these biological events, laser therapy is associated with a decrease in prostaglandin E2, cyclooxygenase-2 and bradykinin levels as well as enhanced circulation on the inflamed site improving oxygenation (Prianti, Silva, Dos Santos, Rosseti, & Costa, 2014; Tsai & Hamblin, 2017).

On the other hand, laser therapy showed inferior results for postoperative pain management in comparison to palatal stent (qualitative analysis), ozone therapy and PRF (NMA), without differences regarding spontaneous healing (NMA). An effective pain control provided by laser therapy in palatal donor area is expected because it has a direct

action on the nerve trunk, which results in changes in the Na/K concentration and cell membrane stabilization (Bjordal, Johnson, Iversen, Aimbire, & Lopes-Martins, 2006). Moreover, endorphin secretion as well as neurotransmitters release to enhance endorphin action were observed after laser therapy (Pires de Sousa et al., 2016). However, the laser therapy effectiveness depends on the interaction between laser light and target tissue, and factors such as distance from source to tissue, energy density, wavelength, irradiance, treatment interval and amount of irradiation time applied may influence the therapy results (Bitencourt et al., 2022). Although the included studies have been used diode laser, variable parameters and treatment interval were described, and the lack of well-established protocols can limit the clinical applicability of laser therapy (Chung et al., 2012).

The use of cyanoacrylate adhesives in palatal wound was also evaluated in this review. Cyanoacrylate adhesives, composed by acrylic resins(Inal, Yilmaz, Nisbet, & Güvenç, 2006), have bacteriostatic and hemostatic properties, which facilities wound management and hemostasis (Herod, 1990). The monomers polymerization after its application creates a layer that closes small capillaries, blocks nociceptive nerve endings, and protects against trauma from food detritus or hygiene measures (Gümüş & Buduneli, 2014; Ochstein, Hansen, & Swenson, 1969). Compared to sutures, cyanoacrylates were found to have less inflammation (Kumar et al., 2013) and the rapid adhesion of tissues enable wound closure more rapidly than conventional suture (Stavropoulou et al., 2019). In this review, the qualitative analysis showed that better postoperative pain control can be obtained when cyanoacrylate adhesives are associated with other materials such as collagen agents and PRF. In NMA, cyanoacrylate adhesives showed higher postoperative pain compared to PRF, electrotherapy and EMD but promoted less pain levels in comparison to hemostatic sponge. In wound healing evaluation, cyanoacrylate adhesives provide better repair in comparison to spontaneous healing (suture) at 14 days, however inferior results were observed in comparison to other agents and spontaneous healing at 21 days (NMA).

Ozone is a natural gaseous molecule with three oxygen atoms used in gaseous and liquid (dissolved in water and oil) forms (16 do Tasdemir, 2016). The wound-healing mechanism of ozone therapy can be associated in parts to its antimicrobial effect (Patel et al., 2011). Increased bacterial colonization of the wound surface promoted an increased in inflammation levels and granulation tissue formation, resulting in repair

delays(Bucknall, 1980). Associated with that, ozone increased release of TGF-β, interferons (b, a, g), interleukins (IL-1, IL-2, IL-6, IL-8), tumor necrosis factor- α (TNF-α) and activate local antioxidant mechanisms which are important for wound healing(Martínez-Sánchez et al., 2005; Patel et al., 2012). In this review, ozone therapy seems to promote pain control (superior to laser therapy, electrotherapy and hemostatic sponge at 1 day; and superior to periodontal dressing and hemostatic sponge at 7 days) and wound healing (superior to all agents included after 14 days and superior to suture and laser after 21 days) in palatal area. However, variable parameters in ozone concentration, forms application (water, oil or gaseous) and treatment interval were used in the included studies making the comparison between the studies unreliable.

Hyaluronic acid has also been proposed to cover palatal donor area based on its unique physiochemical and biological properties including anti-inflammatory, anti-edematous, antioxidant and anti-bacterial effects (Dahiya & Kamal, 2013). Hyaluronic acid is a member of a large family of glycosaminoglycans, which are the main components of the extracellular matrix (A. A. A. Hassan et al., 2020). This agent promoted tissue regeneration, preventing scar formation, through its ability to retain a large amount of water (A. A. A. Hassan et al., 2020). Hyaluronic acid gel was evaluated in the studies included in this review in combination with periodontal dressing and/or collagen hemostatic sponge. This wound healing agent seems to improve pain levels but not wound healing in comparison to collagen hemostatic sponge and/or periodontal dressing (qualitative analysis).

Some important aspects need to be considered when interpreting the results of this NMA. The inclusion of fewer studies in the statistical model may have a direct impact on the pain levels and wound healing rankings. It can be explained by the variability in assessed pain and wound healing between the RCT included regarding to methodology and periods of analysis. Even with 56 RCT included, the mean and standard deviation for VAS were not included in some studies. Moreover, the evaluation of wound area reduction in NMA was not possible due to the variability in report the outcomes. Finally, the certainty of evidence analysis showed that low or very low levels of confidence were obtained to the pain assessment results. This result was associated with imprecision and within-study bias observed in the studies included.

Within the limits of this systematic review and NMA, it can be concluded that L-PRF was the most effective agent in reducing postoperative pain, accelerate wound

healing and reduce postoperative complications occurrence after soft tissue graft harvesting from palatal area.

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4 ARTIGO 2

Effect of a gel containing green tea extract and hyaluronic acid on pain scores and wound healing after free gingival graft: a quasi-randomized controlled clinical trial[2]

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ABSTRACT

Objectives: The aim of this study was to evaluate the effect of a gel containing green tea extract and hyaluronic acid on pain scores and wound healing in donor sites after free gingival graft (FGG). **Materials and methods:** Forty-two patients requiring FGG were included into three groups: (1) Control group (n=14) no material was placed in the donor area, only the clot was kept in position by sutures; (2) Placebo group (n=14) vehicle gel applied 3 times a day for 7 days; (3) Test group (n=14) gel containing green tea extract and hyaluronic acid applied 3 times a day for 7 days. The wound size by clinical measurement (WS-CM) and photographic image (WS-PI), complete wound epithelialization (CWE) and palatal mucosa color were evaluated after 3 days, 1, 2 and 4 weeks postoperatively. The visual analogue scale (VAS) for pain and analgesic consumption were used to assess participant's perception.

Results: A similar progressive reduction in the wound size, associated with an improvement in the color pattern, was observed in all groups ($p>0.05$). No significant differences were found for CWE and pain assessment between the examined groups ($p>0.05$).

Conclusion: The gel containing green tea extract and hyaluronic acid application in palatal wounds after FGG removal does not provide clinical healing benefits using this investigated protocol.

Clinical Relevance: Morbidity and patient discomfort are associated with harvesting free gingival graft (FGG) from hard palate. Postoperative pain, bleeding and delayed wound healing are the most common side effects and adversely affect patient comfort.

Keywords: Wound Healing. Pain. Palate. Green Tea. Hyaluronic Acid.

INTRODUCTION

Free gingival graft (FGG) is a well-established and versatile technique, which involves the use of an autogenous graft for keratinized tissue augmentation [1]. The hard palate is the region most used to obtain autogenous grafts from the oral cavity [2]. After removal of the autogenous graft, the surgical wound in the palatal area repairs by secondary intention within 2–4 weeks, depending on wound size [3]. Morbidity and patient discomfort are expected, particularly after FGG harvest, due to thermal, chemical and/or mechanical trauma wherein the surgical wound is exposed in donor area [3]. Postoperative pain, bleeding and/or delayed healing in donor area are the most common side effects associated with FGG technique which adversely affect patient comfort and treatment adherence [4]. Based on that, several approaches have been proposed to improve post-harvesting healing and reduced morbidity with variable clinical efficacy [5-9].

The use of herbal medicines to improve wound healing have been proposed based on its antioxidant properties which reduces the inflammatory process and accelerate tissue repair [10-12]. Particularly, topical green tea extract reduced inflammation, osteoclastic activity, and alveolar bone loss when used as adjuvant therapy in experimental periodontitis [10, 13]. In addition, the use of green tea extract in gingival epithelial keratinocytes treated with lipopolysaccharide (LPS) demonstrated a significant increase in cell viability (1.5 times), pro-inflammatory cytokines gene expression reduction [Interleukin (IL)-1β, IL- 6 and tumor necrosis factor α (TNF- α)] and acceleration of wound closure [11]. Further, clinical studies showed that the use of toothpaste and mouthwash with green tea extract reduced biofilm accumulation, inflammation levels and clinical attachment loss after periodontal treatment [12, 14].

Local application of bioactive substances, such as hyaluronic acid (HA), has also been proposed to stimulate repair process due to its physiochemical and biological properties [7]. HA is a connective tissue component found in periodontal ligament and gingival tissue with also presents bacteriostatic, anti-inflammatory and antioxidant properties [15]. Previous studies evaluated the effects of HA gel associated with periodontal dressing and/or collagen hemostatic sponge in palatal wound healing [7, 16-18] and better pain control was reported with HA gel in comparison to control group However, only one study [16] showed better wound healing with HA application.

Association between HA and agents with antioxidant properties (green tea, raspberry and vitamin E) showed promising results in a pre-clinical wound healing assay using fibroblasts [19]. However, there is a lack of clinical studies designed to evaluate the use of green tea extract associated with HA in palatal wound healing after FGG harvesting. Therefore, based on the many benefits of green tea and HA in terms of wound healing, the aim of this clinical study was to evaluate the effect of a gel containing green tea extract and HA on soft tissue healing of donor sites, as well as on pain scores and patient discomfort following FGG.

MATERIALS AND METHODS

Trial design

The study was a quasi-randomized clinical controlled study with parallel design and masked examiner. The study was approved by the Ethics Committee of the Alfenas Federal University (CAAE: 45014621.2.0000.5142) and Uberlandia Federal University (CAAE: 45014621.2.3001.5152). All 42 selected patients gave full written informed consent following Helsinki Declaration. The complete study protocol was registered in the ClinicalTrials.gov (NCT05270161) and the study was reported following the CONSORT 2010 statement [20].

The selected patients (n=42) were quasi-randomly divided into three groups according to the therapeutic modality: Control group (n=14): no material was placed in the donor area, only the clot was kept in position by sutures; Placebo group (n=14): donor area on the palate was treated using the placebo gel (N&W, Ribeirão Preto, São Paulo, Brazil) applied by the participant 3 times a day for 7 days and; Test group (n=14): donor area on the palate was treated using a gel with green tea extract (0.5%) and hyaluronic acid (0.05%) (Professional Soft Tissue Gel, N&W, Ribeirão Preto, São Paulo, Brazil) applied by participant 3 times a day for 7 days.

Participants

Participants were recruited from patients referred to Alfenas Federal University and Federal University of Uberlandia in Brazil between July 2021 and December 2022. Participants were selected according to the following inclusion criteria: patients aged 18 to 60 years who were systemically healthy, with isolated or multiple Recession type 1 and 2 [21] with probing depth less than 3 mm at the sites involved. Exclusion criteria were:

patients who smoked or use other types of drugs, in a pregnancy or lactation period, who did not agree to return for follow-ups and who used corticosteroids, chemotherapy, immunomodulators during the last 6 months.

Interventions

Preparation phase

All selected patients were informed about the etiology of gingival recessions, instructed about oral hygiene (atraumatic toothbrushing techniques) and submitted to supragingival biofilm and calculus removal. Prior to the surgical procedure, 2 mm silicone plates were made to protect the palate.

Surgical phase

The FGG technique was applied for all groups by same experienced operator (S.C.P). The surgical procedure started with intra- and extra-oral asepsis performed with 0.12% and 2% chlorhexidine gluconate, respectively. Local anesthesia was performed using a 4% solution of articaine with 1:100,000 epinephrine (Nova DFL, Rio de Janeiro, Brazil). The mold of the prepared recipient area was performed using sterile paper. The donor area extended from the distal of the first premolar to the distal of the first molar in the palatal region. The mold was transferred to the donor area on the palate and the edges of the mold were delimited with a 15C scalpel blade. The mold was removed and deeper incisions were made on the edges with the scalpel perpendicular to the palate, aiming to obtain a graft approximately 1.5 mm thick. With a parallel scalpel blade, the graft was removed (epithelium and connective graft) maintaining its uniform thickness. After graft removal, two to three "X" sutures were placed to stabilize the clot in the donor area using 5.0 Nylon thread (Shalon medical, Brazil).

In the Control group, no material was placed in the donor area, only the clot was kept in position by sutures and the palatal wound was protected with the silicone plate (Figure 1A). In the Placebo group, the palatal wound was treated with the placebo gel (gel without green tea extract and hyaluronic acid additives) (N&W Dental Care, Ribeirão Preto, São Paulo, Brazil) (Figure 1B). In Test group, the palatal wound was treated with gel containing green tea extract (0.5%) and hyaluronic acid (0.05%) (Professional Soft Tissue Gel, N&W, Ribeirão Preto, São Paulo, Brazil) (Figure 1B). The composition of the gel is described in Supplementary material – Table S1. In Placebo and Test groups, the gel was inserted and protected by a protective silicone plate. The participant reapplied

the gel at home 3 times a day (morning, after lunch and before going to bed) for 7 days. The gel was applied in the morning and before going to bed after rinsing with 0.12% chlorhexidine digluconate. As a monitoring method, a calendar was provided to each participant to record daily gel use. Subjects were instructed not to use any other product in the donor area during the study.

For all groups, the participants were oriented to maintain the silicone plate in position in the first 24 hours after surgical procedure. After this period, the silicone plate was used only during foods and drinks ingestions. For Placebo and Test groups, the participant was also oriented to keep the silicone plate for 30 minutes after gel application.

As postoperative medications were prescribed: mouthwash with 0.12% chlorhexidine digluconate (Periogard, Colgate, Brazil) twice a day for 15 days (toothbrushing was discontinued in the surgical area during this period of time); Amoxicilin 500 mg every 8 hours for 7 days (or clindamycin 300 mg every 8 hours for 7 days for penicillin-allergic participants) to prevent possible postoperative infection; Spidufen® (Ibuprofen 600mg + Arginine 555 mg) 3g, 12/12h for 3 days and Dipyrone sodium, 500 mg, 6/6h for 3 days. In case of severe pain, ketorolac trometamol 10 mg was prescribed 8/8h for 3 days. After 3 days, the suture was removed and the area was cleaned with 0.12% chlorhexidine digluconate (Periogard, Colgate, Brazil) was performed.

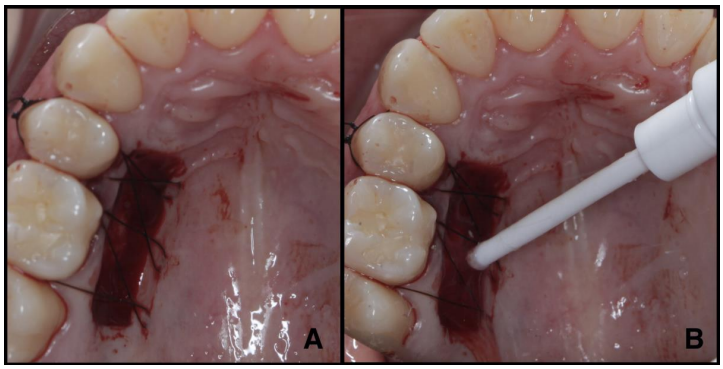

Figure 1: Therapeutic approaches in experimental groups. A: Control group only with "X" sutures for clot stabilization. B: Application of gels in Placebo and Test groups.

Outcomes

Clinical measurements were taken during the surgical procedure and after 3 days, 1, 2 and 4 weeks. Postoperative complications such as the presence of bleeding, swelling, infection, and necrosis in the donor area were recorded after 3 and 7 days. Measurements were performed by a single trained examiner (J.A.O.), using a millimeter periodontal

probe (North Carolina, Hu-Friedy, Brazil). The examiner/participant were masked for treatment type (double-blind). In addition, the time necessary to complete all the surgical procedure steps (not only the time necessary to graft removal) were registered using a digital clock.

Graft clinical parameters

Using the periodontal probe, the length and height of the graft were determined for graft total area calculation (Figure 2A and B). Graft thickness was achieved using an extra short needle that was inserted 1.5 mm apical from the coronal edge into the center of the graft. The rubber marker was then placed in contact with the graft (Figure 2C). The distance between the marker and the tip of the needle was determined using a digital caliper (stainless steel 150 mm, Mtx, Mundo das Ferramentas do Brasil LTDA, São Paulo, Brazil)

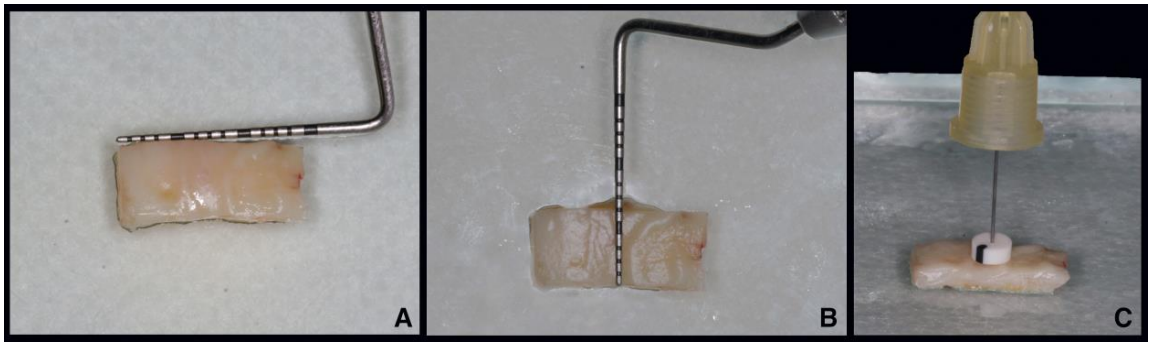

Figure 2: Clinical parameters of the graft. A: length; B: height; C: thickness.

Wound size by clinical measurement (WS-CM)

The height and length of the wound were determined using a periodontal probe for total area calculation in the same position for all periods of analysis. The open wound (non-epithelialized area) identification was made using hydrogen peroxide (3%).

Wound size by photographic image (WS-PI)

Standardized clinical photographs (Canon Rebel T3i with Canon Ef 100mm f/2.8 Macro Usm lens and Canon Macro Ring Light MR-14 EX II flash) were used to measure the wound size at day of surgery and after 3 days, 1, 2 and 4 weeks. The total wound area size was determined using Image J software (Bethesda, USA) by a calibrated and blinded examiner (J.A.O; r = 0.99) (Figure 3). A periodontal probe was positioned next to the wound at the time of taking the photos to calibrate the analysis in the software. The open

wound identification (non-epithelialized area) was made by color matched in comparison to adjacent and opposite normal palatal mucosa.

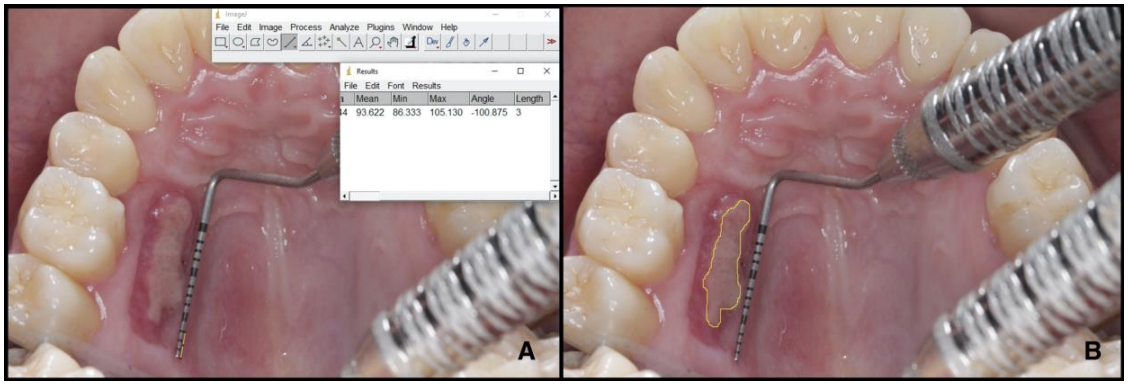

Figure 3: Analysis of the wound size by photographic image. A: Image J NIH software calibration with the aid of the periodontal probe; B: Delimitation of the wound to calculate the total size.

Complete wound epithelialization (CWE)

Epithelialization analysis was performed using a cotton swab moistened with hydrogen peroxide (3%) to observe the presence of blistering in the wound. The absence of epithelialization was characterized by the formation of bubbles after contact of hydrogen peroxide with the wound [22] (Figure 4). The outcomes were recorded as non-epithelialized (positive for bubbles) and completely-epithelialized (negative for bubbles).

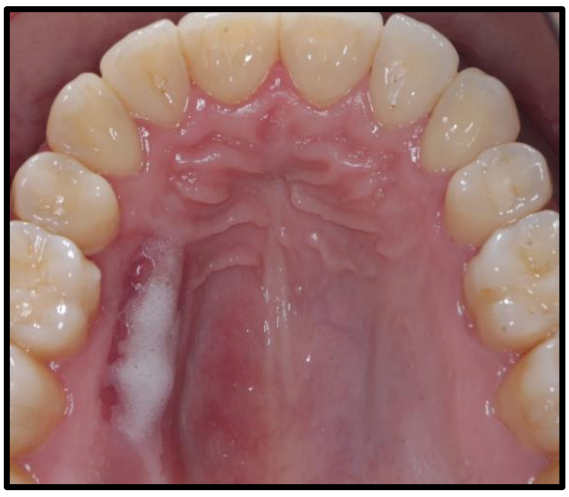

Figure 4: Blistering on the non-epithelialized surface after application of 3% hydrogen peroxide.

Color match

The color of the palatal mucosa was evaluated by the visual analogue scale (VAS) in comparison with the color of the adjacent and opposite mucosa. In this evaluation, on

a horizontal scale, 0 points will represent no color match, 50 points medium match and 100 points excellent color match [23].

Postoperative Pain

Pain score was recorded by the patient using the VAS at the operated sites. Patients recorded the pain level in the first 3 days, 1, 2 and 4 weeks after the procedure on a horizontal scale, where the left endpoint will mean no pain (0), the mean pain point (50) and the right outcome severe pain (100). The total consumption of analgesics in the first 7 postoperative days was also recorded in the participant's file.

Sample Size

The sample size calculation was made based on Dias, Fonseca, Dos Santos, Mathias, Martinho, Junior, Jardini and Santamaria [24] and the wound size reduction was considered as the primary variable. It was determined that the minimum variance for detecting differences between groups should be 10% with a standard deviation of 5%. Considering β power at 0.9 and the α power at 0.05 in a two-sided statistical test, a minimum sample size of 13 participants per group was require in each group.

Quasi-randomization, allocation and blinding

A quasi-randomized trial design was used, whereby participants were assigned to a treatment or comparison group in the order in which they enrolled in the study (the first 14 participants were assigned to the Control group and the last 28 participants to the Test and Placebo groups, respectively). This quasi-randomization method was not revealed to the outcome assessor (J.A.O) that was blinded to allocation to avoid differences in assessment. All surgeries were performed by the same surgeon (S.C.P.) not blinded to the treatment allocated to the participants. Participants from Placebo and Test groups were also blinded to the treatments. For this, the gels were available in equal syringes and only the researcher responsible for the quasi-randomization (M.I.S.) was aware of the allocation.

Statistical methods

Demographic data, surgery time, graft clinical parameters and wound size data from clinical and photographic measurements were distributed according to normality as

verified by the Shapiro-Wilk normality test. VAS data for pain and color, as well as medication consumption were not distributed according to normality. CWE and gender data were analyzed in the proportion's forms. Age, surgery time, graft clinical parameters and wound size data were compared between the groups using the one-way ANOVA test, complemented by the Tukey test, while the comparison within each group varying the experimental period was performed through the ANOVA test for repeated samples complemented by the Tukey test. VAS data for pain and color and medication consumption were compared between groups using the Kruskall-Wallis test, complemented by the Dunn test, while comparison within each group, varying the experimental period, was performed using means of the Friedman test complemented by the Dunn test. Data from the analysis of CWE and gender were compared between groups using the chi-square test. The GraphPad Prism 8 software (San Diego, CA, USA) was used for inferential data analysis and all statistical tests were applied at a significance level of 5%.

RESULTS

Study population

Forty-two patients (31.5 ± 9.35 years old, 31 females, 11 males) were included to the study (Table 1). All included patients completed the study (Figure S1 in supplementary materials). No significant differences were observed for participants age and gender between the groups (Table 1). However, surgery time was significantly longer for Test group compared to Placebo group ($p<0.05$) (Table 1).

Table 1: Demographic characteristics

Parameters	Control	Placebo	Test	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	33.79 ± 8.84	29.93 ± 11.12	30.86 ± 8.09	0.5344
Gender				
Male (%)	4 (28.57%)	4 (28.57%)	3 (21.43%)	0.8841
Female (%)	10 (71.43%)	10 (71.43%)	11 (78.57%)	
Surgery time (min)	69.64 ±12.41	**81.29 ± 21.16***	**63.57 ±16.85***	**0.030**

One-way ANOVA test complemented by the Tukey test was used for age and surgery time; Chi-square test was used for gender. *$p<0.05$

Clinical outcomes

A representative case from each group was included in Figure 6. For all cases, it was possible to observe complete closure of the wound and improvement in donor area

color at the end of 4 weeks. Regarding postoperative complications, two patients in Control group, three patients in Placebo group and one patient in Test group reported postoperative bleeding. In addition, three patients in Test group reported burning sensation in the palatal wound area after gel application.

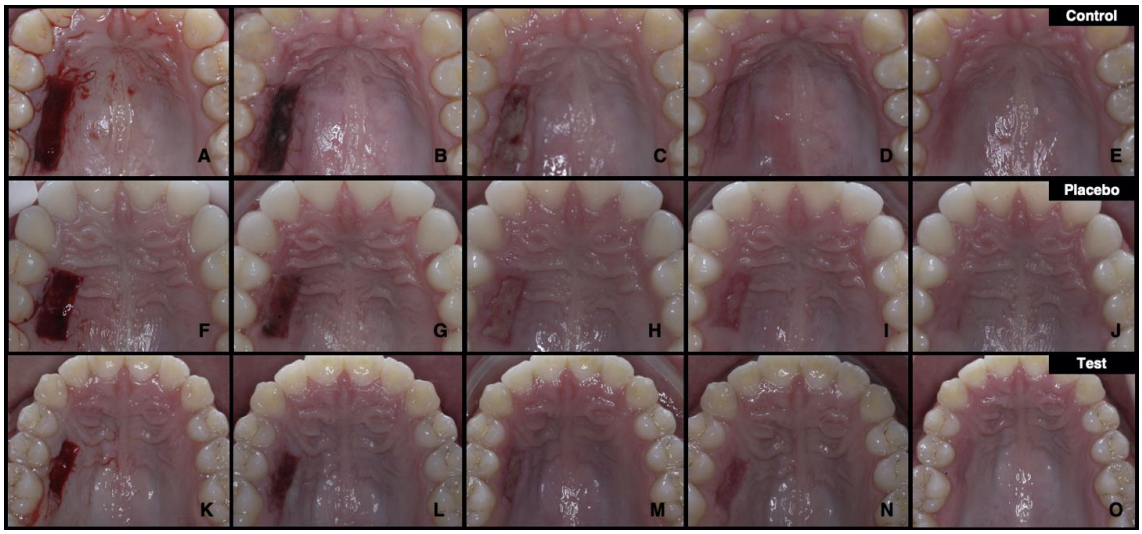

Figure 5: Postoperative follow-up for control, placebo and test groups. A, F and K: immediate postoperative; B, G and L: 3 days; C, H and M: 1 week; D, I and N: 2 weeks and E, J and O: 4 weeks.

The grafts harvested from the palatal area were similar in area and thickness dimensions between all groups (Table 2).

Table 2: Mean and standard deviation data of grafts dimensions in all groups.

Parameter / Group	Control	Placebo	Gel	p-values
Thickness (mm)	2.09 ± 0.50	2.08 ± 0.19	2.01 ± 0.39	0.8462
Height (mm)	6.96 ± 1.20	7.03 ± 1.21	7.42 ± 3.36	0.8366
Length (mm)	14.32 ± 2.47	14.77 ± 1.90	14.18 ± 3.12	0.8254
Area (mm^2)	101.2 ± 30.19	102.6 ± 28.41	99.75 ± 27.63	0.9667

One-way ANOVA test complemented by the Tukey test was used for all parameters. No differences were observed between groups.

A progressive reduction in the wound size by clinical measurements and photographic images, and postoperative pain, in addition to an improvement in the color pattern and aspect of the palatal mucosa were obtained in the three groups with the increase of experimental period, but without statistically significant differences between groups (p=0.4138; p=0.8745; p=0.1015 and p=0.8378, respectively) (Table 3). No complete wound closure was observed for one patient in the Placebo group after 4 weeks

in WS-CM analysis. In WS-PI analysis, one patient in each Placebo and Test groups did not show complete wound closure within 4 weeks (Table 3).

No significant differences were found for CWE between analyzed groups (p= 0.3590) (Table 4), however, CWE was observed in two patients in the Control group, one in the Test group and none in the Placebo group after 2 weeks. After 4 weeks, only one patient in the Placebo group did not show CWE (Table 4). Higher ketorolac trometamol and dipyrone consumption were observed for Placebo group in comparison to other groups but without significant difference (p=0.1314 and p=0.9073, respectively) (Table 5).

Table 3: Mean (median) and standard deviation data from the wound area analysis and VAS color and pain for the control, placebo and test groups in all evaluation periods.

Groups/Periods		Baseline	3 days	1 week	2 weeks	4 weeks
Control	WS-CM (mm^2)	114.2 ± 27.78^{d}	$101.9\pm24.14^{c,d}$	$90.61\pm31.47^{b,c}$	29.93 ± 21.42^{b}	0.00 ± 0.00^{a}
Placebo		126.4 ± 26.13^{d}	$119.3\pm27.20^{c,d}$	$109.2\pm26.11^{b,c}$	42.43 ± 29.21^{b}	0.42 ± 1.06^{a}
Test		115.7 ± 24.69^{d}	$110.1\pm32.93^{c,d}$	$98.61\pm30.47^{b,c}$	36.95 ± 26.13^{b}	0.00 ± 0.00^{a}
Control	WS-PI (mm^2)	97.52 ± 31.26^{e}	81.53 ± 23.30^{d}	62.45 ± 25.30^{c}	22.48 ± 17.52^{b}	0.00 ± 0.00^{a}
Placebo		99.07 ± 25.03^{d}	88.19 ± 23.25^{c}	79.55 ± 25.52^{c}	30.07 ± 17.23^{b}	0.83 ± 2.17^{a}
Test		103.20 ± 33.11^{d}	96.03 ± 36.23^{d}	85.82 ± 35.38^{c}	34.06 ± 17.27^{b}	0.67 ± 2.52^{a}
Control	Pain (VAS)	-	$1.30(0.70)\pm1.89^{b}$	$1.50(0.50)\pm2.62^{a,b}$	$0.56(0.50)\pm0.92^{a,b}$	$0.03(0.00)\pm0.13^{a}$
Placebo		-	$3.40(1.75)\pm3.44^{b}$	$3.70(1.82)\pm3.65^{b}$	$1.89(0.70)\pm2.66^{a,b}$	$0.04(0.00)\pm0.16^{a}$
Test		-	$2.97(2.10)\pm3.06^{b}$	$3.32(1.70)\pm3.73^{b}$	$0.83(0.75)\pm0.78^{b}$	$0.007(0.00)\pm0.02^{a}$
Control	Color (VAS)	-	$7.14(5.00)\pm9.13^{c}$	$38.21(40.00)\pm14.89^{b,c}$	$73.57(75.00)\pm12.00^{a,b}$	$97.50(98.00)\pm1.55^{a}$
Placebo		-	$6.42(10.00)\pm6.33^{c}$	$37.14(40.00)\pm11.39^{b,c}$	$66.67(70.00)\pm14.30^{a,b}$	$95.79(96.50)\pm3.74^{a}$
Test		-	$10.00(5.00)\pm11.77^{c}$	$38.57(35,00)\pm11.67^{b,c}$	$65.35(70.00)\pm11.17^{a,b}$	$95.54(96.00)\pm3.77^{a}$

WS-CM: Wound Size by Clinical Measurement; WS-PI: Wound Size by Photographic Image; VAS: Visual analogic scale.
For WS-CM and WS-PI, one-way ANOVA test complemented by the Tukey test were used for comparison between the groups, while ANOVA test for repeated samples complemented by the Tukey test was used for comparison within each group varying the experimental period.
For pain and color, Kruskall-Wallis test complemented by the Dunn test were used for comparison between groups, while Friedman test complemented by the Dunn test were used for comparison within each group varying the experimental period.
Different letters represent statistically significant differences between each follow-up period (columns in the same row) in the same group. No differences were observed between groups.

Table 4: Complete wound epithelialization frequency for control, placebo and test groups in all evaluated periods.

Groups/Periods	CWE	3 days	1 week	2 weeks	4 weeks
Control	N	14	14	12	0
	E	0	0	2	14
Placebo	N	14	14	14	1
	E	0	0	0	13
Test	N	14	14	13	0
	E	0	0	1	14

CWE: Complete wound epithelialization; N: not epithelized; E: epithelized. Chi-square test. No differences were observed between groups.

Table 5: Mean (median) ± standard deviation of medication consumption by participants during the postoperative phase.

Groups/Medications	Dypirone	Spidufen®	Toragesic
Control	7.78(6.00)±9.13	6.57(6.00)±1.45	0.64(0.00)±2.13
Placebo	9.64(5.00)±9.15	7.14(6.00)±3.23	2.57(0.00)±4.34
Test	7.85(5.50)±7.12	6.64(6.00)±1.73	0.50(0.00)±1.87

Kruskall-Wallis test complemented by the Dunn test. No differences were observed between groups.

DISCUSSION

This quasi-randomized controlled trial aimed to evaluate whether gel containing green tea extract and hyaluronic acid accelerate tissue healing and reduce the patient's morbidity compared to blood clot (control) and placebo gel after FGG harvesting. The findings of this study demonstrated that all groups had a normal postoperative healing course from the palatal wound and no statistically significant difference was observed between groups for any of the examined clinical or patient-centered outcomes.

To the best of our knowledge, this is the first clinical study evaluating the effect of gel containing green tea extract and hyaluronic acid on postoperative pain control and wound healing after FGG. The FGG technique has been associated with postoperative pain and complications including hemorrhage, infection, and surgical wound necrosis [25, 26]. These side effects are associated with the bloody bed left in the palatal donor area, which heals by secondary intention[27]. Although many approaches with primary intention healing have been proposed for gingival graft removal [28], the use of FGG technique in the present study can be

justified because it provides a higher quality graft with more uniform thickness and less glandular and fatty tissue favoring vascularization and epithelial keratinization [1, 2]. Moreover, FGG is easier to obtain, requires less operative time and can be removal even in patients with thin palatal fibromucosa [1]. In addition, many authors have preferably used this technique because the FGG can be used with or without the epithelium and provides a stable and dense graft which is less prone to shrinkage in comparison with other techniques [2, 29].

The wound healing in the present study was assessed by wound size reduction by clinical and photographs measurements of surface areas without epithelialization and CWE (by hydrogen peroxide bubbling test). Moreover, the color of the palatal wound was also evaluated by comparing the color of the operated area and area adjacent to the wound by using the objective VAS. As FGG healing occurs by secondary intention, the color change may reflect the degree of reepithelization and inflammation level [24, 30]. Although no significant difference was observed between the groups for the wound repair assessments, one participant of each experimental groups (test and placebo groups) not showed complete wound closure after 4 weeks in photographs measurements. In clinical measurements and CWE analysis, only one participant from placebo group does not show complete wound repair after 4 weeks. This divergence between the wound healing analysis methods can be explain since in photographs measurements, the wound size was determined based on the color difference between the operated area and the adjacent area. On the other hand, the hydrogen peroxide bubbling test is used to identify the non-epithelialized area in clinical measurements and CWE analysis making the analysis less subjective.

In addition, the wound healing in control group seems to be faster in comparison to experimental groups since two participants of control group and one participant of test group showed CWE after two weeks. For placebo group, no CWE was observed after 2 weeks. A superior clinical performance was expected for the test group based on green tea extract antioxidant [31, 32], antibacterial [33-35] and inflammatory-inhibitory potential that may improve wound healing process [10-12]. In addition, some studies have reported that catechins present in green tea can improve wound repair by promoting collagen fibers maturation [36, 37]. In contrast to our findings, a pre-clinical study evaluated the effect of 0.6% green tea extract associated with Vaseline on healing process of surgical wounds in rat and reported a decrease in the healing duration [38].

The 0.05% HA incorporation in gel formulation was proposed based on its role in wound healing process. HA binds to fibrin creating a scaffold for peripheral neutrophils, monocytes, macrophages, and fibroblasts migration into the wound to initiate granulation tissue formation

[15]. However, similarly to our study, Hassan, Ahmed, Ghalwash and Elarab [7] showed no differences between 0.2% HA gel associated with periodontal dressing in comparison to periodontal dressing alone in wound healing evaluation by color match and wound size area analysis. Moreover, HA gel associated with collagen hemostatic sponge showed similar wound repair (assessed by Landry index and wound size area analysis) in comparison to collagen hemostatic sponge alone [18]. For vascularization analysis, no differences were found between HA associated with periodontal dressing and palatal stent in comparison to periodontal dressing with palatal stent [39]. In contrast, Yıldırım, Ozener, Doğan and Kuru [16] reported that HA gel associated with periodontal dressing promoted better wound repair (by color match and CWE evaluated visually) in comparison to periodontal dressing.

It could be hypothesized that the components of the gel vehicle may have negatively interfered with the palatal wound healing and masked the effect of the additive's green tea extract and HA. One of the components of the gel, the sodium lauryl sulfate (0.5%) detergent, have been associated with intraoral adverse effects including burning mouth sensation, epithelial desquamation and recurrent aphthous ulceration [40-42]. A previous in vitro study, using a three-dimensional human oral epithelium cell culture model [43], showed that higher sodium lauryl sulfate concentrations (≥0.15%) promoted a gradually decrease in epithelial thickness, cell proliferation and E-cadherin expression. Moreover, cells detached from each other and underwent cell death in the central areas of exposed regions. Furthermore, it is also known that the presence of tetrasodium pyrophosphate (an anti-calculus component also reported in the gel composition) in dentifrices result in an alkaline solution that, in combination with other predispositions factor, could irritate oral mucous membrane [44].

Patient's morbidity was evaluated in this study using VAS for pain and medication consumption. A higher pain levels, with greater number of analgesics consumed, were reported in Placebo group participants, without statistical significance. On the other hand, other studies have reported significant pain reduction with the HA gel associated with periodontal dressing and/or collagen hemostatic sponge [7, 16-18]. Among these studies, two reported that the HA concentrations used was greater than or equal to 0.2% [7, 16]. Then it can be suggested that the HA concentration (0.05%) in gel evaluated in the present study can be not enough to accelerate the palatal wound repair and consequently reduce postoperative pain after FGG harvesting. In addition, the gel consistency seems to not be suitable to remain in the wound area. To improve its retention, the participants were instructed to keep the palatal stent for 30 minutes after gel application.

It is important to highlight that the average on the VAS scale for all groups corresponds to a mild a moderate discomfort even in the first three days of postoperative. The low levels of pain reported in this study may be associated with the palatal stent use in all groups which acts a mechanical barrier against oral trauma providing greater post-operative comfort. In addition, pain is subjective, personal, and private experience that usually varied a lot between individuals. Therefore, the evaluation of postoperative morbidity after surgery using VAS, despite being a valid method, has certain limitations [30, 45]. Furthermore, Bradshaw, Hariharan and Chen [46] also showed that dental anxiety was correlated to the postoperative pain scores and number of analgesic consumed, being a potential confounder for pain assessment.

Postoperative bleeding was reported by five participants in this study. In all cases, the bleeding was short-lived and resolved by the patient. In the experimental groups, the bleeding occurrence may be related to the incorrect application of the product, once it was performed by the patient himself in a region that is difficult to visualize. Another possible reason was the non-use of the palatal stent while eating. Other studies reported that bleeding occurrence was also associated with postoperative irritation or trauma caused by the patient [47, 48].

Differences in patient characteristics, such as age and gender, can influence postoperative pain levels and morbidity [49]. In the present study, there were no significant differences about patients' characteristics between the groups. On the other hand, longer surgery time has been reported for placebo group. This difference in surgery time is due to the fact that patients received different surgical techniques for root coverage of multiple and single recessions, and the time was counted from the beginning to the end of surgery. Studies have shown that shorter surgery time may be related to less inflammation, edema, and pain during the postoperative period [50, 51]. However, the longer surgery time in the placebo group is related to only one patient that reported no pain in VAS analysis in all periods of analysis..

The grafts in this study were used for different root coverage techniques and no template for standardize graft size (length and height) was used for ethical reasons. However, standardized surgical procedures were established to ensure a minimum graft size and similar graft thickness among the groups. The comparison between the groups showed that graft dimensions were quite similar in three groups providing an accurate comparison.

The present study design with a quasi-randomization protocol can be considered as a limitation. Date of patient presentation can be considered as inadequate methods of sequence generation. However, the participants and grafts characteristics did not vary significantly between the groups, except for the time of surgery. Moreover, a meta-analysis of seven meta-epidemiological studies found that an inadequate method of sequence generation was

associated with a small exaggeration of intervention effect estimates, being the bias greater in trials reporting subjective outcomes [52]. In addition, the efficacy of the gel depends on the compliance of the patient for proper efficacy. Finally, state-trait anxiety of the patients included and oral health-related quality of life were not evaluated in this study.

In conclusion, the gel containing green tea extract and hyaluronic acid application in palatal wounds after FGG removal does not provide clinical healing benefits using this investigated protocol.

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Supplementary materials

Table S1: Gel containing green tea extract and hyaluronic acid composition

Constituent	%	Function
Carboxymethylcellulose	1,00	Thickener
Glycerin	5,00	Humectant
Sorbitol	60,0	Humectant
Sodium benzoate	0,30	Preservative
Xylitol	0,50	Sweetener, anti-caries
Lauryl glucoside	1,50	Non-ionic surfactant
Sodium lauryl sulfate	0,50	Anionic surfactant
Hyaluronic acid	0,05	Mucosa regenerator
Polyvinylpyrrolidone k 30	0,50	Film forming agent
Dimethylsilanediol Salicylate (dsbc)	0,50	Antiseptic and mucous regenerator
Thixosil 43 b	10,00	Thickener and thixotropic agent
Thixosil 73	5,00	Abrasive
Tetrasodium pyrophosphate	0,50	Anti-tartar
Saccharin	0,05	Sweetener
Green tea extract (*camellia sinensis)*	0,50	Antioxidant, antiseptic
Hydrogenated castor oil	2,0	Solubilizer
Edta	0,05	Chelating agent
Blue dye ci 42090	Q.s.	Dye
Yellow dye ci 1910	Q.s.	Dye
Purified water	11,45	Vehicle

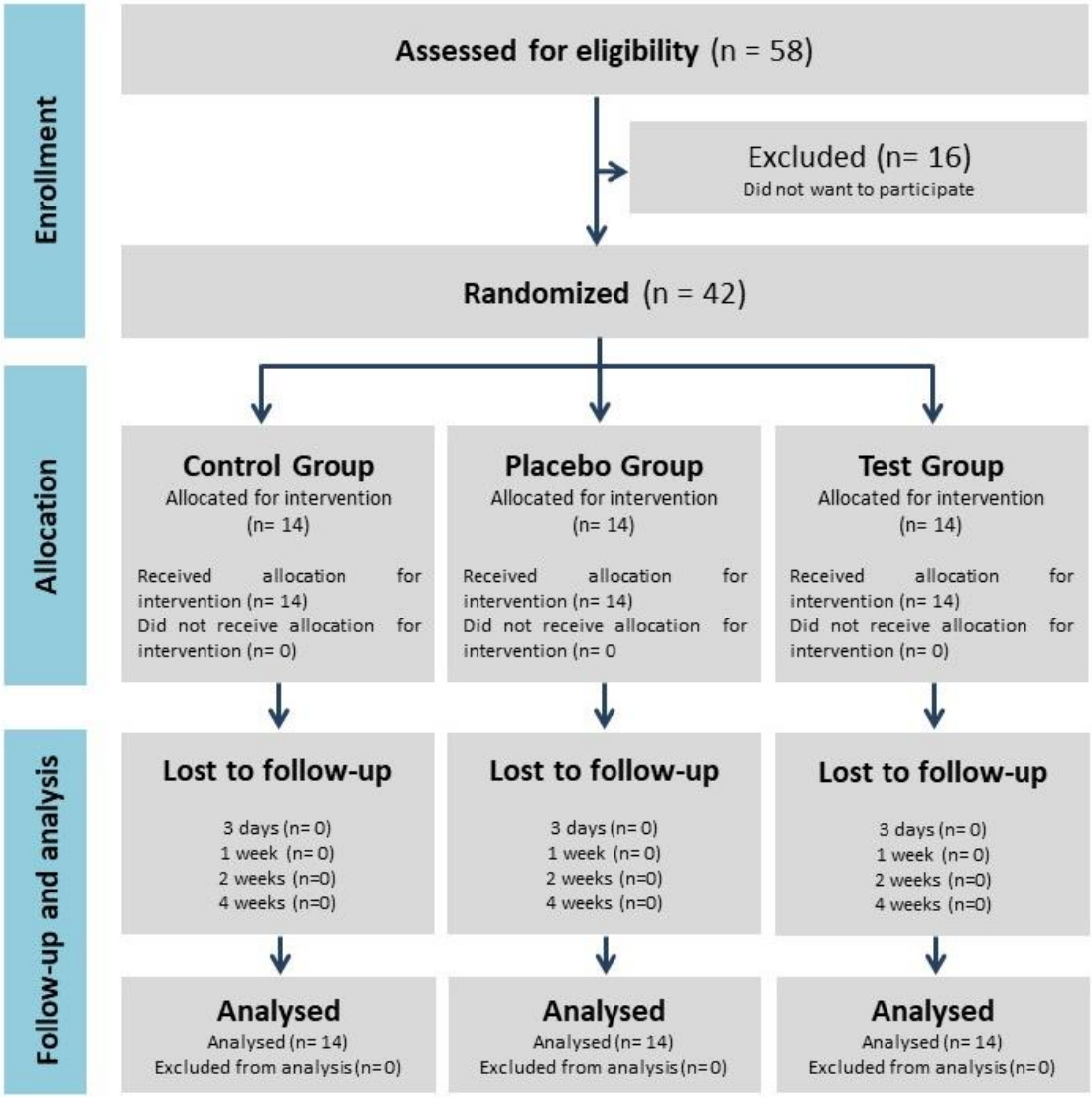

Figure S1: CONSORT flow chart.

5 DISCUSSÃO GERAL

A expectativa de dor associada à área doadora é o principal motivo da menor concordância do paciente em se submeter a procedimentos peri-implantares e periodontais com enxertos de tecidos moles (BEAUDETTE *et al.,* 2018). Portanto, a escolha do agente de cicatrização de feridas mais eficaz precisa ser feita pelos médicos para garantir proteção adequada da ferida palatina e um pós-operatório mais confortável, com menos experiência de dor. Com base nisso, a revisão sistemática foi feita para avaliar a eficácia dos agentes de cicatrização de feridas disponíveis para o manejo da área doadora palatina após a colheita de enxertos de tecidos moles. Além disso, uma meta-análise em rede (NMA) foi projetada para determinar a melhor abordagem terapêutica para redução da dor pós-operatória (avaliada por VAS) e aceleração da cicatrização de feridas (avaliação completa da epitelização usando o teste de peróxido de hidrogênio) após a colheita do enxerto de tecidos moles.

O estudo clínico controlado quase-randomizado teve como objetivo avaliar se o gel contendo extrato de chá verde e ácido hialurônico acelera a cicatrização tecidual e reduz a morbidade do paciente em comparação com coágulo sanguíneo (controle) e gel placebo após a colheita de FGG. Os resultados deste estudo demonstraram que todos os grupos tiveram um curso normal de cicatrização pós-operatória da ferida palatina e nenhuma diferença estatisticamente significativa foi observada entre os grupos para qualquer um dos resultados clínicos ou centrados no paciente examinados.

No geral, os resultados resumidos da análise qualitativa (revisão sistemática) e quantitativa (NMA) mostraram que todos os agentes de cicatrização de feridas avaliados promoveram melhor controle da dor e cicatrização de feridas em comparação com a cicatrização espontânea (sutura) e esponjas hemostáticas isoladamente. Os resultados da NMA revelam que o L-PRF foi o agente mais eficaz na redução da dor pós-operatória em todos os períodos analisados (1, 3 e 7 dias). Além disso, considerando os resultados da revisão sistemática, o PRF parece acelerar a cicatrização de feridas e reduzir a ocorrência de complicações pós-operatórias (necrose palatal e sangramento) em comparação com outros agentes.

O PRF é um concentrado de plaquetas de segunda geração obtido a partir de sangue autólogo por meio de um processo econômico, fácil e simplificado, sem manipulação bioquímica do sangue (CHOUKROUN *et al.,* 2006). É composto por uma rede de fibrina tridimensional que retém altos níveis de potentes fatores de crescimento [ou seja, fator de crescimento derivado de plaquetas (PDGF), fator de crescimento transformador beta (TGF-β),

fatores de crescimento derivados de fibroblastos, fator de crescimento endotelial vascular (VEGF) e fator de crescimento semelhante à insulina-1 (IGF-1)], células vivas e proteínas da matriz (ou seja, trombospondina-1, fibronectina, vitronectina, heparina e ácido hialurônico) que promovem a angiogênese e os processos de cicatrização (DEL CORSO *et al.*, 2012; DOHAN EHRENFEST *et al.*, 2009;). Uma lenta liberação sustentada de fatores de crescimento do PRF foi relatada por até 28 dias, sugerindo que o processo de cicatrização de feridas pode ser estimulado pelo PRF até a completa epitelização da área palatina (DOHAN *et al.*, 2006). Além disso, a rede de fibrina PRF também atua como um andaime para a migração de células endoteliais, que é necessária para a angiogênese e vascularização (GAMAL;ABDEL GHAFFAR;ALGHEZWY, 2016). Finalmente, o PRF aumenta a proliferação de fibroblastos e queratinócitos, resultando em cicatrização precoce acelerada de feridas (HOUDE, 1982).

Pode-se levantar a hipótese de que o uso do PRF como bandagem palatina proporciona oclusão mecânica que protege as estruturas danificadas expostas pela cirurgia, proporcionando mais conforto e hemostasia durante o período pós-operatório (FEMMINELLA *et al.*, 2016), Além disso, os leucócitos presentes na rede de fibrina PRF têm efeitos anti-nociceptivos pela liberação de citocinas anti-inflamatórias (IL-13, IL-4 e IL-10), quimiocinas e peptídeos opioides (metenkefalina, dinorfina-A, e β-endorfina) (DOHAN EHRENFEST *et al.*, 2014). Ademais, mediadores como histamina, dopamina e serotonina também são liberados dos grânulos densos de plaquetas, contribuindo para a redução da dor na área doadora após a retirada do enxerto (KIZILTOPRAK; USLU, 2020). Portanto, os resultados relatados nesta revisão são apoiados pelo papel do modulador do PRF em muitos aspectos da cicatrização de feridas, incluindo hemostasia primária, resposta imunoinflamatória, quimiotaxia, angiogênese e proliferação celular (DOHAN *et al.*, 2006; CHOUKROUN *et al.*, 2006). No entanto, é importante enfatizar que o sucesso da técnica PRF depende significativamente de um protocolo adequado de coleta de sangue e centrifugação (BAHAMMAM, 2018)

Outra abordagem frequentemente relatada nos estudos incluídos nesta revisão foi a laserterapia de baixa intensidade. Melhor cicatrização de feridas foi observada com terapia a laser em comparação com cicatrização espontânea (análise qualitativa e NMA). Esse resultado pode ser explicado pelo potencial da laserterapia em estimular a síntese de colágeno e a proliferação celular (CONLAN;RAPLEY;COBB, 1996), o que provavelmente acelera o processo inflamatório e aumenta a cicatrização de feridas (DE FARIAS GABRIEL *et al.*, 2019). A laserterapia também aumenta os níveis de fatores de crescimento, proteínas de remodelação da matriz extracelular, síntese de trifosfato de adenosina, proliferação fibroblástica e angiogênese de maneira dependente da dose (DE MEDEIROS *et al.*, 2017;

USTAOGLU;ERCAN;TUNALI, 2017; WANG *et al.*, 2015). Além desses eventos biológicos, a laserterapia está associada à diminuição dos níveis de prostaglandina E2, ciclooxigenase-2 e bradicinina, bem como melhora da circulação no local inflamado, melhorando a oxigenação (PRIANTI *et al.*, 2014; TSAI; HAMBLIN, 2017).

Por outro lado, a terapia a laser mostrou resultados inferiores para o controle da dor pós-operatória em comparação com stent palatino (análise qualitativa), ozonioterapia e PRF (NMA), sem diferenças em relação à cicatrização espontânea (NMA). Espera-se um controle eficaz da dor proporcionado pela laserterapia na área doadora palatina, pois tem ação direta sobre o tronco nervoso, o que resulta em alterações na concentração de Na/K e estabilização da membrana celular (BJORDAL *et al.*, 2006). Além disso, a secreção de endorfina, bem como a liberação de neurotransmissores para aumentar a ação da endorfina foram observadas após a terapia a laser (PIRES DE SOUSA *et al.*, 2016). No entanto, a eficácia da terapia a laser depende da interação entre a luz do laser e o tecido alvo, e fatores como distância da fonte ao tecido, densidade de energia, comprimento de onda, irradiância, intervalo de tratamento e quantidade de tempo de irradiação aplicada podem influenciar os resultados da terapia (BITENCOURT *et al.*, 2022). Embora os estudos incluídos tenham utilizado laser de diodo, parâmetros variáveis e intervalo de tratamento foram descritos, e a falta de protocolos bem estabelecidos pode limitar a aplicabilidade clínica da laserterapia (CHUNG *et al.*, 2012).

O uso do gel com extrato de chá verde e ácido hialurônico no controle da dor pós-operatória e cicatrização de feridas após FGG foi avaliado pela primeira vez no presente estudo clínico. A cicatrização da ferida foi avaliada pela redução do tamanho da ferida por medidas clínicas e fotográficas de áreas de superfície sem epitelização e completa epitelização da ferida (CEF) (pelo teste de borbulhamento de peróxido de hidrogênio). Além disso, a cor da ferida palatina também foi avaliada comparando-se a cor da área operada com a área adjacente à ferida por meio da VAS. Como a cicatrização da FGG ocorre por segunda intenção, a mudança de cor pode refletir o grau de reepitelização e nível de inflamação (DA SILVA NEVES *et al.*, 2016; DIAS *et al.*, 2015) . Embora nenhuma diferença significativa tenha sido observada entre os grupos para as avaliações de reparação de feridas, um participante de cada grupo experimental (grupos gel e placebo) não apresentou fechamento completo da ferida após 4 semanas em medições fotográficas. Nas medições clínicas e na análise CEF, apenas um participante do grupo placebo não apresentou cicatrização completa da ferida após 4 semanas. Essa divergência entre os métodos de análise da cicatrização de feridas pode ser explicada, pois nas medições fotográficas o tamanho da ferida foi determinado com base na diferença de cor entre a área operada e a área adjacente. Por outro lado, o teste de borbulhamento de peróxido de hidrogênio

é usado para identificar a área não epitelizada em medições clínicas e análise CEF tornando a análise menos subjetiva.

Além disso, a cicatrização da ferida no grupo controle parece ser mais rápida em comparação aos grupos experimentais, pois dois participantes do grupo controle e um participante do grupo gel apresentaram CEF após duas semanas. Para o grupo placebo, nenhum CEF foi observado após 2 semanas. Esperava-se um desempenho clínico superior para o grupo de gel à base de extrato de chá verde antioxidante (CAO;SOFIC;PRIOR, 1996; LIN *et al.*, 1998), antibacteriano (HIRASAWA *et al.*, 2002; TAGURI;TANAKA;KOUNO, 2004; YAM;SHAH;HAMILTON-MILLER, 1997) e potencial inibitório inflamatório que pode melhorar o processo de cicatrização de feridas (DE ALMEIDA *et al.*, 2019; HAGIU *et al.*, 2020; HRISHI *et al.*, 2016). Além disso, alguns estudos relataram que as catequinas presentes no chá verde podem melhorar o reparo de feridas, promovendo a maturação das fibras de colágeno (KAPOOR *et al.*, 2004; KIM *et al.*, 2008). Em contraste com nossos achados, um estudo pré-clínico avaliou o efeito do extrato de chá verde a 0,6% associado à vaselina no processo de cicatrização de feridas cirúrgicas em ratos e relatou uma diminuição na duração da cicatrização (ASADI *et al.*, 2013).

A incorporação de 0,05% de AH na formulação de gel foi proposta com base em seu papel no processo de cicatrização de feridas. O AH se liga à fibrina criando um andaime para a migração periférica de neutrófilos, monócitos, macrófagos e fibroblastos para a ferida para iniciar a formação de tecido de granulação (DAHIYA; KAMAL, 2013). Porém, assim como em nosso estudo, Hassan *et al.* (2021) não mostraram diferenças entre o gel AH 0,2% associado ao curativo periodontal em comparação com o curativo periodontal sozinho na avaliação da cicatrização de feridas por correspondência de cores e análise da área do tamanho da ferida. Além disso, o gel AH associado à esponja hemostática de colágeno mostrou reparo de feridas semelhante (avaliado pelo índice de Landry e análise da área da ferida) em comparação com a esponja hemostática de colágeno isoladamente (HASSAN;AKL;ADEL-KHATTAB, 2020). Para análise da vascularização, não foram encontradas diferenças entre AH associado ao curativo periodontal e stent palatino em comparação ao curativo periodontal com stent palatino (ÇANKAYA *et al.*, 2020). Em contraste, Yıldırım *et al.* (2018) relataram que o gel AH associado ao curativo periodontal promoveu melhor reparo da ferida (por correspondência de cores e CEF avaliado visualmente) em comparação ao curativo periodontal.

Pode-se supor que os componentes do veículo do gel podem ter interferido negativamente na cicatrização da ferida palatina e mascarado o efeito do extrato de chá verde e AH. Um dos componentes do gel, o detergente lauril sulfato de sódio (0,5%), tem sido

associado a efeitos adversos intraorais, incluindo sensação de queimação na boca, descamação epitelial e ulceração aftosa recorrente (BARKVOLL, 1996; HERLOFSON; SKAARE;RÖLLA;BARKVOLL, 1997; JENKINS;ADDY;NEWCOME, 1991). Um estudo in vitro anterior, usando um modelo tridimensional de cultura de células de epitélio oral humano (NEPPELBERG *et al.*, 2007), mostrou que maiores concentrações de lauril sulfato de sódio (≥0,15%) promoveram uma diminuição gradual na espessura epitelial, proliferação celular e expressão de E-caderina. Além disso, as células se destacaram umas das outras e sofreram morte celular nas áreas centrais das regiões expostas. Além disso, sabe-se também que a presença de pirofosfato tetrassódico (componente anticálculo também relatado na composição do gel) nos dentifrícios resulta em uma solução alcalina que, em combinação com outros fatores predisponentes, pode irritar a mucosa oral (DELATTRE, 1999). A morbidade do paciente foi avaliada neste estudo usando VAS para dor e consumo de medicamentos. Maiores níveis de dor, com maior número de analgésicos consumidos, foram relatados nos participantes do grupo Placebo, sem significância estatística. Por outro lado, outros estudos relataram redução significativa da dor com o gel AH associado ao curativo periodontal e/ou esponja hemostática de colágeno (HASSAN;AKL;ADEL-KHATTAB, 2020; HASSAN *et al.*, 2021; KHALIL *et al.*, 2022; YILDIRIM *et al.*, 2018). Entre esses estudos, dois relataram que as concentrações de AH utilizadas foram maiores ou iguais a 0,2% (HASSAN *et al.*, 2021; YILDIRIM *et al.*, 2018). Então pode-se sugerir que a concentração de HA (0,05%) no gel avaliada no presente estudo pode não ser suficiente para acelerar o reparo da ferida palatina e, consequentemente, reduzir a dor pós-operatória após a colheita de FGG. Além disso, a consistência do gel parece não ser adequada para permanecer na área da ferida. Para melhorar sua retenção, os participantes foram instruídos a manter o stent palatino por 30 minutos após a aplicação do gel.

Alguns aspectos importantes precisam ser considerados na interpretação dos resultados da NMA e do estudo clínico. Na NMA, a inclusão de menos estudos no modelo estatístico pode ter um impacto direto nos níveis de dor e nos rankings de cicatrização de feridas. Isso pode ser explicado pela variabilidade na dor avaliada e na cicatrização de feridas entre os ECR incluídos em relação à metodologia e períodos de análise. Mesmo com 56 ECR incluídos, a média e o desvio padrão para VAS não foram incluídos em alguns estudos. Além disso, a avaliação da redução da área da ferida em NMA não foi possível devido à variabilidade em relatar os resultados. Finalmente, a análise da certeza das evidências mostrou que níveis de confiança baixos ou muito baixos foram obtidos para os resultados da avaliação da dor. Esse resultado foi associado à imprecisão e ao viés intra-estudo observado nos estudos incluídos. Com relação ao estudo clínico, o desenho com um protocolo de quase-randomização pode ser considerado uma

limitação. A data de apresentação do paciente pode ser considerada um método inadequado de geração de sequências. No entanto, as características dos participantes e dos enxertos não variaram significativamente entre os grupos, exceto pelo tempo de cirurgia. Além disso, uma meta-análise de sete estudos meta-epidemiológicos descobriu que um método inadequado de geração de sequências estava associado a um pequeno exagero nas estimativas do efeito da intervenção, sendo o viés maior em ensaios que relatavam resultados subjetivos (PAGE *et al.*, 2016). Ademais, a eficácia do gel depende da adesão do paciente para uma eficácia adequada. Finalmente, a ansiedade estado-traço dos pacientes incluídos e a qualidade de vida relacionada à saúde bucal não foram avaliadas neste estudo.

Dentro dos limites da revisão sistemática e da NMA, pode-se concluir que o L-PRF foi o agente mais eficaz na redução da dor pós-operatória, na aceleração da cicatrização de feridas e na redução da ocorrência de complicações pós-operatórias após a coleta de enxerto de tecido mole da área palatina. Além disso, a aplicação de gel contendo extrato de chá verde e ácido hialurônico em feridas palatinas após a remoção do FGG não fornece benefícios clínicos de cicatrização usando este protocolo investigado.

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APÊNDICE A – Metodologia Detalhada da Pesquisa

6.1 ESTUDO 1: REVISÃO SISTEMÁTICA

6.1.1 Protocolo e registro

O presente estudo foi realizado e redigido de acordo com o guia atualizado para revisões sistemáticas e meta-análises (PRISMA; do inglês *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) (Apêndice B). Além disso, um protocolo desta pesquisa foi registrado no Registro Prospectivo Internacional de Revisões Sistemáticas (PROSPERO) ID: CRD42023398675.

6.1.2 Pergunta principal

A pergunta principal deste estudo foi elaborada de acordo com o acrônimo PVO (População, Variável e *Outcome*): “Em pacientes submetidos a remoção de enxerto gengival (P), qual agente (V), é mais efetivo para acelerar a cicatrização e reduzir o desconforto pós-operatório (O)?”

6.1.3 Busca na literatura

Uma extensa busca na literatura foi conduzida, de acordo com a estratégia PICO, abrangendo todos os artigos publicados até a data de 22 de setembro de 2022. As bases de dados utilizadas foram: *PubMed/MEDLINE, Embase, Web of Science, Scopus, LILACS* e *The Cochrane Library*. As seguintes palavras-chave foram selecionadas de acordo com os termos do *MeSH (Medical Subject Heading)* e respeitando as particularidades de busca de cada database (as palavras-chave estão redigidas na língua inglesa para alcançar resultados da literatura internacional):

a) PubMed/MEDLINE: *("Gingival recession"[All Fields] OR "Recession defect"[All Fields] OR "Recession-type defect"[All Fields] OR "Root coverage"[All Fields] OR "Periodontal surgery"[All Fields]) AND ("Palate"[All Fields] OR "Palatal area"[All Fields] OR "Palatal graft"[All Fields] OR "Free gingival graft"[All Fields] OR "Connective tissue graft"[All Fields] OR "Gingival graft"[All Fields] OR "Palatal donor site"[All Fields] OR "Soft tissue graft"[All Fields] OR "Palatal wound"[All Fields]) AND ("Palatal healing"[All Fields] OR "Palatal repair"[All Fields] OR "Palatal pain"[All Fields] OR "Wound heal"[All Fields] OR "Wound healing"[All Fields] OR "Wound closure"[All Fields] OR "Wound closure techniques"[All Fields] OR ("pain"[MeSH Terms] OR "pain"[All Fields]) OR ("healed"[All Fields] OR "Wound healing"[MeSH Terms] OR ("wound"[All Fields] AND "healing"[All*

Fields]) OR "Wound healing"[All Fields] OR "healing"[All Fields] OR "healings"[All Fields] OR "heals"[All Fields]) OR "Postoperative complications"[All Fields] OR "Morbidity"[All Fields] OR ("discomfort"[All Fields] OR "discomforting"[All Fields] OR "discomforts"[All Fields]) OR ("epithelialise"[All Fields] OR "epithelialised"[All Fields] OR "epithelialize"[All Fields] OR "epithelialized"[All Fields] OR "epithelializes"[All Fields] OR "epithelializing"[All Fields] OR "Re-Epithelialization"[MeSH Terms] OR "Re-Epithelialization"[All Fields] OR "epithelialisation"[All Fields] OR "epithelialization"[All Fields]) OR "Re-Epithelialization"[All Fields] OR "Wound Epithelialization"[All Fields] OR "epithelialization wound"[All Fields] OR "Analgesia"[All Fields] OR "Bleeding"[All Fields] OR "Hemostasis"[All Fields] OR "Hemostases"[All Fields] OR "Hemostatics"[All Fields] OR "Hemorrhage"[All Fields])

b) Embase: *('gingival recession' OR 'recession defect' OR 'recession-type defect' OR 'root coverage' OR 'periodontal surgery') AND (palate OR (palatal AND area) OR (palatal AND graft) OR graft OR autografting OR (free AND gingival AND graft) OR (connective AND tissue AND graft) OR (gingival AND graft) OR (palatal AND donor AND site) OR (soft AND tissue AND graft) OR (palatal AND wound)) AND (palatal AND healing OR (palatal AND repair) OR (palatal AND pain) OR (wound AND heal) OR (wound AND healing) OR (wound AND closure) OR (wound AND closure AND techniques) OR pain OR healing OR (postoperative AND complications) OR morbidity OR discomfort OR epithelialization OR 're epithelialization' OR (wound AND epithelialization) OR (epithelialization, AND wound) OR analgesia OR bleeding OR hemostases OR hemostatics OR hemorrhage)*

c) Web of Science**:** *((((ALL=(“Gingival recession”)) OR ALL=("Recession defect")) OR ALL=("Recession-type defect")) OR ALL=("Root coverage")) OR ALL=("Periodontal surgery") AND ((((((((((ALL=(“Palate”)) OR ALL=("Palatal área")) OR ALL=("Palatal graft")) OR ALL=(Graft)) OR ALL=(“Autografting”)) OR ALL=("Free gingival graft")) OR ALL=("Connective tissue graft")) OR ALL=("Gingival graft")) OR ALL=("Palatal donor site")) OR ALL=("Soft tissue graft")) OR ALL=("Palatal wound") AND ((((((((((((((((((((ALL=("Palatal healing")) OR ALL=("Palatal repair")) OR ALL=("Palatal pain")) OR ALL=("Wound heal")) OR ALL=(“Wound healing”))) OR ALL=("Wound closure")) OR ALL=("Wound closure techniques")) OR ALL=(Pain)) OR ALL=(Healing)) OR ALL=(“Postoperative complications”)) OR ALL=(“Morbidity”)) OR ALL=(Discomfort)) OR ALL=(Epithelialization)) OR ALL=("Re-Epithelialization")) OR ALL=("Wound Epithelialization")) OR ALL=("Epithelialization, Wound")) OR ALL=("Analgesia")) OR*

ALL=("Bleeding")) OR ALL=("Hemostasis")) OR ALL=("Hemostases")) OR ALL=("Hemostatics")) OR ALL=("Hemorrhage")

d) The Cochrane Library: *“Gingival recession” OR "Recession defect" OR "Recession-type defect" OR "Root coverage" OR "Periodontal surgery" in All Text AND “Palate” OR "Palatal area" OR "Palatal graft" OR Graft OR “Autografting” OR "Free gingival graft" OR "Connective tissue graft" OR "Gingival graft" OR "Palatal donor site" OR "Soft tissue graft" OR "Palatal wound" in All Text AND "Palatal healing" OR "Palatal repair" OR "Palatal pain" OR "Wound heal" OR “Wound healing” OR "Wound closure" OR "Wound closure techniques" OR Pain OR Healing OR “Postoperative complications” OR “Morbidity” OR Discomfort OR Epithelialization OR "Re-Epithelialization" OR "Wound Epithelialization" OR "Epithelialization, Wound" OR "Analgesia" OR "Bleeding" OR "Hemostasis" OR "Hemostases" OR "Hemostatics" OR "Hemorrhage" in All Text*

e) Scopus: *(ALL ("Gingival recession" OR "Recession defect" OR "Recession-type defect" OR "Root coverage" OR "Periodontal surgery") AND ALL ("Palatal graft" OR "Free gingival graft" OR "Connective tissue graft" OR "Gingival graft" OR "Palatal donor site" OR "Soft tissue graft" OR "Palatal wound") AND ALL ("Wound healing" OR "Wound closure" OR "Wound closure techniques" OR pain OR "Postoperative complications" OR epithelialization OR "Re-Epithelialization" OR "Wound Epithelialization" OR "Epithelialization, Wound" OR "Bleeding" OR "Hemostasis" OR "Hemostases" OR "Hemostatics" OR "Hemorrhage"))*

f) LILACS: *(“Gingival recession” OR "Recession defect" OR "Recession-type defect" OR "Root coverage" OR "Periodontal surgery") AND (“Palate” OR "Palatal area" OR "Palatal graft" OR Graft OR “Autografting” OR "Free gingival graft" OR "Connective tissue graft" OR "Gingival graft" OR "Palatal donor site" OR "Soft tissue graft" OR "Palatal wound") AND ("Palatal healing" OR "Palatal repair" OR "Palatal pain" OR "Wound heal" OR “Wound healing” OR "Wound closure" OR "Wound closure techniques" OR Pain OR Healing OR “Postoperative complications” OR “Morbidity” OR Discomfort OR Epithelialization OR "Re-Epithelialization" OR "Wound Epithelialization" OR "Epithelialization, Wound" OR "Analgesia" OR "Bleeding" OR "Hemostasis" OR "Hemostases" OR "Hemostatics" OR "Hemorrhage")*

A busca em todos os bancos de dados eletrônicos foi exportada para o software EndNote Program™ X9 (Thomson Reuters, Nova York, NY, EUA), a fim de eliminar as referências duplicadas. Após a remoção das duplicatas, a busca foi exportada para o software online Rayyan (OUZZANI *et al.*, 2016), para seleção dos trabalhos por título e resumo. As listas de

referências dos artigos incluídos também foram pesquisadas manualmente para estudos adicionais.

6.1.4 Critérios de elegibilidade

Em relação aos critérios de inclusão, foram selecionados artigos de pesquisas originais do tipo relato de caso, séries de casos e ensaios clínicos nos quais apresentam-se dados de pacientes submetidos a abordagens terapêuticas para a cicatrização do palato após a remoção de enxerto gengival. Foram excluídos estudos laboratoriais (*in vitro e in vivo*), artigos de revisão, anais de conferências, artigos de protocolo, cartas ao editor, capítulos de livros ou estudos publicados em um idioma diferente do inglês.

6.1.5 Seleção dos artigos

Os estudos foram selecionados para elegibilidade por dois revisores independentes (JAO e MIS), analisando títulos e resumos de acordo com os critérios de inclusão/ exclusão descritos acima, e os estudos irrelevantes foram excluídos. A seguir, os textos completos dos estudos que atenderam aos critérios de elegibilidade foram acessados pelos dois pesquisadores para inclusão. As discordâncias entre os revisores foram resolvidas por consenso ou encaminhadas a um terceiro autor (SCP) para a decisão final. Os estudos que atenderam aos critérios de seleção seguiram para extração de dados.

6.1.6 Processo de extração de dados, tabulação e apresentação dos resultados

Dois revisores (JAO e MIS) extraíram os dados dos artigos de forma independente. Os seguintes parâmetros foram extraídos de cada estudo selecionado para a análise qualitativa (revisão sistemática): a) tipo de estudo; b) número e gênero dos participantes; c) idade dos participantes (média e desvio padrão); d) fumo e) tipo de técnica de remoção do enxerto gengival f) tipos de abordagens terapêuticas (grupos); g) número de palatos reparados; h) utilização de stent i) acompanhamentos pós-operatórios; j) dor pós-operatória k) reparo do palato (redução da área da ferida, epitelização e cor da mucosa palatina); e l) ocorrência de complicações pós-operatórias.

6.1.7 Avaliação da qualidade dos estudos

Dois revisores (JAO e MIS) avaliaram separadamente a qualidade dos estudos incluídos. Qualquer desacordo foi discutido com um terceiro autor (SCP). A qualidade metodológica dos relatos de casos e séries de casos foi avaliada utilizando a estrutura de

avaliação sugerida por Murad *et al.* (2018) com base nos domínios de seleção, apuração, causalidade e relato. As questões 4 a 6 do domínio causalidade não foram aplicadas neste estudo por se destinarem a casos de eventos adversos a medicamentos. Os estudos clínicos randomizados (ECR), por sua vez, foram avaliados usando a ferramenta de colaboração Cochrane (RoB 2.0) (STERNE *et al.*, 2019).

6.1.8 Métodos para síntese dos resultados

6.1.8.1 Meta-análise pareada

Uma meta-análise com comparações diretas entre intervenções foi realizada usando o software Review Manager (versão 5.4, Copenhagen, Dinamarca, 2020). Para as variáveis analisadas, as estimativas dos efeitos entre intervenção foram expressas como diferenças médias (DMs) com intervalos de confiança de 95% (ICs), por meio de um modelo de efeitos fixos. A eficácia do agente na cicatrização de feridas palatinas foi estimada usando odds ratio (OR) em um modelo de efeitos fixos de Mantel-Haenszel. Por meio dos Testes de Qui-quadrado avaliou-se a heterogeneidade entre estudos para escolha do modelo aplicado (fixo ou randômico), que foi considerada baixa para valores $\leq 25\%$, moderada para valores entre 25% e 50% e alta para valores > 50% (HIGGINS *et al.*, 2003).

6.1.8.2 Meta-análise em rede (NMA)

Posteriormente, uma meta-análise em rede (NMA) Bayesiana de efeitos randômicos foi conduzida por meio do pacote ‘gemtc’ do software RStudio (versão 4.0.4, Boston, Estados Unidos, 2020). Dessa forma, simulações estatísticas por meio de Cadeias de Markov Monte Carlo (MCMC) foram criadas para calcular MDs entre as intervenções, com 95% de Intervalo de Credibilidade Bayesiano (CrI). Número de cadeias ('n.chain'), simulações descartadas ('n.adapt'), número total de simulações ('n.iter') e intervalo de extração de simulação ('thin') foram adaptados ao número de estudos incluídos e interações entre intervenções no modelo gerado. Além disso, métodos de análise de consistência de Brooks-Gelman-Rubin e critérios de informação de desvio (DIC), bem como a geração de gráficos de densidade a partir de Trace plots e Node-splitting foram usados para avaliar a convergência e o ajuste do modelo (DIAS *et al.*, 2010).

A combinação de comparações de evidências diretas e indiretas pela NMA forneceu a probabilidade de escolha e classificação entre os melhores tratamentos e a DM entre as intervenções avaliadas. Além disso, uma tabela de classificação, com comparações entre as intervenções e as estimativas de valores de superfície sob a curva de classificação cumulativa (SUCRA) foram usadas para interpretar os resultados (CIPRIANI *et al.*, 2009).

6.1.9 Certeza da evidência

A análise de viés de relatórios usando gráficos de funil foi realizada usando o software Review Manager 5.4. A certeza da evidência dos resultados gerados pelo NMA foi avaliada usando a ferramenta CINEMA (*Confidence in Network Meta-Analysis*) originalmente enquadrada no GRADE (*Grading of Recommendations, Assessment, Development and Evaluation*) (NIKOLAKOPOULOU *et al.*, 2020; PAPAKONSTANTINOU *et al.*, 2020).

6.2 ESTUDO 2: EFICÁCIA DO GEL COM EXTRATO DE CHÁ VERDE E ÁCIDO HIALURÔNICO

6.2.1 Desenho do Estudo

O presente estudo clínico randomizado controlado com modelo paralelo foi realizado na Faculdade de Odontologia da Universidade Federal de Alfenas (UNIFAL-MG) (instituição proponente) e na Faculdade de Odontologia da Universidade Federal de Uberlândia (FOUFU; instituição coparticipante). Todas as etapas da pesquisa foram realizadas nas duas instituições incluindo seleção dos participantes da pesquisa, procedimentos cirúrgicos e acompanhamentos pós-operatórios.

O presente estudo clínico randomizado controlado foi aprovado pelo Comitê de Ética em Pesquisa (CAAE: 45014621.2.0000.5142) da UNIFAL/MG [instituição proponente; número do parecer de aprovação: 5.458.306 (Anexo A)] e da UFU [instituição coparticipante; número do parecer de aprovação: 5.628.514 (Anexo B)]. Os participantes incluídos na pesquisa assinaram o Termo de Consentimento Livre e Esclarecido (TCLE) disponibilizado pelo pesquisador responsável.

O estudo foi conduzido de acordo com o protocolo CONSORT para conduta de estudos clínicos (Apêndice C) e registrado no ClinicalTrials.gov (NCT05270161). Os géis testados no estudo foram disponibilizados pela empresa N&W Dental Care (Ribeirão Preto, São Paulo, Brasil).

Para determinar o tamanho da amostra, o cálculo de amostra foi obtido tomando como N por base o estudo de DIAS *et al.* (2015). No cálculo realizado nesse estudo os autores determinaram que o mínimo de variação para detecção de diferenças entre os grupos deveria ser de 10% com desvio padrão de 5%, e que determinando o poder β em 0.9 e o poder α em 0.05 em um teste estatístico bilateral seria necessária uma amostra mínima de 13 participantes por grupo para receber os tratamentos.

Os participantes foram divididos em 3 grupos de acordo com a modalidade terapêutica de reparo do palato: (1) **Grupo Coágulo (CO)** (n=14): nenhum material foi colocado na área doadora, apenas o coágulo foi mantido em posição por meio de suturas; (2) **Grupo Placebo (P)** (n=14): área doadora no palato foi tratada utilizando o gel placebo (N&W, Ribeirão Preto, São Paulo, Brasil) aplicado pelo participante 3 vezes ao dia por 7 dias; (3) **Grupo Gel (G)** (n=14): a área doadora no palato foi tratada utilizando o gel com extrato de chá verde e ácido hialurônico (Gel profissional Soft Tissue, N&W, Ribeirão Preto, São Paulo, Brasil) aplicado pelo participante 3 vezes ao dia por 7 dias.

Para randomização, os primeiros 14 participantes foram destinados ao grupo CO, os próximos 14 para o grupo G e os últimos 14 para o grupo V. Todas as cirurgias foram realizadas pelo mesmo cirurgião (SCP) que estava ciente do tratamento alocado nos participantes, porém as avaliações foram realizadas por um examinador treinado (JAO) que foi mantido cego em relação à alocação, para evitar as diferenças na avaliação.

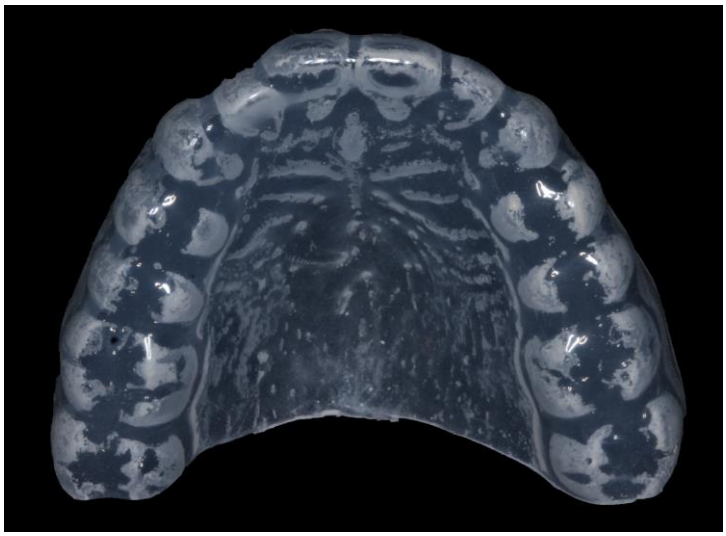
Esses participantes foram selecionados de acordo com os seguintes critérios de inclusão: (1) em relação a idade devem ter entre 18 e 60 anos; (2) apresentar RG isoladas ou múltiplas Classe I, II ou III de Miller (MILLER, 1985) [ou Recessão tipo 1 e 2 (CAIRO *et al.*, 2011)]; (3) ser sistemicamente saudáveis sem contraindicações para cirurgia periodontal; (4) ter profundidade de sondagem menor que 3mm nos sítios envolvidos. Foram excluídos do estudo: (1) participantes que fazem o uso de tabaco ou outros tipos de drogas; (2) participantes que foram submetidos a qualquer tratamento periodontal nos 6 meses precedentes do início exame; (3) participantes gestantes; (4) participantes que não aceitaram voltar nos acompanhamentos e (5) participantes que fizeram uso de antibióticos, corticosteroides, quimioterápicos, imunomoduladores ou outros que modifiquem os resultados terapia periodontal durante os últimos 6 meses.

6.2.2 Tratamento das Recessões Gengivais

6.2.2.1 Fase Inicial

Todos os participantes selecionados foram informados sobre a etiologia das recessões gengivais e instruídos em relação a medidas meticulosas de controle de placa. Os participantes também foram instruídos para realizarem uma escovação atraumática utilizando escova macia. Todos os participantes foram então submetidos a raspagem e alisamento radicular. Após 15 dias, índice de placa e sangramento marginal foram avaliados e apenas os participantes que apresentaram adequado controle de placa foram submetidos ao procedimento cirúrgico. Previamente ao procedimento cirúrgico foram confeccionadas placas de silicone 2 mm para proteção do palato (Figura 1).

Figura 1 - Placa de silicone para proteção do palato



Fonte: Autores (2023).

6.2.2.2 Procedimento Cirúrgico

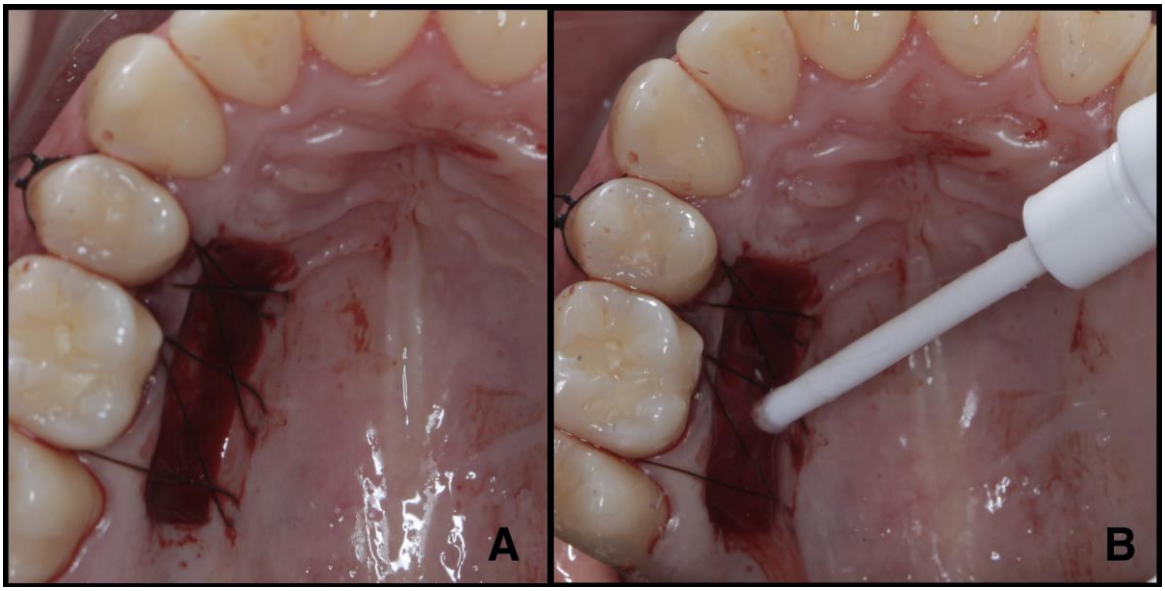
O mesmo operador (S.C.P) realizou todos os procedimentos cirúrgicos. O procedimento cirúrgico foi iniciado com assepsia intra e extra-oral realizadas com gluconato de clorexidina a 0,12% e 2%, respectivamente. A anestesia local foi realizada utilizando uma solução de articaína a 4% com epinefrina 1: 100.000 (Nova DFL). A obtenção do enxerto gengival foi realizada utilizando a técnica do EGL para todos os grupos. O molde da área receptora preparada foi realizado utilizando papel estéril. A área doadora se estendeu da distal do primeiro pré-molar a distal do primeiro molar na região palatina. O molde foi transferido para a área doadora no palato e as bordas do molde delimitadas com lâmina de bisturi 15C. Em seguida, o

molde foi removido e incisões mais profundas foram realizadas nas bordas com o bisturi perpendicular ao palato, visando obter um enxerto com aproximadamente 1.5 mm de espessura. Com a lâmina de bisturi paralela, o enxerto foi removido (epitélio e enxerto conjuntivo) mantendo sua espessura uniforme. Após a remoção do enxerto, duas a três suturas em "X" foram feitas para estabilizar o coágulo na área doadora utilizando fio de Nylon 5.0 (Shalon medical, Brasil).

No **grupo CO**, nenhum material foi colocado na área doadora, apenas o coágulo foi mantido em posição por meio de suturas e a ferida palatina foi protegida com a placa de silicone (Figura 2). No **grupo P**, a ferida palatina foi tratada com o gel placebo (gel sem os aditivos de extrato de chá verde e ácido hialurônico) (N&W Dental Care, Ribeirão Preto, São Paulo, Brasil). No **grupo G**, a ferida palatina foi tratada com gel com extrato de chá verde e ácido hialurônico (Gel profissional Soft Tissue, N&W Dental Care, Ribeirão Preto, São Paulo, Brasil). A composição do gel está descrita no Quadro 1. Nos grupos P e G, o gel foi inserido e protegido por uma placa protetora de silicone. O participante reaplicou o gel em casa 3 vezes ao dia (manhã, após o almoço e antes de dormir) por 7 dias. A aplicação do gel no período da manhã e antes de dormir foi realizada após o bochecho com digluconato de clorexidina a 0,12%. Como um método de monitoramento, um calendário foi fornecido a cada participante para registro do uso diário do gel. Os indivíduos foram orientados a não utilizar qualquer outro produto na área doadora durante o estudo.

Como medicações pós-operatórias foram prescritos: bochecho com digluconato de clorexidina a 0,12% (Periogard, Colgate, Brasil) duas vezes ao dia por 15 dias (a escovação dentária foi descontinuada na área cirúrgica durante este período de tempo); Amoxilicina 500 mg, de 8/8h por 7 dias (ou clindamicina 300 mg, 8 em 8 horas por 7 dias para participantes alérgicos à penincilina) para evitar uma possível infecção pós-operatória; Spidufen 600 mg, 12/12h por 3 dias e Dipirona sódica, 500 mg, 6/6h por 3 dias. Em caso de dor forte, foi prescrito trometamol cetorolaco 10 mg, 8/8h por 3 dias. Após 3 dias, a sutura foi removida e limpeza da área com digluconato de clorexidina a 0,12% (Periogard, Colgate, Brasil) foi realizada.

Figura 2 – Abordagens terapêuticas nos grupos experimentais.



Fonte: Autores (2023).
Legenda: A: Grupo CO apenas com suturas em "X" para estabilização do coágulo; B: Aplicação dos géis nos grupos G e P.

Quadro 1 – Composição do gel com extrato de chá verde e ácido hialurônico

Constituinte	**%**	**Função**
Carboximetilcelulose	1,00	Espessante
Glicerina	5,00	Umectante
Sorbitol	60,0	Umectante
Benzoato de sódio	0,30	Conservante
Xilitol	0,50	Edulcorante, anticárie
Lauril glucosideo	1,50	Tensoativo não-iônico
Lauril sulfato de sodio	0,50	Tensoativo anionico
Ácido hialurônico	0,05	Regenerador de mucosa
Polivinilpirrolidona k 30	0,50	Agente formador de pelicula
Salicilato de dimetilsilanodiol (dsbc)	0,50	Antisséptico e regenerador de mucosa
Tixosil 43 b	10,00	Espessante e agente tixotrópico
Tixosil 73	5,00	Abrasivo
Pirofosfato tetrassódico	0,50	Anti-tártaro
Sacarina	0,05	Edulcorante
Extrato de chá verde (*camellia sinensis)*	0,50	Antioxidante, antisséptico
Óleo de rícino hidrogenado	2,0	Solubilizante
Edta	0,05	Agente quelante
Corante azul ci 42090	Q.s.	Corante
Corante amarelo ci 1910	Q.s.	Corante
Água purificada	11,45	Veículo

Fonte: Autores (2023).

6.2.2.3 Acompanhamento Pós-operatório

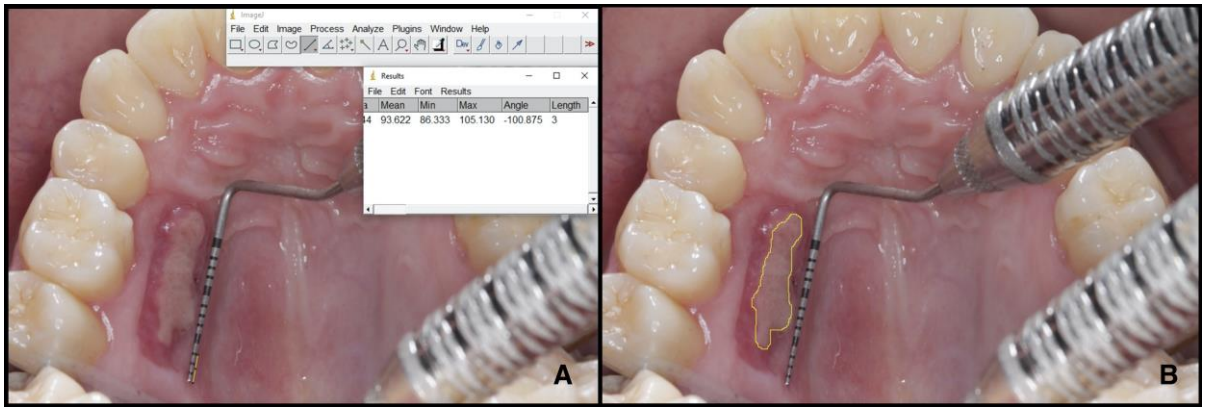
As medidas clínicas foram realizadas durante o procedimento cirúrgico e após 3 dias, 1, 2 e 4 semanas. As medidas foram realizadas por um único examinador treinado (JAO),

utilizando uma sonda periodontal milimetrada (Carolina do Norte, Hu-Friedy, Brasil). O examinador/participante não sabiam qual gel foi utilizado nos momentos das medidas (duplo-cego).

Os seguintes parâmetros clínicos foram avaliados na *área doadora* após a remoção do enxerto e após 3 dias, 1, 2 e 4 semanas:

a) Área da Ferida por Medida Clínica (AFMC): utilizando a sonda periodontal foram determinados a altura e o comprimento da ferida para posterior determinação da área total da região doadora nos diferentes períodos de análise;
b) Área da Ferida por Imagem Fotográfica (AFIF): está sendo realizada utilizando imagens fotográficas padronizadas (Canon Rebel T3i com lente Canon Ef 100mm f/2.8 Macro Usm e flash Canon Macro Ring Light MR-14 EX II). Para a análise das imagens fotográficas, a sonda periodontal milimetrada foi posicionada ao lado da ferida no momento da obtenção das fotos para calibrar o software de análise de imagens (Image J NIH, Bethesda, USA) que será utilizado para calcular a área total da região doadora nos diferentes períodos de análise (Figura 3). Para a análise da AFIF todas as imagens foram misturadas por um pesquisador (J.A.O.), para que outro pesquisador (M.I.S.), cego com relação aos grupos e períodos das imagens, pudesse calcular o tamanho da ferida;

Figura 3 - Análise da área da ferida por imagem fotográfica

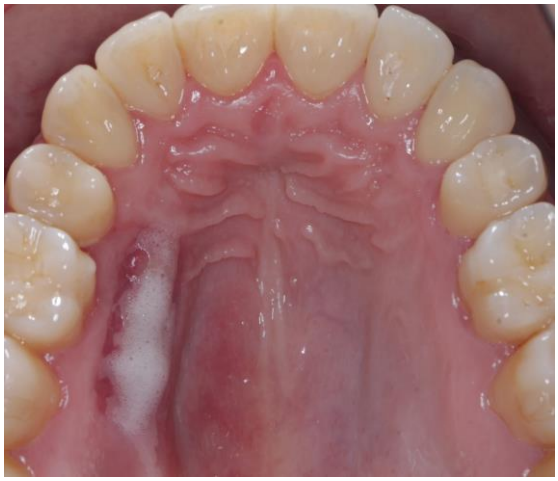


Fonte: Autores (2023).
Legenda: A: Calibração do software Image J NIH com o auxílio da sonda periodontal; B: Delimitação da ferida para o cálculo da área total.

c) Completa Epitelização da Ferida (CEF): A análise da epitelização foi executada utilizando um cotonete umedecido com peróxido de hidrogênio a 3% para observar a presença de formação de bolhas na ferida. A ausência de epitelização foi caracterizada

pela formação de bolhas após o contato do peróxido de oxigênio com a ferida (SILVA *et al.*, 2010). Esse parâmetro foi anotado de forma dicotômica (Presença/ausência de bolhas), sendo anotado como sim ou não, respectivamente, na ficha do participante (Figura 4);

Figura 4 - Formação de bolhas na superfície não epitelizada após a aplicação do peróxido de hidrogênio a 3%



Fonte: Autores (2023).

d) Cor da Mucosa Palatina (CMP): a cor da mucosa palatina foi avaliada pela escala visual analógica (VAS) em comparação com a cor da mucosa adjacente e oposta. Nesta avaliação, em uma escala horizontal, 0 pontos representarão ausência de correspondência de cores, 50 pontos correspondência média e 100 pontos excelente correspondência de cores com os tecidos avaliados (USTAOĞLU;ERCAN;TUNALI, 2016);

As complicações pós-operatória como presença de sangramento, inchaço, infecção e necrose na área doadora foram registradas após 3 e 7 dias.

A percepção do participante em relação a área doadora foi avaliada por meio das ferramentas abaixo:

a) Escala VAS de dor: a percepção da dor do participante foi registrada usando a escala VAS nos locais operados. Os participantes registraram o nível de dor na doadora nos primeiros 3 dias, 1, 2 e 4 semanas após o procedimento em uma escala horizontal, onde

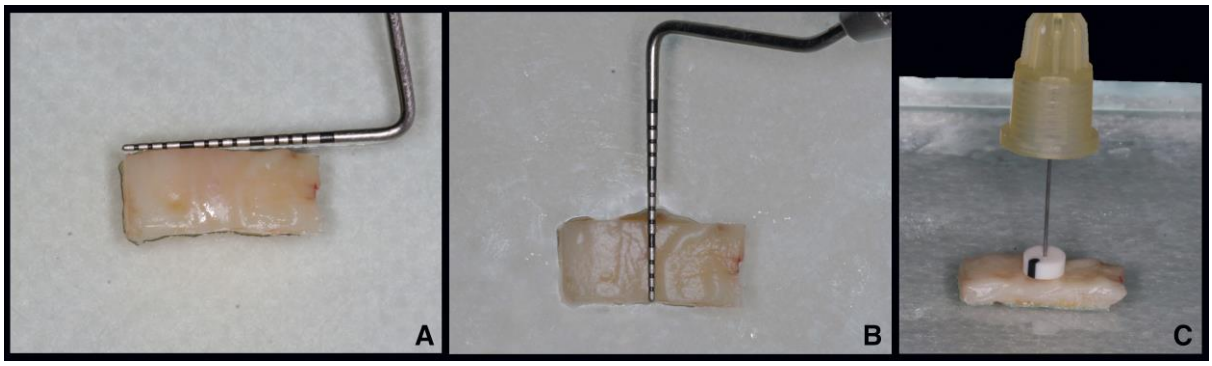
o desfecho esquerdo significará sem dor (0), o ponto médio de dor média (50) e o desfecho direito dor intensa (100);

b) Consumo de analgésicos: O consumo total de analgésicos pelos participantes nos primeiros 7 dias de pós-operatório também foi registrado na ficha do participante.

Os seguintes parâmetros clínicos foram avaliados no enxerto gengival:

a) Espessura do Enxerto Após a Remoção: a espessura do enxerto foi avaliada imediatamente após a remoção utilizando uma agulha extra curta que foi inserida 1.5mm apical da borda coronal no centro do enxerto. O marcador de borracha foi então colocado em contato com o enxerto (Figura 5). A distância entre o marcador e a ponta da agulha foi determinada utilizando um paquímetro digital;
b) Área total do enxerto: utilizando a sonda periodontal foram determinados a altura e o comprimento do enxerto para posterior determinação da área total do enxerto (Figura 5).

Figura 5 – Parâmetros clínicos do enxerto



Fonte: Autores (2023).
Legenda: A: Comprimento do enxerto; B: Altura do enxerto; C: Espessura do enxerto.

6.2.2.4 Desfecho Primário e Secundário

A variável primária desse estudo foi área da ferida que foi avaliada por meio de medidas clínicas/imagens fotográficas. Os outros parâmetros clínicos descritos no item 5.2.2.3 foram considerados variáveis secundárias.

6.2.3 Análise dos dados

Os dados da área da ferida por medidas clínicas e fotográficas se distribuíram de acordo com a normalidade tal como verificado pelo teste de normalidade de Shapiro-Wilk. Os dados

das escalas VAS e do consumo de medicamentos não se distribuíram de acordo com a normalidade. Os dados de CEF foram analisados na forma de proporções. Dessa forma, os dados da área da ferida foram comparados entre os grupos por meio do teste de one-way Anova complementado pelo teste de Tukey, enquanto que a comparação dentro de cada grupo variando-se o período experimental foi executada por meio do teste de Anova para amostras repetidas complementado pelo teste de Tukey. Os dados da escala VAS e do consumo de medicamento foram comparados entre os grupos por meio do teste de Kruskall-Wallis complementado pelo teste de Dunn, enquanto a comparação dentro de cada grupo, variando-se o período experimental foi executada por meio do teste de Friedman complementado pelo teste de Dunn. Os dados da análise de CEF foram comparados entre os grupos por meio do teste de quiquadrado. O software GraphPad Prism 8 (San Diego, CA, USA) foi utilizado para análise inferencial dos dados sendo que todos os testes estatísticos foram aplicados ao nível de significância de 5%.

APÊNDICE B – PRISMA NMA Checklist

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	3
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	5

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	6
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	6
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	6
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	6

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	7
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	supplemetary materials
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12-13
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	supplemetary materials
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	not applied
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment*	17

		on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

APÊNDICE C – CONSORT Checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No #
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applied
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applied
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applied
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	Not applied
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applied
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
According to the manuscript pages that was submitted to Clinical Oral Invastigations.

ANEXO A – Aprovação do Comitê de Ética em Pesquisa da UNIFAL

UNIVERSIDADE FEDERAL DE ALFENAS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: AVALIAÇÃO COMPARATIVA DA TÉCNICA DE TÚNEL E DO ENXERTO LIVRE NO TRATAMENTO DE RECESSÕES GENGIVAIS: ESTUDO CLÍNICO, CONTROLADO E RANDOMIZADO.

Pesquisador: SUZANE CRISTINA PIGOSSI

Área Temática:

Versão: 3

CAAE: 45014621.2.0000.5142

Instituição Proponente: UNIVERSIDADE FEDERAL DE ALFENAS - UNIFAL-MG

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.458.306

Apresentação do Projeto:

Trata-se de um estudo Clínico, Controlado e Randomizado, de um projeto de pesquisa individual do docente, com financiamento próprio no qual objetiva-se comparar a duas técnica s cirúrgicas no tratamento de Recessões Gengivais (RG) isoladas/múltiplas na região anterior da mandíbula.

Objetivo da Pesquisa:

O presente estudo tem como objetivo comparar a técnica de túnel/túnel fechado lateralmente e a técnica do EGL no tratamento de RG isoladas/múltiplas na região anterior da mandíbula. Como objetivo secundário, propõe-se avaliar o efeito do gel de ácido hialurônico e chá verde na cicatrização da área doadora após a remoção do EGL do palato.

Os Objetivos estão:

- claros e bem definidos;
- coerentes com a propositura geral do projeto;
- e exequíveis.

Avaliação dos Riscos e Benefícios:

Em relação dos riscos e benefícios da pesquisa:

Endereço: Rua Gabriel Monteiro da Silva, 700 - Sala O 314 E
Bairro: centro **CEP:** 37.130-001
UF: MG **Município:** ALFENAS
Telefone: (35)3701-9153 **Fax:** (35)3701-9153 **E-mail:** comite.etica@unifal-mg.edu.br

UNIVERSIDADE FEDERAL DE ALFENAS

- Os riscos de execução do projeto são bem avaliados e estão bem descritos no projeto;
- Os benefícios oriundos da execução do projeto justificam os riscos corridos;
- e, para cada risco descrito, o pesquisador apresentou uma correta ação minimizadora/corretiva desse risco.

Comentários e Considerações sobre a Pesquisa:

- Método da pesquisa: Está adequado aos objetivos do projeto, é atualizado, é o melhor disponível;
- Referencial teórico da pesquisa: Está atualizado e é suficiente para aquilo que se propõe;
- Cronograma de execução da pesquisa: É coerente com os objetivos propostos e está adequado ao tempo de tramitação do projeto.

Considerações sobre os Termos de apresentação obrigatória:

a. Termo de Consentimento Livre e Esclarecido (TCLE) – presente e adequado
b. Termo de Assentimento (TA) – não se aplica
c. Termo de Assentimento Esclarecido (TAE) – não se aplica
d. Termo de Compromisso para Utilização de Dados e Prontuários (TCUD) UFU – presente e adequado
e. Termo de Anuência Institucional (TAI) – presente e adequado
f. Folha de rosto - presente e adequado
g. Projeto de pesquisa completo e detalhado – presente e adequado
h. Termo de compromisso para execução de projeto em tempos de pandemia - presente e adequado
I. Declaração de Instituição Coparticipante: Presente e adequado.

Recomendações:

não há.

Conclusões ou Pendências e Lista de Inadequações:

Recomenda-se Aprovação da Emenda.

Considerações Finais a critério do CEP:

Após discussão em reunião remota ordinária, o colegiado emitiu parecer.

Endereço: Rua Gabriel Monteiro da Silva, 700 - Sala O 314 E
Bairro: centro **CEP:** 37.130-001
UF: MG **Município:** ALFENAS
Telefone: (35)3701-9153 **Fax:** (35)3701-9153 **E-mail:** comite.etica@unifal-mg.edu.br

UNIVERSIDADE FEDERAL DE ALFENAS

Continuação do Parecer: 5.458.300

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1949348_E1.pdf	26/05/2022 15:54:22		Aceito
Outros	CoParticipante.pdf	26/05/2022 15:53:10	SUZANE CRISTINA PIGOSSI	Aceito
Outros	TCUDUFU.pdf	26/05/2022 15:49:05	SUZANE CRISTINA PIGOSSI	Aceito
Outros	JustificativaEmenda.pdf	16/05/2022 17:13:43	SUZANE CRISTINA PIGOSSI	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEEmenda.pdf	16/05/2022 17:11:38	SUZANE CRISTINA PIGOSSI	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoEmenda.pdf	16/05/2022 17:10:32	SUZANE CRISTINA PIGOSSI	Aceito
Cronograma	Cronograma.pdf	29/03/2021 10:55:33	SUZANE CRISTINA PIGOSSI	Aceito
Folha de Rosto	Folha.pdf	24/03/2021 14:42:56	SUZANE CRISTINA PIGOSSI	Aceito
Orçamento	Orcamento.pdf	23/03/2021 16:19:40	SUZANE CRISTINA PIGOSSI	Aceito
Declaração de Instituição e Infraestrutura	TAI.pdf	23/03/2021 16:18:09	SUZANE CRISTINA PIGOSSI	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

ALFENAS, 09 de Junho de 2022

Assinado por:
CARLA HELENA FERNANDES
(Coordenador(a))

Endereço: Rua Gabriel Monteiro da Silva, 700 - Sala O 314 E
Bairro: centro **CEP:** 37.130-001
UF: MG **Município:** ALFENAS
Telefone: (35)3701-9153 **Fax:** (35)3701-9153 **E-mail:** comite.etica@unifal-mg.edu.br

ANEXO B – Aprovação do Comitê de Ética em Pesquisa da UFU

UFU Comitê de Ética em Pesquisa — UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG — Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO COMPARATIVA DA TÉCNICA DE TÚNEL E DO ENXERTO LIVRE NO TRATAMENTO DE RECESSÕES GENGIVAIS: ESTUDO CLÍNICO, CONTROLADO E RANDOMIZADO.

Pesquisador: SUZANE CRISTINA PIGOSSI

Área Temática:

Versão: 2

CAAE: 45014621.2.3001.5152

Instituição Proponente: Hospital Odontológico da Universidade Federal de Uberlândia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.628.514

Apresentação do Projeto:

De acordo com o arquivo "AVALIAÇÃO COMPARATIVA DA TÉCNICA DE TÚNEL E DO ENXERTO LIVRE NO TRATAMENTO DE RECESSÕES GENGIVAIS: ESTUDO CLÍNICO, CONTROLADO E RANDOMIZADO", postado em: 09/06/2022.

INTRODUÇÃO - O enxerto gengival livre (EGL) é uma técnica simples considerada oprocedimento mais eficaz para obter aumento gengival em sítios com quantidade mínima de gengiva queratinizada.

METODOLOGIA - Algumas das etapas da pesquisa também serão realizadas na Faculdade de Odontologia da Universidade Federal de Uberlândia (instituição co-participante) incluindo: seleção dos participantes da pesquisa, procedimentos cirúrgicos e acompanhamentos pós-operatórios.

(A) Pesquisa/Estudo. O presente estudo clínico randomizado controlado.

(B) Tamanho da amostra. 60 participantes.

(C) Recrutamento e abordagem dos participantes - Portanto, serão incluídos 60 participantes

nesse estudo uma vez que no objetivo 1 serão 4 grupos (n=15 por grupo) e os mesmos participantes serão divididos em 3 grupos (n=20 por grupo) no objetivo 2. Gerou pendência.

(D) Local e instrumento de coleta de dados / Experimento - Faculdade de Odontologia da Universidade Federal de Alfenas (UNIFAL-MG) e Faculdade de Odontologia da Universidade Federal de Uberlândia / Experimento: Grupos intervenção, controle e placebo.

(E) Metodologia de análise dos dados - Os dados numéricos desse estudo serão avaliados quanto a distribuição em relação ao teorema da distribuição central dos dados.

(F) Desfecho Primário - A variável primária desse estudo será a altura da recessão gengival que será avaliada por meio de análises clínicas para área receptora e porcentagem da redução da ferida que será avaliada por meio de análises clínicas/fotográficas para a área doadora. Os outros parâmetros clínicos descritos no item B3 serão considerados variáveis secundárias.

CRITÉRIOS DE INCLUSÃO - devem ter entre 18 e 60 anos; apresentar RG isoladas (4mm) ou múltiplas em região anterior da mandíbula (dente 33 ao 43) Classe I, II ou III de Miller (87) (ou Recessão tipo (RT) 1 ou RT2 (88)); ser sistemicamente saudáveis sem contraindicações para cirurgia periodontal; ter profundidade de sondagem menor que 3mm nos sítios envolvidos; apresentar os dentes selecionados adequadamente posicionados, livres de tratamento endodôntico, qualquer tipo de tratamento restaurador, cárie ou lesão cervical não cariosa.

CRITÉRIOS DE EXCLUSÃO - participantes que fazem o uso de tabaco ou outros tipos de drogas; participantes que foram submetidos a qualquer tratamento periodontal nos 6 meses precedentes do início exame; participantes gestantes; participantes que não aceitarem voltar nos acompanhamentos e participantes que fizeram uso de antibióticos, corticosteróides, quimioterápicos, imunomoduladores ou outros que modifiquem os resultados terapia periodontal durante os últimos 6 meses.

CRONOGRAMA
Análise Estatística (05/06/2024-05/06/2025)
Seleção dos pacientes (05/06/2021-05/12/2023)
Procedimentos Cirúrgicos (05/07/2021-05/06/2024)

Publicação do estudo em periódicos internacionais (05/01/2025-05/06/2025)
Confecção do Relatório Científico (05/01/2025-05/06/2025)
Acompanhamento Pós-operatório (05/06/2021-05/06/2025)

ORÇAMENTO - R$ 3.505,30.

Objetivo da Pesquisa:

OBJETIVO PRIMÁRIO - O presente estudo tem como objetivo comparar a técnica de túnel/túnel fechado lateralmente e a técnica do EGL no tratamento de RG isoladas/múltiplas na região anterior da mandíbula.

OBJETIVO SECUNDÁRIO - Como objetivo secundário, propõe-se avaliar o efeito do gel de ácido hialurônico e chá verde na cicatrização da área doadora após a remoção do EGL do palato.

HIPÓTESE - A técnica de túnel/túnel fechado lateralmente apresenta desempenho clínico (recobrimento radicular, ganho de GQ e estabilidade da margem gengival) superior, igual ou inferior a técnica do EGL no tratamento de RG isoladas/múltiplas na região anterior da mandíbula. O uso do gel de ácido hialurônico e chá verde acelera/atrasa a cicatrização da área doadora em comparação com o grupo controle.

Avaliação dos Riscos e Benefícios:

RISCOS - a) Risco de hemorragia trans e pós cirúrgica durante a remoção do EGL da mucosa palatina. Para minimizar o risco de hemorragia, o procedimento cirúrgico será feito por um cirurgião experiente preservando as estruturas anatômicas e prevenindo a ocorrência de hemorragias Em caso de hemorragias, esponjas hemostática de colágeno com ação hemostática e cicatrizante serão utilizadas. b) O participante também deverá estar ciente da possível ocorrência de edema e hematomas decorrentes do descolamento do retalho. Para minimizar esses riscos, o participante será instruído a fazer compressas com gelo e será prescrito antibiótico, antiinflamatório e analgésico para maior conforto pós-operatório. c) Outros desconfortos cirúrgicos incluindo tempo de cirurgia extenso, apreensão do participante e medo também devem ser considerados. Para minimizar tais situações todos os pacientes serão instruídos sobre o procedimento a ser realizado de modo a esclarecer possíveis dúvidas e tranquilizá-los. d) Infecções locais no leito receptor podem ocorrer, no entanto podem ser minimizadas pela

realização dos procedimentos em condições de assepsia. e) Considera-se também como risco o fato de que o recobrimento completo das recessões não é garantido com nenhuma das técnicas propostas. Para minimizar esse risco, será proposto um novo procedimento cirúrgico na tentativa de obter o recobrimento completo.

BENEFÍCIOS - Os benefícios dos procedimentos cirúrgicos que serão realizados nesse estudo incluem o tratamento das RG utilizando técnicas descritas na literatura como eficazes e seguras. O tratamento da RG irá facilitar a higienização, reduzir/eliminar a sensibilidade dentinária e prevenir a ocorrência de lesões cervicais cariosas e não cariosas nos participantes do estudo. Além disso, no grupo G será utilizado um gel que apresenta o potencial de acelerar o reparo da área doadora.

Comentários e Considerações sobre a Pesquisa:

As pendências listadas no Parecer Consubstanciado nº 5.565.225, de 05 de agosto de 2022, seguem abaixo, bem como a resposta da equipe de pesquisa e a análise de atendimento ou não da pendência feita pelo CEP/UFU.

Pendência 1 - Explicitar as etapas da pesquisa e as etapas da coleta de dados a serem realizadas na FOUFU, informando ainda uma escala temporal de quando estas etapas serão realizadas. Adequar nos itens Metodologia e Cronograma do Projeto Detalhado.

RESPOSTA - Primeiramente gostaria de agradecer ao parecerista por ter analisado o projeto e feito suas considerações extremamente pertinentes.

Foi incluído no item Metodologia as etapas da pesquisa e da coleta de dados que serão realizadas na FOUFU de maneira detalhada. Segue abaixo o parágrafo adicionado:

"Algumas etapas da pesquisa também serão realizadas na Faculdade de Odontologia da Universidade Federal de Uberlândia [FOUFU (instituição coparticipante)]. Na FOUFU também será realizado (após aprovação do CEP/UFU) o recrutamento e seleção dos participantes da pesquisa de acordo com os critérios de inclusão e exclusão descritos. Após a seleção dos participantes, será realizado o tratamento das recessões gengivais como descrito no item B; o tipo de tratamento executado será definido de acordo com o grupo em que o participante foi alocado após a randomização. Os participantes serão atendidos após 3, 7, 15, 30 dias, 3, 6 e 12 meses para acompanhamento pós-operatório (item B3). Os parâmetros clínicos avaliados no início do estudo

(antes do procedimento cirúrgico) e nos períodos de pós-operatórios estão descritos no item B3. O mesmo cirurgião especialista em Periodontia irá executar os procedimentos cirúrgicos em ambas as instituições (FOUFU e UNIFAL/MG). As análises serão feitas pelos mesmos examinadores cegos em ambas as instituições. Os dados obtidos dos participantes selecionados na FOUFU serão incluídos aos dados obtidos dos participantes da UNIFAL na análise estatística final"

Para atender a solicitação em relação a "escala temporal de quando as etapas serão realizadas" foi incluído no Cronograma do Projeto Detalhado o período em que cada etapa será realizada na FOUFU. A cópia do cronograma encontra-se abaixo:

Identificação da Etapa	Início (dd/mm/aaaa)	Término (dd/mm/aaaa)
Seleção dos participantes na UNIFAL	05/06/2021	05/12/2023
Seleção dos participantes na FOUFU	03/10/2022	03/10/2024
Procedimentos Cirúrgicos na UNIFAL	05/07/2021	05/06/2024
Procedimentos Cirúrgicos na FOUFU	03/11/2022	03/04/2025
Acompanhamento Pós-operatório na UNIFAL	05/07/2021	05/06/2025
Acompanhamento Pós-operatório na FOUFU	03/11/2022	03/04/2026
Análise Estatística	03/04/2026	03/05/2026
Confecção do Relatório Científico	03/05/2026	03/06/2026
Publicação do estudo em periódicos internacionais	03/07/2026	03/12/2026

Todas as alterações estão destacadas em cinza no Projeto Detalhado e no Cronograma do Projeto Detalhado.

ANÁLISE DO CEP/UFU - Pendência atendida.

Considerações sobre os Termos de apresentação obrigatória:

1) Termo de compromisso da utilização de dados assinado, datado e carimbado pelo diretor do Hospital Odontológico.

2) Justificativa da emenda.

3) Declaração da instituição copartipante assinado e datado.
4) TCLE emenda em acordo com as normas do CEP.
5) Projeto emenda em acordo com as normas do CEP.

Recomendações:
Vide campo "Conclusões ou Pendências e Lista de Inadequações".

Conclusões ou Pendências e Lista de Inadequações:
As pendências apontadas no Parecer Consubstanciado nº 5.565.225, de 05 de agosto de 2022, foram atendidas. Portanto, nessa versão o CEP/UFU não encontrou nenhum óbice ético.

De acordo com as atribuições definidas nas Resoluções CNS nº 466/12, CNS nº 510/16 e suas complementares, o CEP/UFU manifesta-se pela aprovação do protocolo de pesquisa.

Prazo para a entrega dos Relatórios Parciais ao CEP/UFU: MARÇO/2023; SETEMBRO/2023; MARÇO/2024; SETEMBRO/2024; MARÇO/2025.

Prazo para a entrega do Relatório Final ao CEP/UFU: JULHO/2025*.

* Tolerância máxima de 01 mês para o atraso na entrega dos relatórios finais e relatório final.

Considerações Finais a critério do CEP:
O CEP/UFU LEMBRA QUE QUALQUER MUDANÇA NO PROTOCOLO DE PESQUISA DEVE SER INFORMADA, IMEDIATAMENTE, AO CEP PARA FINS DE ANÁLISE ÉTICA.

O CEP/UFU alerta que:

a) Segundo as Resoluções CNS nº 466/12 e nº 510/16, o pesquisador deve manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período mínimo

de 5 (cinco) anos após o término da pesquisa;

b) O CEP/UFU poderá, por escolha aleatória, visitar o pesquisador para conferência do relatório e documentação pertinente ao projeto;

c) A aprovação do protocolo de pesquisa pelo CEP/UFU dá-se em decorrência do atendimento às Resoluções CNS nº 466/12 e nº 510/16 e suas complementares, não implicando na qualidade científica da pesquisa.

ORIENTAÇÕES AO PESQUISADOR:

- O participante da pesquisa tem a liberdade de recusar-se a participar ou retirar seu consentimento em qualquer fase da pesquisa, sem penalização e sem prejuízo (Resoluções CNS nº 466/12 e nº 510/16) e deve receber uma via original do Termo de Consentimento Livre e Esclarecido – TCLE, na íntegra, por ele assinado.

- O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado pelo CEP/UFU e descontinuar o estudo após a análise, pelo CEP que aprovou o protocolo (Resolução CNS nº 466/12), das razões e dos motivos para a descontinuidade, aguardando a emissão do parecer, exceto quando perceber risco ou dano não previsto ao participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa que requeiram ação imediata.

- O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Resolução CNS nº 466/12). É papel do pesquisador assegurar medidas imediatas e adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro); e enviar a notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – apresentando o seu posicionamento.

- Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, destacando a parte do protocolo a ser modificada e suas justificativas. No caso de projetos do Grupo I ou II, apresentados à ANVISA, o pesquisador ou patrocinador também deve

UFU Comitê de Ética em Pesquisa — UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG — Plataforma Brasil

Continuação do Parecer: 5.628.514

Informá-la, enviando o parecer aprobatório do CEP, para ser anexado ao protocolo inicial (Resolução nº 251/97, item III.2.e).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1963947.pdf	09/08/2022 19:01:18		Aceito
Outros	Resposta.pdf	09/08/2022 18:59:34	SUZANE CRISTINA PIGOSSI	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.pdf	09/08/2022 18:58:47	SUZANE CRISTINA PIGOSSI	Aceito
Outros	CoParticipante.pdf	26/05/2022 15:53:10	SUZANE CRISTINA PIGOSSI	Aceito
Outros	TCUDUFU.pdf	26/05/2022 15:49:05	SUZANE CRISTINA PIGOSSI	Aceito
Outros	JustificativaEmenda.pdf	16/05/2022 17:13:43	SUZANE CRISTINA PIGOSSI	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEEmenda.pdf	16/05/2022 17:11:38	SUZANE CRISTINA PIGOSSI	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoEmenda.pdf	16/05/2022 17:10:32	SUZANE CRISTINA PIGOSSI	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UBERLANDIA, 06 de Setembro de 2022

Assinado por:
ALEANDRA DA SILVA FIGUEIRA SAMPAIO
(Coordenador(a))

Endereço: Av. João Naves de Ávila 2121- Bloco "1A", sala 224 - Campus Sta. Mônica
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ANEXO C – Normas da revista Clinical Oral Implants Research

Author Guidelines

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://wiley.atyponrex.com/journal/CLR.

Data protection

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protection-policy.html.

Preprint policy

Please find the Wiley preprint policy here.

This journal accepts articles previously published on preprint servers.

Clinical Oral Implants Research will consider for review articles previously available as preprints. Authors may also post the submitted version of a manuscript to a preprint server at any time. Authors are requested to update any pre-publication versions with a link to the final published article.

2. AIMS AND SCOPE

Clinical Oral Implants Research conveys scientific progress in the field of implant dentistry and its related areas to clinicians, teachers and researchers concerned with the application of this information for the benefit of patients in need of oral implants. The journal addresses itself to clinicians, general practitioners, periodontists, oral and maxillofacial surgeons and prosthodontists, as well as to teachers, academicians and scholars involved in the education of professionals and in the scientific promotion of the field of implant dentistry.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

Original research articles of high scientific merit in the field of surgical and prosthetic aspects of clinical oral implant dentistry including material sciences, physiology of wound healing, prevention and treatment of pathologic processes jeopardizing the longevity of implants, clinical trials on implant systems, stomatognathic physiology related to oral implants, oral tissue regeneration related to oral implants, digital technologies in the field of implant dentistry, new developments in therapeutic concepts and prosthetic rehabilitation.

Clinical Oral Implants Research also publishes preclinical in vivo and in vitro research of high scientific merit which has translational relevance to clinical oral implant dentistry.

Clinical Oral Implants Research encourages complete reporting of all data in one manuscript as opposed to reporting data (for example clinical and radiographic data) in multiple manuscripts.

Review articles by experts on new developments in basic sciences related to implant dentistry and clinically applied concepts. Reviews are by invitation only from the Editor-in-Chief.

Perspective articles on topical areas related to implant dentistry and clinically applied concepts by invitation only from the Editor-in-Chief.

Case reports and case series, but only if they provide or document new fundamental knowledge and if they use language understandable to the clinician.

Novel developments if they provide a technical novelty for any implant system

Short communications of important research findings in a concise format and for rapid publication.

Proceedings of international meetings may also be considered for publication at the discretion of the Editor-in-Chief.

4. PREPARING THE SUBMISSION

Clinical Oral Implants Research now offers Free Format submission for a simplified and streamlined submission process.

Before you submit, you will need:

Your manuscript: this should be an editable file including text, figures, and tables, or separate files – whichever you prefer. All required sections should be contained in your manuscript, including abstract, introduction, methods, results, and conclusions. Figures and tables should

have legends. Figures should be uploaded in the highest resolution possible. References may be submitted in any style or format, as long as it is consistent throughout the manuscript. Supporting information should be submitted in separate files. If the manuscript, figures or tables are difficult for you to read, they will also be difficult for the editors and reviewers, and the editorial office will send it back to you for revision. Your manuscript may also be sent back to you for revision if the quality of English language is poor.

An ORCID ID, freely available at https://orcid.org. (Why is this important? Your article, if accepted and published, will be attached to your ORCID profile. Institutions and funders are increasingly requiring authors to have ORCID IDs.)

The title page of the manuscript, including:

Your co-author details, including affiliation and email address. (Why is this important? We need to keep all co-authors informed of the outcome of the peer review process.)

Statements relating to our ethics and integrity policies, which may include any of the following (Why are these important? We need to uphold rigorous ethical standards for the research we consider for publication):

data availability statement

funding statement

conflict of interest disclosure

ethics approval statement

patient consent statement

permission to reproduce material from other sources

clinical trial registration

If you are invited to revise your manuscript after peer review, the journal will also request the revised manuscript to be formatted according to journal requirements as described below.

Parts of the Manuscript

The manuscript should be submitted in separate files: main text file; figures.

Main Text File

Manuscripts can be uploaded either as a single document (containing the main text, tables and figures), or with figures and tables provided as separate files. Should your manuscript reach revision stage, figures and tables must be provided as separate files. The main manuscript file can be submitted in Microsoft Word (.doc or .docx) or LaTex (.tex) format.

When submitting your manuscript file in LaTex format via Research Exchange, select the file designation “Main Document – LaTeX .tex File” on upload. When submitting a Latex Main Document, you must also provide a PDF version of the manuscript for Peer Review. Please

upload this file as “Main Document - LaTeX PDF.” All supporting files that are referred to in the Latex Main Document should be uploaded as a “LaTeX Supplementary File.”

The text file should be presented in the following order:

i. A short informative title containing the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips). Trade/product names should not be included in the title;

Please include study design in the title;

ii. A short running title of less than 60 characters;

iii. The full names of the authors;

iv. The author's institutional affiliations where the work was conducted, with a footnote for the author’s present address if different from where the work was conducted;

v. Acknowledgments;

vi. Author contributions: Please provide a statement listing the contributions made by each of the authors. Example: A.S. and K.J. conceived the ideas; K.J. and R.L.M. collected the data; R.L.M. and P.A.K. analysed the data; and A.S. and K.J. led the writing. Please refer to the journal’s Authorship policy in the Editorial Policies and Ethical Considerations section for details on author listing eligibility;

vii. Abstract, MeSH term keywords and word count;

viii. Main text;

ix. References;

x. Tables (each table complete with title and footnotes);

xi. Figure legends;

xii. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

Authorship

Please refer to the journal’s authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the section ‘Conflict of Interest’ in the Editorial

Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Abstract

Abstracts should not to exceed 250 words. This should be structured into: objectives, material and methods, results, conclusions, and no other information. Trade/product names must not be included in the abstract.

Keywords

Please provide 3-8 keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Main Text of Original Research Articles

The main text should include Introduction, Material and Methods, Results and Discussion.

Introduction: Summarise the rationale and purpose of the study, giving only strictly pertinent references. Do not review existing literature extensively. State clearly the working hypothesis.

Material and Methods: Material and methods should be presented in sufficient detail to allow confirmation of the observations. Published methods should be referenced and discussed only briefly, unless modifications have been made. Indicate the statistical methods used, if applicable.

Clinical trial registration number and name of the trial register should be included in the Materials and Methods at the submission stage.

Authors who have completed the ARRIVE guidelines, STROBE or CONSORT checklist should include as the last sentence in the Methods section a sentence stating compliance with the appropriate guidelines/checklist.

Results: Present your results in a logical sequence in the text, tables, and illustrations. Do not repeat in the text all data in the tables and illustrations. The important observations should be emphasised.

Discussion: Summarise the findings without repeating in detail the data given in the Results section. Relate your observations to other relevant studies and point out the implications of the findings and their limitations. Cite other relevant studies.

Main Text of Short Communications

Short communications are limited to two printed pages including illustrations and references and need not follow the usual division into material and methods, etc., but should have an abstract.

References

This journal uses APA (American Psychological Association, 6th edition) referencing style; as the journal offers Free Format submission, however, this is for information only and you do not need to format the references in your article. This will instead be taken care of by the typesetter. APA references requires text citations to follow the author-date method whereby the author's last name and the year of publication for the source should appear in the text, for example, (Jones, 1998). The complete reference list should appear alphabetically by name at the end of the paper.

A sample of the most common entries in reference lists appears below. Please note that a DOI should be provided for all references where available. For more information about APA referencing style, please refer to the APA FAQ. Please note that for journal articles, issue numbers are not included unless each issue in the volume begins with page one.

Journal article:

Beers, S. R. , & De Bellis, M. D. (2002). Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. The American Journal of Psychiatry, 159, 483–486. doi:10.1176/appi.ajp.159.3.483

Book edition:

Bradley-Johnson, S. (1994). Psychoeducational assessment of students who are visually impaired or blind: Infancy through high school (2nd ed.). Austin, TX: Pro-ed.

Internet Document:

Norton, R. (2006, November 4). How to train a cat to operate a light switch [Video file]. Retrieved from http://www.youtube.com/watch?v=Vja83KLQXZs

In-text citations:

If your source has two authors, always include both names in each in-text citation.

If your source has three, four, or five authors, include all names in the first in-text citation along with the date. In the following in text citations, only include the first author’s name and follow it with et al.

Example:

1st in-text citation: (Gilley, Johnson, Witchell, 2015)

2nd and any other subsequent citations: (Gilley, et al.)

If your source has six or more authors, only include the first author’s name in the first citation and follow it with et al. Include the year the source was published and the page numbers (if it is a direct quote).

Example:

1st in-text citation: (Jasper, et al., 2017)

2nd and any other subsequent citations: (Jasper, et al., 2017)

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

All figures should clarify the text and their number should be kept to a minimum. Details must be large enough to retain their clarity after reduction in size. Micrographs should be designed to be reproduced without reduction, and they should be dressed directly on the micrograph with a linear size scale, arrows, and other designators as needed. Each figure should have a legend. Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted.

Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Color Figures. Figures submitted in color may be reproduced in colour online free of charge. Please note, however, that it is preferable that line figures (e.g. graphs and charts) are supplied in black and white so that they are legible if printed by a reader in black and white.

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Additional Files

Appendices

Appendices will be published after the references. For submission they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

The following points provide general advice on formatting and style.

Abbreviations: In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only. Use only standard abbreviations. In cases of doubt, the spelling orthodoxy of Webster's third new international dictionary will be adhered to. Avoid abbreviations in the title.

Symbols: The symbol % is to be used for percent, h for hour, min for minute, and s for second. In vitro, in vivo, in situ and other Latin expressions are to be italicised.

Units of measurement: Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website for more information about SI units.

Numbers: numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils). Use no roman numerals in the text.

Decimals: In decimals, a decimal point and not a comma will be used.

Scientific Names: Proper names of bacteria should be binomial and should be singly underlined on the typescript. The full proper name (e.g., Streptococcus sanguis) must be given upon first mention. The generic name may be abbreviated thereafter with the first letter of the genus (e.g., S. sanguis). If abbreviation of the generic name could cause confusion, the full name should be used. If the vernacular form of a genus name (e.g., streptococci) is used, the first letter of the vernacular name is not capitalised and the name is not underlined. Use of two letters of the genus (e.g., Ps. for Peptostreptococcus) is incorrect, even though it might avoid ambiguity.

Trade Names: Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary

drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

P values should be written in full and should be in italics (e.g p = 0.04) - 3 decimal places

Submission of Revised Manuscripts

When submitting revised manuscripts, authors are requested to highlight revisions in yellow rather than using track changes features. In addition, an author response letter should be provided including a detailed response to each point from each reviewer.

Wiley Author Resources

Manuscript Preparation Tips: Wiley has a range of resources for authors preparing manuscripts for submission available here. In particular, authors may benefit from referring to Wiley's best practice tips on Writing for Search Engine Optimization.

Article Preparation Support: Wiley Editing Services offers expert help with English Language Editing, as well as translation, manuscript formatting, figure illustration, figure formatting, and graphical abstract design – so you can submit your manuscript with confidence.

Also, check out our resources for Preparing Your Article for general guidance about writing and preparing your manuscript.

Guidelines for Cover Submissions: If you would like to send suggestions for artwork related to your manuscript to be considered to appear on the cover of the journal, please follow these general guidelines.

5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Peer Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to journal readership. Manuscripts are single-blind peer reviewed. Papers will only be sent to review if the Editor-in-Chief determines that the paper meets the appropriate quality and relevance requirements.

Wiley's policy on the confidentiality of the review process is available here.

Appeal of Decision

The decision on a paper is final and cannot be appealed.

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants (even if the study is retro-spective), a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example:

Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; or European Medicines Agency Guidelines for Good Clinical Practice. It should also state clearly in the text that all persons gave their informed consent prior to their inclusion in the study. A pdf of the ethics approval must be uploaded at the time of submission. The ethics approval number should be included in the Materials and Methods section. If the study is exempt from ethics approval a PDF of the ethics exemption letter from the relevant ethics committee/authorized body is required.

Patient anonymity should be preserved. When detailed descriptions, photographs, or videos of faces or identifiable body parts are used that may allow identification, authors should obtain the individual's free prior informed consent. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a standard patient consent form available for use. Where photographs are used they need to be cropped sufficiently to prevent human subjects being recognized; black eye bars should not be used as they do not sufficiently protect an individual's identity).

Clinical Trial Registration

The journal requires that all clinical trials which have a commencement date after 31st January 2017 are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. For further information about Clinical Trial Registration please see:

https://grants.nih.gov/policy/clinical-trials/definition.htm

https://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

https://www.who.int/clinical-trials-registry-platform

Research Reporting Guidelines

Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. Authors are required to adhere to recognised research reporting standards. The EQUATOR Network collects more than 370 reporting guidelines for many study types, including for:

Randomised trials : CONSORT

Clinical trials should be reported using the CONSORT guidelines. A CONSORT checklist should also be included in the submission material under "Supplementary Files for Review".

If your study is a randomized clinical trial, you will need to fill in all sections of the CONSORT Checklist. If your study is not a randomized trial, not all sections of the checklist might apply to your manuscript, in which case you simply fill in N/A.

All prospective clinical trials which have a commencement date after the 31st January 2017 must be registered with a public trials registry.

Observational studies : STROBE

Clinical Oral Implants Research requires authors of human observational studies in epidemiology to review and submit a STROBE statement. Authors who have completed the STROBE checklist should include as the last sentence in the Methods section a sentence stating compliance with the appropriate guidelines/checklist. Checklists should be included in the submission material under “Supplementary Files for Review”. Please indicate on the STROBE checklist the page number where the corresponding item can be located within the manuscript e.g. Page 4.

Systematic reviews : PRISMA

Case reports : CARE

Qualitative research : SRQR

Diagnostic / prognostic studies : STARD

Quality improvement studies : SQUIRE

Economic evaluations : CHEERS

Pre-clinical in vivo studies : ARRIVE

Clinical Oral Implants Research requires authors of pre-clinical in vivo studies submit with their manuscript the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines checklist. Authors who have completed the ARRIVE guidelines checklist should include as the last sentence in the Methods section a sentence stating compliance with the appropriate guidelines/checklist. Checklists should be included in the submission material under “Supplementary Files for Review”.

Study protocols : SPIRIT

Clinical practice guidelines : AGREE

We also encourage authors to refer to and follow guidelines from:

Future of Research Communications and e-Scholarship (FORCE11)

National Research Council's Institute for Laboratory Animal Research guidelines

The Gold Standard Publication Checklist from Hooijmans and colleagues

Minimum Information Guidelines from Diverse Bioscience Communities (MIBBI) website

FAIRsharing website

Conflict of Interest

The journal requires that all authors disclose any potential sources of conflict of interest. Any interest or relationship, financial or otherwise that might be perceived as influencing an author's

objectivity is considered a potential source of conflict of interest. These must be disclosed when directly relevant or directly related to the work that the authors describe in their manuscript. Potential sources of conflict of interest include, but are not limited to: patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a conflict of interest does not preclude publication. If the authors have no conflict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to disclose with the submission ALL pertinent commercial and other relationships.

The above policies are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced by the International Committee of Medical Journal Editors (http://www.icmje.org/).

It is the responsibility of the corresponding author to have all authors of a manuscript fill out a conflict of interest disclosure form, and to upload all forms together with the manuscript on submission. Please find the form form below:

Funding

Authors should list all funding sources in the Acknowledgments section. Authors are responsible for the accuracy of their funder designation. If in doubt, please check the Open Funder Registry for the correct nomenclature: https://www.crossref.org/services/funder-registry/

Authorship

The list of authors should accurately illustrate who contributed to the work and how. All those listed as authors should qualify for authorship according to the following criteria:

Have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and

Been involved in drafting the manuscript or revising it critically for important intellectual content; and

Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A maximum of 6 authors are allowed unless there is sufficient justification according to the ICJME guidelines for authorship: ICMJE | Recommendations | Defining the Role of Authors and Contributors.

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section (for example, to recognize contributions from people who provided technical help, collation of data, writing assistance, acquisition of funding, or a department chairperson who provided general support). Prior to submitting the article all authors should agree on the order in which their names will be listed in the manuscript.

Additional Authorship Options. Joint first or senior authorship: In the case of joint first authorship, a footnote should be added to the author listing, e.g. 'X and Y should be considered joint first author' or 'X and Y should be considered joint senior author.'

Data Sharing and Data Accessibility

Clinical Oral Implants Research expects that data supporting the results in the paper will be archived in an appropriate public repository. Authors are required to provide a data availability statement to describe the availability or the absence of shared data. When data have been shared, authors are required to include in their data availability statement a link to the repository they have used, and to cite the data they have shared. Whenever possible the scripts and other artefacts used to generate the analyses presented in the paper should also be publicly archived. If sharing data compromises ethical standards or legal requirements then authors are not expected to share it.

See the Standard Templates for Author Use to select an appropriate data availability statement for your dataset.

Publication Ethics

This journal is a member of the Committee on Publication Ethics (COPE). Note this journal uses iThenticate's CrossCheck software to detect instances of overlapping and similar text in submitted manuscripts. Read Wiley'sTop 10 Publishing Ethics Tips for Authors here. Wiley's Publication Ethics Guidelines can be found here.

ORCID

As part of the journal's commitment to supporting authors at every step of the publishing process, the journal requires the submitting author (only) to provide an ORCID iD when submitting a manuscript. This takes around 2 minutes to complete. Find more information here.

ANEXO D – Normas da revista Clinical Oral Investigations

Instructions for Authors

Types of papers

Papers may be submitted for the following sections:

Research Article

Reviews

Brief Report – with up to 2000 words and up to two figures and/or tables

Correspondence (Discussion paper)

Debate (Letter to the Editor)

Perspective (by Editor invitation only)

Perspective articles are focused articles on topics of interest to a broad audience, but are written from a personal viewpoint. They are intended to provide a forum to be more speculative than Reviews, but should remain balanced and are intended to cover timely and relevant topics. These articles are peer reviewed.

Limited to 1,500-3,000 words (excluding abstract, references and figure legends); Unstructured abstract 200 words; 4 tables/figures; 60 references

It is the general policy of this journal not to accept case reports and pilot studies.

Title Page

The title page should include:

The name(s) of the author(s)

A concise and informative title

The affiliation(s) and address(es) of the author(s)

The e-mail address, telephone and fax numbers of the corresponding author

Abstract

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

Objectives (stating the main purposes and research question) 77

Materials and Methods

Results

Conclusions

Clinical Relevance

These headings must appear in the abstract.

Keywords

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

Text

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, 78 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"). 79

J*ournal 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 80

If you are unsure, please use the full journal title.

Authors preparing their manuscript in LaTeX can use the bibliography style file sn-basic.bst which is included in the Springer Nature Article Template.

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.

Line Art

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.

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 81 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).

Clinical Trial Registration

Clinical trials must be registered prior to submission of manuscripts. The registration site must be publicly available in English.

Author contributions

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

Disclosure of potential conflicts of interest

Research involving Human Participants and/or Animals

Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.