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Original Article

Bioactive materials for post-operative healing and pain relief following palatal epithelialized graft harvesting: A meta-analysis of randomized clinical trials

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Abstract *Background/purpose:* Palatal epithelial graft harvesting requires secondary healing, and various materials have been used to accelerate this and reduce discomfort. However, comparisons against standardized controls remain limited, especially in randomized clinical trials. This meta-analysis assessed the efficacy of bioactive materials of hyaluronic acid, platelet-rich fibrin, collagen, and cyanoacrylate in promoting healing and reducing pain after epithelial graft harvesting.

Materials and methods: Clinical trials were identified from PubMed, Scopus, Web of Science and Embase up to August 2024. The efficacies of bioactive materials were assessed using Review Manager Analysis, with odds ratios calculated for complete wound healing and mean differences in Visual Analog Scale (VAS) scores for pain.

Results: Of 787 references, 9 clinical trials met eligibility: 6 on healing and 7 on pain. Meta-analysis showed significant improvement in complete epithelialization for the overall materials vs. control (OR = 4.28). Subgroup analysis showed improvements for HA (OR = 4.80) and PRF (OR = 12.81), but not cyanoacrylate. Similar results were seen for VAS pain scores on days 1–3

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and day 7, with benefits for the overall materials and individually for HA, PRF, and collagen, except cyanoacrylate. High heterogeneity was found on days 1–3 ($I^2 = 66$) and day 7 ($I^2 = 90\%$). Subgroup analysis reduced most heterogeneity, except for HA on days 1–3 ($I^2 = 91\%$).

Conclusion: HA, PRF, and collagen may relieve pain, and HA and PRF might aid healing after epithelialized gingival graft harvest (no trials recruited in evaluating the collagen's effect on wound healing). Cyanoacrylate may not support pain relief or healing. Further trials are needed.

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Introduction

Gingival connective tissue graft is widely regarded as the most predictable method for periodontal and peri-implant plastic surgeries.^{1,2} In most situations, these procedures involve harvesting tissue from palatal donor site. Various techniques are involved in harvesting gingival connective tissue for grafting.^{3–6} However, in terms of the healing process on donor site, there is a significant difference between epithelialized and subgingival grafts: the palatal wound from an epithelialized free gingival graft requires a secondary healing process of about 2–4 weeks and often leads to complications such as postoperative pain, compared to subgingival harvesting.^{7,8}

Studies have focused on exploring various materials to accelerate healing and reduce discomfort after epithelialized graft harvesting. Bioactive materials such as hyaluronic acid (HA),^{9–13} platelet-rich fibrin (PRF),^{14–21} collagen sponges,^{20,22} cyanoacrylate adhesives,^{23–26} gelatin sponge,^{15,27} enamel matrix derivative²⁸ and others have been applied to the palatal wound. However, most comparisons have been conducted among different materials or combinations of various materials, while comparisons of each single material against a standardized control are still limited, particularly within the framework of randomized clinical trials.^{13,14,29} Other challenges arise from disparate observation intervals, non-standardized material preparations, diverse outcome measurements, and inconsistent results. As a result, reaching definitive conclusions about the effect of a single material on the healing process becomes difficult. For instance, one study found statistically significant differences in Visual Analog Scale (VAS) pain scores between the HA group and the non-dressing control group on post-operative days 2 and 3,¹⁰ while another study reported significantly lower VAS pain scores at 14 and 21 days in the group using the HA gelatin sponge compared to those without HA.¹³ Additionally, the quantitative healing outcomes following bioactive materials have been broadly reported; however, the methods for evaluating healing varied, including assessments of complete epithelialization,¹⁹ defect size,²⁰ tissue thickness,³⁰ or even a healing index.¹⁸

In this meta-analysis, we evaluated the evidence regarding the efficacy of bioactive materials on post-operative outcomes at the palatal donor site following epithelialized gingival graft harvesting. We included clinical

trials that assessed wound healing (complete epithelialization at 14 days post-operation) and postoperative pain (VAS pain scores within the initial three days and at seven days post-surgery). Due to study limitations, the bioactive materials included were HA, PRF, collagen, and cyanoacrylate.

Materials and methods

Search strategy

In this study, four electronic databases, namely PubMed, Scopus, Web of Science and Embase were searched to identify relevant studies. The outcomes were reported as the number of patients with complete epithelialization of the surgical wound and those measured by the Visual Analog Scale for pain.²³ Randomized clinical trials were identified using the following search terms: ((cyanoacrylate) OR (collagen) OR (hyaluronic acid) OR (platelet-rich fibrin) OR (platelet rich plasma)) AND ((free gingival graft) OR (palatal graft) OR (connective tissue graft) OR (palatal wound) OR (palatal healing) OR (wound heal) OR (wound healing)) AND ((palatal pain) OR (visual analogic scale) OR (patient reported outcome)) AND (clinical trial). Additionally, the references cited in the included papers were reviewed to ensure the inclusion of all relevant research. The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and was registered on the OSF platform (Open Science Framework platform, registration DOI: <https://doi.org/10.17605/OSF.IO/C9AWV>) (Fig. 1).

Inclusion and exclusion criteria

The included studies were controlled clinical trials with at least 2 weeks of follow-up, published in English up to August 2024. The inclusion criteria were based on the PICO principle. The patients (participant, P) included were those who underwent surgical removal of epithelialized tissue grafts from the palatal donor site. The intervention (I) involved the protection of the palatal harvested area using bioactive materials, including cyanoacrylate tissue adhesive, collagen, HA, PRF, or platelet-rich plasma. In the control group (C), no additional dressing material was applied to

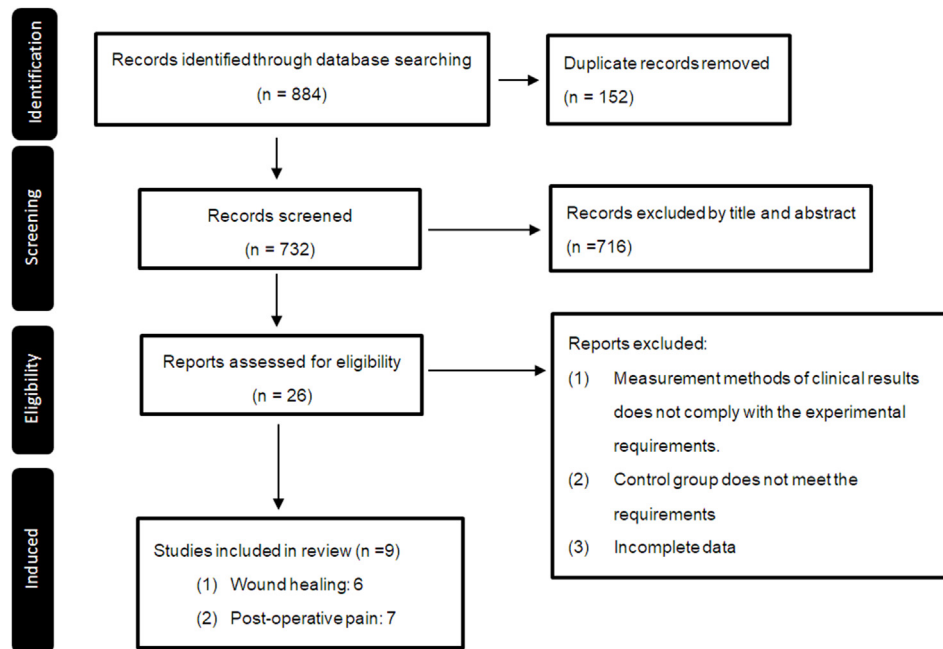


Figure 1 PRISMA flow diagram of the search results from the databases.

the wound at the palatal donor site, except for suturing and/or Coe-packing/stent application. The outcomes (O) encompassed postoperative pain, assessed using a visual analog scale within three days and again at seven days post-surgery, as well as wound healing, evaluated by complete epithelialization of the wound at 14 days post-surgery. Articles that matched the inclusion criteria were further screened using the exclusion criteria: (i) letters, reviews, abstracts, case reports, and case series. We made the decision not to include any other dressing materials due to limitations in time and resources. Therefore, the present meta-analysis was confined to the following materials: cyanoacrylate adhesive, collagen, HA, and PRF.

Data extraction

Among the included studies, the following variables were extracted and recorded in a standardized format: publication year, author, study design, number of participants, patient classification, duration of treatment and follow-up, measurement methods, and clinical results (Table 1).

Quality assessment

The quality of each controlled clinical trial was assessed by two reviewers (CSL and EF) using the Risk of Bias 2 (RoB 2) tool. Following the guidelines in the Cochrane Handbook (available at: <https://training.cochrane.org/handbook/current/chapter-08>) and the RoB 2 tool, five main domains were evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Based on the quality assessment,

the studies were categorized into three groups: low risk of bias, some concerns, and high risk of bias (Fig. 1-II).

Statistical analysis

In this meta-analysis, nine studies were included for analysis.^{9,12,15,17,19,21–23,31} Using Review Manager Version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), the mean difference (MD), 95 % confidence intervals (CI), and effect size were calculated for the continuous outcome of VAS scales (post-operative pain), while the odds ratio (OR) was used to assess the dichotomous outcome of wound healing (complete epithelialization at 14 days post-surgery). In this study, statistical significance was considered when $P \leq 0.05$. Heterogeneity was assessed using the I^2 static, which ranges from 0 % to 100 %. $I^2 = 0$ % indicated no heterogeneity, whereas ≥ 50 % suggested high heterogeneity.³² In general, fixed effect models are used when heterogeneity is low, whereas the random effects models are used when heterogeneity is high. The potential publishing bias was estimated by funnel plots. All statistical analyses were performed using Review Manager.

Results

Study selection

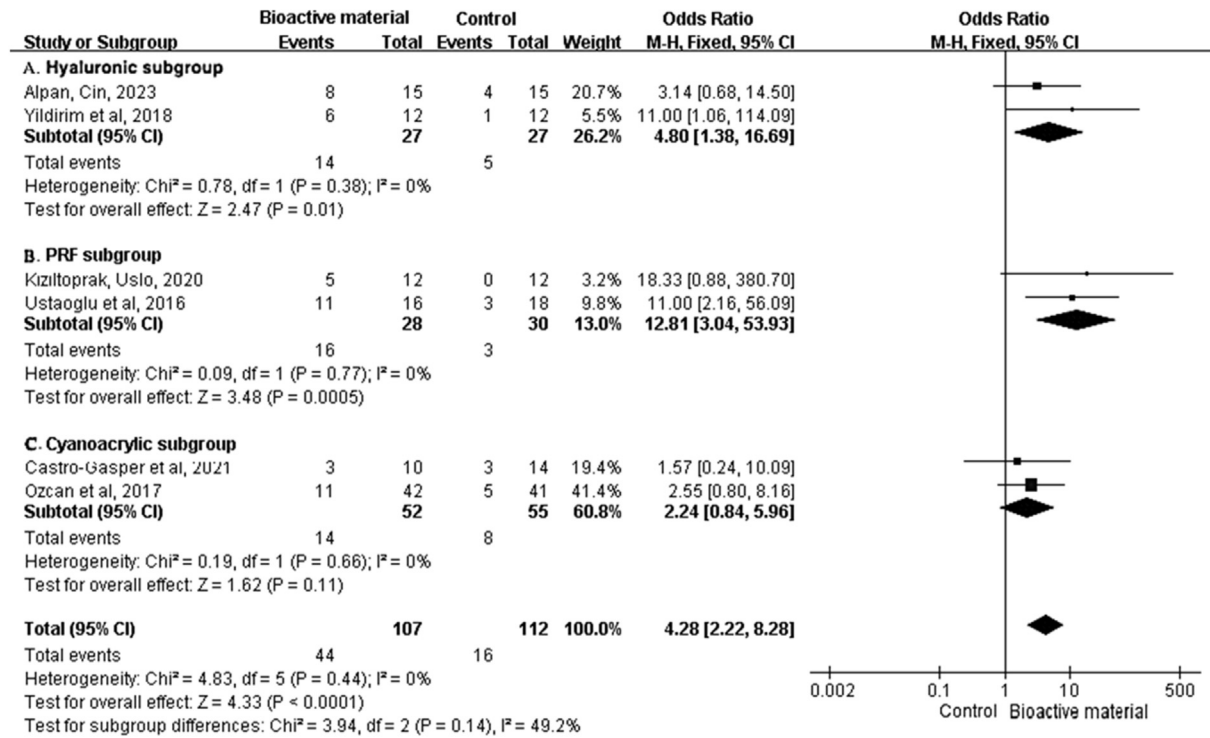
The flow chart for the procedure of study collection is presented in Fig. 1. According to the exclusion criteria, nine studies were included, while 875 publications were excluded. The nine randomized clinical trials included in this study, along with their risks of bias are summarized in Table 1 and Fig. 1. As illustrated in Fig. 2, six studies were

Table 1 Characteristics and risk of bias of eight randomized clinical trials included in this Meta-analysis.

	Experimental group	Control group	Observing parameters post-operatively	Positive impacts on wound healing and pain relief	Risk of bias					
					D1	D2	D3	D4	D5	overall
Shanmugam et al. ²² (2010)	Collagen dressing (CollaCote®) & stent (n = 16)	Coe-pack & stent (n = 16)	Pain (VAS), histology healing, color match, consistency, and tissue thickness	Collagen: 1) accelerating healing; 2) reducing postoperative pain.	⊖	+	+	⊖	+	⊖
Ustaoglu et al. ²¹ (2016)	Titanium-prepared PRF with stent (n = 16)	Suture with stent (n = 18)	Epithelization (H ₂ O ₂), color match, analgesics taken, and tissue thickness	PRF: 1) accelerating healing; 2) no difference in VAS and analgesics.	+	+	+	+	+	+
Ozcan et al. ¹⁹ (2017)	Cyanoacrylate (PeriAcryl) alone and PeriAcryl with PRF (n = 42/group).	Compression with gauze (n = 41)	Epithelization (H ₂ O ₂), pain (VAS), immediate bleeding time, sensibility disorders, and feeding habits	1) PRF with PeriAcryl: Significant benefits in pain and healing; 2) cyanoacrylate alone: no difference.	+	+	+	+	+	+
Yildirim et al. ¹² (2018)	Hyaluronic acid gels (0.2 and 0.8 %) (n = 12/group)	Periodontal dressing (n = 12)	Epithelization (inspection), pain (VAS), and burning sensation	Hyaluronic acid: 1) accelerating healing; 2) reducing pain	+	+	+	⊖	+	⊖
Isler et al. ¹⁶ (2019)	Collagen, PRF, retainer, ozone, & laser (n = 50)	Spontaneous healing (n = 10)	Pain (VAS) and Oral Health Impact Profile (OHIP-14) questions	Reducing postoperative pain for both collagen sponge and PRF.	+	+	+	⊖	+	⊖
Kızıltoprak, Uslu ¹⁷ (2020)	Injectable PRF, and autologous fibrin glue (AFG) (n = 12/group)	Moist sterile tamponade (n = 12)	Epithelization (H ₂ O ₂), pain (VAS), soft tissue healing, scar, bleeding, and tissue thickness	Injectable PRF/AFG: 1) accelerating healing; 2) reducing pain	+	+	+	⊖	+	⊖
Castro-Gaspar et al. ²³ (2021)	Cyanoacrylate adhesive (Periacryl®90) (n = 10)	Suture (n = 14)	Epithelization (H ₂ O ₂), pain (VAS), inflammation, bleeding, necrosis, etc	Cyanoacrylate: no difference in healing time and pain	+	+	+	⊖	+	⊖
Alpan, Cin ⁹ (2023)	Groups: hyaluronic acid gel (0.6 %), HOCl, and flurbiprofen (n = 15/group)	Spontaneous healing (n = 15)	Epithelization (H ₂ O ₂), pain (VAS), healing index, analgesic consumption, color match, and bleeding	Hyaluronic acid: 1) accelerating healing; 2) reducing pain	+	+	+	⊖	+	⊖
Karimi et al. ³¹ (2024)	Cyanoacrylate adhesive (Periacryl®90) (n = 10)	Suture and periodontal dressing (n = 10)	Epithelization (H ₂ O ₂), pain (VAS), discomfort, analgesic consumption, eating status, bleeding, dimensional change	Cyanoacrylate: 1) no difference in healing time 2) reducing postoperative pain	+	+	+	⊖	+	⊖

D1: Randomisation process; D2: Deviations from the intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; and D5: Selection of the reported result; ⊕ low risk; ⊖ some concerns; ⊖ high risk (VAS: Visual Analog Scale; PRF: platelet-rich fibrin).

Forest plot



Funnel plot

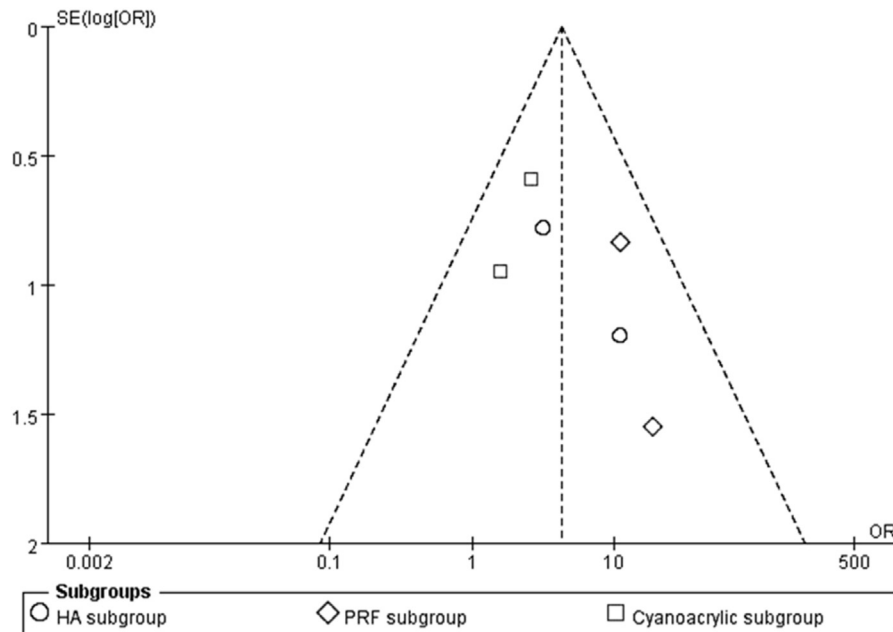


Figure 2 Efficacy of bioactive materials on post-operative healing.

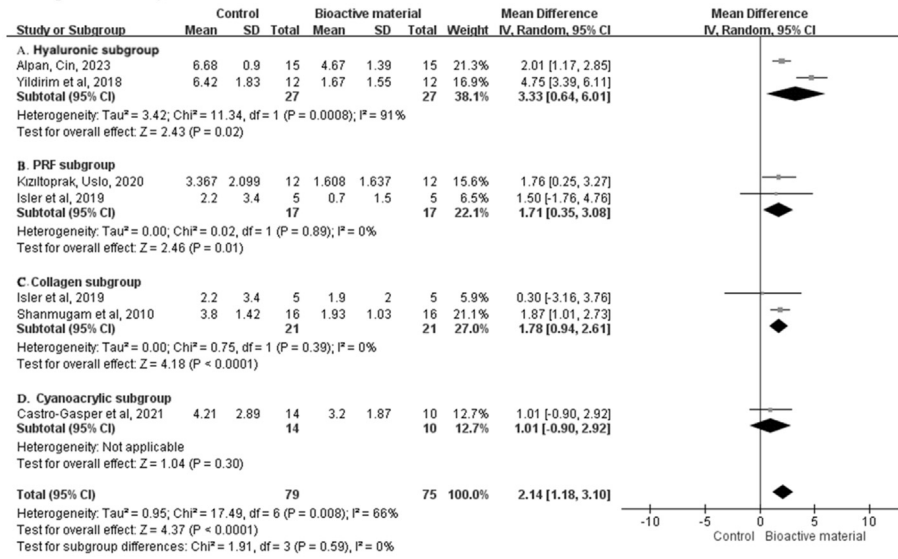
dedicated to the topic of wound healing.^{9,12,17,19,21,23} The four mentioned studies in the context of wound healing,^{9,12,17,23} along with three additional studies,^{16,22,31} were analyzed according to the VAS pain scale, resulting in a total of seven studies in this category (Fig. 3).

Effect of bioactive materials on wound healing

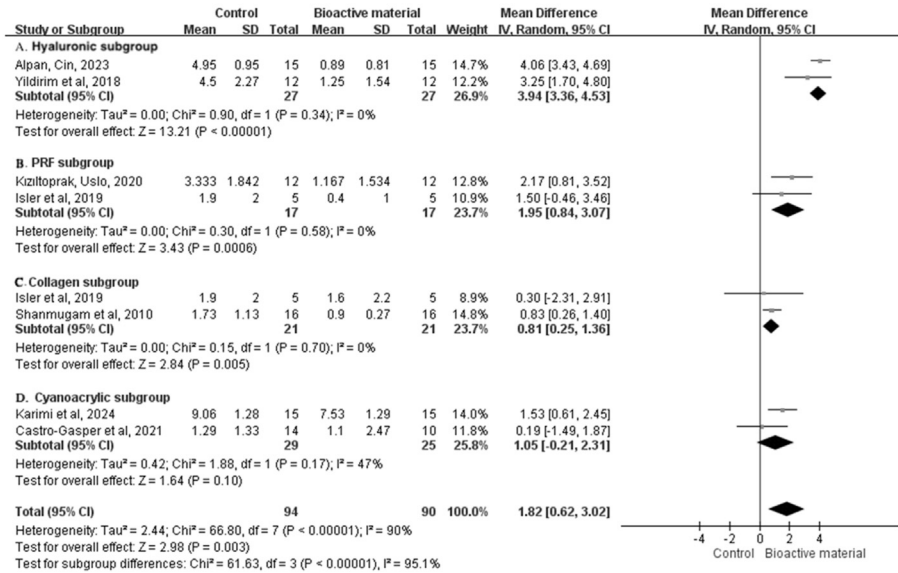
In the six incorporated studies, the assessment compared the number of patients who achieved complete epithelialization on post-operative day 14. Overall, among 107

(I). Forest plots

Post-operative day 1-3



Post-operative day 7



(II) Funnel plots

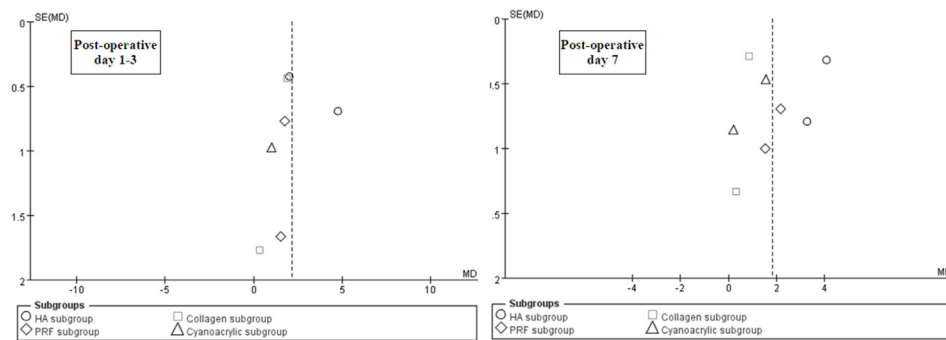


Figure 3 Efficacy of bioactive materials on post-operative pain of day 1–3 and day 7 (I. Forest plots, and II. Funnel plots).

patients with bioactive materials and 112 patients without, exposure to bioactive materials significantly favored healing (OR = 4.28, 95 % CI = 2.22–8.28, $P < 0.0001$, fixed-effects model), with no heterogeneity ($I^2 = 0\%$) (Fig. 2). In addition, the funnel plot did not show obvious sign of dissymmetry, suggesting no significant publication bias. For individual materials, two studies were analyzed for each material of HA, PRF, and cyanoacrylate adhesive subgroups. In the two studies focusing on HA,^{9,12} exposure significantly favored healing, with an increased number of patients achieving complete epithelialization among the 54 patients (27 patients with and 27 without HA) (OR = 4.80, 95 % CI = 1.38–16.69, $P = 0.01$). A similar positive response was also noted with PRF (OR = 12.81, 95 % CI = 3.04–53.93, $P = 0.0005$),^{17,21} but not with cyanoacrylate adhesive (OR = 2.24, 95 % CI = 0.84–5.96, $P = 0.11$).^{19,23} Moreover, all of these subgroups presented no statistical heterogeneity.

Effect of bioactive materials on post-operative pain

In the meta-analysis of pain, two time-point periods for measuring VAS scales were selected: within 3 days (day 1–3) and on day 7 post-operatively (Fig. 3).^{9,12,16,17,22,23,31} Besides, the bioactive material of collagen was further included in the analysis for pain.^{16,22} The results showed that exposure to bioactive materials significantly improved VAS scores within day 1–3 (MD = 2.14; 95 % CI = 1.18–3.10; $P < 0.0001$; Fig. 3-I) and also on day 7 (MD = 1.82; 95 % CI = 0.62–3.02; $P = 0.003$). However, the heterogeneity at both observation time points was high ($I^2 = 66\%$ and 90% , respectively), and the asymmetrical funnel plots suggest a potential publication bias across the studies. By subgrouping, significantly favorable results were observed for HA, PRF, and collagen, but not for cyanoacrylate adhesive, on post-operative day 1–3 and day 7 (Fig. 3-I). No heterogeneity was found in the collagen or PRF subgroups at either time point, and low heterogeneity was noted for cyanoacrylate group on day 7 ($I^2 = 47\%$). Nevertheless, high heterogeneity still persisted in the HA subgroup ($I^2 = 91\%$) on day 1–3.

Discussion

The present meta-analysis aimed to assess the effectiveness of bioactive materials, such as HA, PRF, collagen, and cyanoacrylate adhesive, in promoting healing and managing pain after epithelialized gingival graft harvesting. Overall, significant improvements in healing and pain management were observed (Figs. 2–3). However, in studies examining post-operative pain on days 1–3 and day 7, high heterogeneities were observed ($I^2 = 66\%$ and 90% , respectively; Fig. 3-I), and the asymmetrical funnel plots might express the potential publication bias (Fig. 3-II). Although the exact reasons for this high heterogeneities and the potential publication bias are not known, they may be attributed to variations in material characteristics and tissue engineering mechanisms, such as collagen's role in scaffolding,³³ PRF's provision for growth factors,^{34,35} and cyanoacrylate's function in tissue fixation.^{36,37} Therefore, the subgrouping analyses base on individual material were performed,

revealing the benefits with reduced heterogeneity. However, high heterogeneity persisted for HA on days 1–3 ($I^2 = 91\%$, Fig. 3-I). This could be due to data collection being limited to a single day within the first three post-operative days, leading to varied observation points. Other contributing factors may include differences in pain perception, population backgrounds, and the limited number of studies included. In addition, the current meta-analysis is limited by the narrow selection of bioactive materials and the small number of clinical trials included. Although the alternatives such as Alvogyl,²⁷ enamel matrix derivative,²⁸ erythropoietin,³⁸ honey,³⁹ medicinal plant extracts,⁴⁰ and flurbiprofen oral spray⁴¹ have been used for the treatment of palatal wounds after graft harvesting, these were not included in the analysis due to the limited number of available trials.

In the current subgroup analysis, our results have shown that the advantageous effects of utilizing HA and PRF as a bioactive materials demonstrated favorable outcomes in terms of complete epithelialization and post-operative pain at the palatal donor site following gingival graft harvesting. The wound-healing promoting effects of HA have been acknowledged in both medical and dental fields.⁴² HA, categorized as a natural polymer under glycosaminoglycans, is widely distributed throughout the human body, including in the skin, joints, and connective tissues.⁴³ A recent clinical trial has indicated that the application of HA with a collagen sponge on the palatal donor site during gingival graft harvesting resulted in reduced post-operative pain compared to using a collagen sponge alone.¹¹ However, this study was excluded from the present meta-analysis due to its comparison between the HA with collagen sponge and collagen sponge (control) groups. Additionally, the study by Hassan et al.¹⁰ was excluded because of the absence of provided mean and standard deviation data.

This analysis found that PRF enhances palatal wound healing and mitigates postoperative pain, likely attributable to its release of growth factor.³⁴ However, variability in PRF preparation methods may contribute to inconsistent research outcomes.^{16,17,21} Consistent with our findings, two recent reviews have endorsed PRF for palatal wound healing.^{44,45} However, Meza-Mauricio et al. provided a descriptive review without quantitative analysis due to limited trials and high heterogeneity.⁴⁵ The meta-analysis conducted by Gusman et al.⁴⁴ was based on two clinical trials; however, these trials lacked either a standardized control group or an appropriate test group.^{15,19} Nevertheless, neither of these studies was included in the present meta-analysis.

Collagen, or collagen sponge, often used as a dressing material for its hemostatic and pain-reducing properties,^{15,22,26} is commonly chosen as the carrier^{14,26,29} or the control group^{11,15,20,29,30} in studies on palatal wound healing after gingival graft harvesting. However, only a few studies have compared postoperative outcomes between the exclusive use of collagen and its absence.^{16,22} This meta-analysis included two studies, showing a significant reduction in post-operative pain on days 1–3 and day 7 (Fig. 3-I). However, the analysis on collagen's effectiveness in promoting complete epithelialization was not performed due to differing wound healing criteria in these studies, the remaining area in one study¹⁶ and histological evaluation in another.²²

Cyanoacrylate tissue adhesive have been suggested to reduce post-operative pain and improve healing based on qualitative analyses in two systematic reviews by Verissimo et al. and Escobar et al.^{24,46} However, the present meta-analysis found no significant advantage of cyanoacrylate in promoting healing at week 2 or in providing pain relief on days 1–3 and day 7 (Figs. 2 and 3). Discrepancies in these findings may arise from differences in interval selection, study recruitment, and qualitative versus quantitative synthesis methods. For instance, a study by Ozcan et al.¹⁹ included in both this meta-analysis and Verissimo's review, reported better healing at week 3 with cyanoacrylate but not at week 2, the time point considered in this meta-analysis. The two studies included in Verissimo's review, conducted by Tavelli et al.²⁶ and by Gumus and Buduneli,³⁶ were not included in the present analysis due to differing outcome parameters. Similarly, the systematic review by Escobar et al. suggested the potential efficacy of cyanoacrylate in alleviating post-operative pain based on qualitative synthesis.²⁴ Of the four studies analyzed for pain in Escobar's review, none were included in the current study due to various reasons: two were excluded because of incomplete data,^{19,26} another involved subepithelial connective tissue graft harvesting instead of epithelialized gingival graft harvesting,²⁵ and the fourth lacked a standard control group.²⁹

In conclusion, this meta-analysis aimed to assess evidence on the efficacy of bioactive materials of HA, PRF, collagen, and cyanoacrylate adhesive in promoting healing and pain management at the palatal donor site following epithelialized gingival graft harvesting. HA and PRF showed significant improvements in wound healing at week 2 and pain relief on days 1–3 and 7. Collagen also positively impacted VAS pain scores. However, cyanoacrylate did not offer any advantage in healing or pain relief. Further clinical trials are recommended.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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