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REVIEW

Is the use of platelet-rich fibrin effective in the healing, control of pain, and postoperative bleeding in the palatal area after free gingival graft harvesting? A systematic review of randomized clinical studies

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Abstract

Objective A systematic review (SR) was conducted to answer the following focused question based on PICO strategy: In patients who were submitted to harvesting palatal free gingival graft, could platelet-rich fibrin (PRF) application in comparison with another method improve the healing, pain, and control of postoperative bleeding in the palatal area in randomized clinical trials?

Methods A SR was conducted according to the PRISMA guidelines. The MEDLINE (PubMed), Scopus, Embase, and Web of Science databases were searched, and hand searches were made, covering the period up to August 2020, for randomized clinical trials (RCTs) reporting the effect of PRF membrane in postoperative palatal healing management compared with any other methods. The risk of bias (RoB) of the studies included was assessed by using the RoB 2 tool.

Results The electronic search strategy identified 150 articles. After title screening and abstract reading, 141 studies were excluded, and 9 full-text publications were comprehensively evaluated. Finally, 8 articles were included in the systematic review. Six studies showed that the PRF membrane was effective in improving wound healing during the first 2 weeks. As regards patient-centered outcomes, five studies showed that PRF promoted less postoperative pain. Finally, five studies that evaluated bleeding showed that the PRF membrane improved control of postoperative bleeding. RoB was classified as low in 4 studies, 3 with some concerns, and only one study did not describe the outcome data, and as this was missing, it was not possible to verify the protocol of data analysis for this study; therefore, it was classified as having high RoB.

Conclusion Within the limitations of this study, the collective evidence emerging from this SR may support the use of PRF membrane in the palatal area after free gingival graft harvesting. The results of this review must be interpreted with caution, due to the low number of RCTs included and high degree of heterogeneity among the PRF protocols. Further well-designed RCTs with accurate protocol and standard PRF parameters are required in order to gain clear understanding of the influence of PRF on wound healing and patient-centered outcomes.

Clinical relevance The use of PRF membrane for the protection of the palatal donor site following free gingival graft harvesting procedures improves wound healing and patients' quality of life.

Keywords Systematic review · Platelet-rich fibrin, Free gingival graft · Pain · Wound healing

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Introduction

The de-epithelialized gingival graft is widely used in the treatment of gingival recessions (GR) [1, 2]. In this technique, the graft is harvested as a free gingival graft (FGG), and it is then extra-orally de-epithelialized [1]. The FGG is also the most effective technique for augmentation of the peri-implant keratinized mucosa width [3]. The main drawback of using FGG is the need for two surgical sites (e.g., donor and receptor

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sites). especially in the palatal area, which increase the discomfort and morbidity experienced by the patient [4, 5]. In this technique, the healing process occurs in 2–4 weeks by secondary intention [6, 7]. The highest pain level perceived at the FGG donor sites is experienced on the first day after FGG surgery and diminishes to presurgical levels in about 2 weeks post-surgically [8].

Palatal donor site healing occurs through fibroblast proliferation, collagen synthesis, angiogenesis, and contraction of the wound. In addition, revascularization, immunity, and epithelial cell proliferation are crucial factors for optimal wound healing [9]. In an endeavor to accelerate the healing process and to reduce prolonged bleeding and pain caused by the palatal wound, materials such as hemostatic agents (e.g., absorbable synthetic collagen, absorbable gelatin sponge, cyanoacrylate, oxidized regenerated cellulose, ferric sub sulfate) and more recently platelet concentrate have been used [10–13].

PRF, the second-generation platelet concentrate, was introduced to the field of dentistry, particularly in oral and maxillofacial surgery, by Choukroun and colleagues in 2000 [14]. The blood is collected without any anticoagulant and immediately centrifuged. The natural coagulation process allows for easy collection of the PRF clot [15]. In addition, this fibrin matrix contains platelets and leucocytes, in which white blood cells (WBC) and a number of growth factors and cytokines are trapped [16]. The WBC are necessary and important components during the wound-healing process [17]. Recent studies have suggested that there are promising and beneficial wound-healing effects of PRF in various types of periodontal surgery; however, there is a lack of reports about their results in the literature [18, 19].

Platelet concentrates used in palatal wound healing have growth factors, such as fibroblast growth factor-basic (FGFb), vascular endothelial growth factor (VEGF), and angiopoietin and platelet-derived growth factor (PDGF) which are the main angiogenesis soluble factors [20, 21]. This could facilitate faster healing by exerting a positive influence on the mitogenesis of wound healing cells, angiogenesis, and promotion of cellular differentiation at the wound site [12].

Some clinical studies have shown that the PRF could improve the healing after gingival graft harvesting. [18, 19]. However, at present, it is unknown which are the main clinical benefits of the different protocols of PRF. This is mainly due to differences in methodology among the studies, which make comparisons extremely difficult. Therefore, a systematic review was thus conducted to answer the following focused question based on PICO strategy: In patients who were submitted to harvesting palatal free gingival graft, could PRF application in comparison with another method improve the healing, pain, and control of postoperative bleeding in the palatal area in randomized clinical trials?

Methods

Protocol and registration

This SR was conducted in accordance with the Transparent Reporting of Systematic Reviews and Meta-Analysis – PRISMA Statement [22]. The protocol for this systematic review was registered on INPLASY (registration number 202110113) and is available in full on the inplasy.com (https://inplasy.com/inplasy-2021-1-0113/) platform.

Focused question

In patients who were submitted to harvesting palatal free gingival graft, could PRF application in comparison with another method improve the healing, pain, and control of postoperative bleeding in the palatal area in randomized clinical trials?

Eligibility criteria

The inclusion criteria were based on the PICOS strategy [23]. Only studies meeting the following criteria were included:

Inclusion criteria (PICOS)

(P)opulation: Patients who were submitted to harvesting palatal free gingival graft with 18 years of age or older and no restriction on ethnicity or gender

(I)ntervention: Surgical treatment using PRF on palatal wound

(C)omparison: Surgical treatment using another healing method

(O)utcome: Wound healing (primary outcome variable), pain, and control of postoperative bleeding (secondary variables)

(S)tudy design: RCTs

Exclusion criteria

i. Studies with insufficient information relative to the study design
ii. Duplicated studies
iii. Studies that included individuals with systemic diseases or conditions that might compromise wound healing (e.g., diabetes or smoking)

Search strategy

The MEDLINE (PubMed), Embase, Scopus, and Web of Science databases were searched up to August 2020 by two independent reviewers (J.M.M. and C.P.F.). The search was

without restrictions on dates or language and those conducted with human subjects. The search terms included "platelet rich fibrin," "leucocyte platelet rich fibrin," "advanced platelet rich fibrin," "injectable platelet rich fibrin," "free gingival graft," "palatal graft," "connective tissue graft," "palatal wound," "palatal healing," "palatal pain," "wound heal," "wound healing," "pain," "visual analogic scale," and "patient reported outcome." The search strategy was applied as follows: PubMed: (("platelet rich fibrin"[All Fields] OR "leucocyte platelet rich fibrin"[All Fields] OR "advanced platelet rich fibrin"[All Fields] OR "injectable platelet rich fibrin"[All Fields]) AND ("free gingival graft"[All Fields] OR "palatal graft"[All Fields] OR "connective tissue graft"[All Fields] OR "palatal wound"[All Fields] OR "palatal healing"[All Fields] OR "palatal pain"[All Fields] OR "wound heal"[All Fields] OR "wound healing"[All Fields] OR "pain"[All Fields] OR "visual analogic scale"[All Fields] OR "patient reported outcome"[All Fields])) AND (clinicaltrial[Filter]). In addition, the grey literature in the System for Information on Grey Literature in Europe (http://www.opengrey.eu) and The New York Academy of Medicine Grey Literature Report (http://www.greylit.org) were screened electronically, as recommended by the high standards for systematic reviews (AMSTAR guideline) [24]. Furthermore, a manual search of relevant primary sources related to the topic was made in *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, and *Clinical Oral Investigations.* Finally, the references of studies included were explored to capture any potential additional records, as suggested by Greenhalgh and Peacock [25].

Data collection, extraction, and management

Screening and selection of papers

Eligible titles and abstracts were screened by two reviewers independently (J.M.M and G.M.), and any disagreement was solved through discussion. If disagreement persisted, another researcher was consulted to achieve consensus (M.F). Duplicates were removed and full-text articles were obtained.

Search outcomes and evaluation

The studies that fulfilled the eligibility criteria were processed for data extraction conducted by 2 independent researchers (J.M.M. and A.G), using predefined spreadsheets. Disagreements were resolved by discussion with a third reviewer (M.F). In the event of missing data, a request was sent to the authors. The inter-reviewer consistency of the full-text analysis was calculated by means of the kappa correlation coefficient.

Risk of bias in individual studies

Two reviewers (J.M.M and B.R.V) assessed the risk of bias in the studies selected, using the Cochrane risk-of-bias tool, RoB 2 (version 2, available at: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2).

The authors of this SR decided to assess the result related to "assignment to intervention (the intention to treat effect)," and five domains were examined: (i) bias arising from the process of randomization and allocation concealment, (ii) bias due to deviations from intended interventions that involved masking of participants and our team of researchers, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcome, and (v) bias in selection of the result reported [26]. Based on the responses to signaling questions and algorithms of this tool, we judged each domain to be "low risk of bias," "some concerns relating to the risk of bias," or "high risk of bias." Studies were categorized as being at low risk of bias (all domains were at low risk of bias), high risk of bias (one or more domains were at high risk of bias), and some concerns (if one or more domains had some concerns) [26]. Disagreements were resolved by discussion, consulting a third advisor (V.M).

Summary and measures

The following information was collected from each study and registered in predefined forms:

> Wound healing score: measurements for each group could be performed by visual evaluation by comparing the wound with the contralateral counterpart using a visual analog scale (VAS), clinical color photographs, epithelium chemical reaction with hydrogen peroxide bubbling, and the presence of fibrin or necrosis in the palatal wound, expressed in numbers and/or percentages.
> Postoperative pain: measurements of VAS for each group could be organized by mean (or median) and standard deviations expressed in numbers and/or percentages.
> Control of postoperative bleeding: the patients reported as prolonged hemorrhaging from the palate during the postsurgical period.

Synthesis of results

The synthesis of the results was described as narrative analysis. First, a description per study was made and also a summary of the outcome assessed. Meta-analysis was not justified due to clinical, methodological, and statistical heterogeneity.

Results

Study selection

The electronic search strategy identified 150 articles. After screening titles and reading abstracts, 141 studies were excluded, and 9 full-text publications were comprehensively evaluated. One of the studies was excluded because used platelet-rich plasma [12]. Therefore, 8 articles were included in the systematic review (Fig. 1). Inter-reviewer agreement of the full-text analysis was >90.0% (kappa =0.85).

General description of the studies included

The reports included were eight RCTs (seven [9, 18, 19, 27–30] with a parallel design and one [16] with a split-mouth design) conducted between 2016 and 2020; the main methodological characteristics of studies included are presented in Table 1. Three clinical studies were conducted in Turkey [9, 19, 29] and the others in different countries, such as Italy [18], Saudi Arabia [27], India [30], Thailand [16], and Portugal [28]. All clinical studies evaluated the use of PRF with different control groups: wet gauze compression [19, 29], gelatin sponge [18, 28], collagen dressing [30], sterile tamponade [9], oxidized regenerated cellulose [16], and untreated [27]. A total of 292 (148 test and 144 control) individuals within the age range of 18–78 were included in this systematic review. The participants of three studies had either class I or class II Miller GR defects [18, 19, 30], and in the other three studies, the participants had lack of keratinized tissue [16, 27, 28]. Finally, two studies did not mention the mucogingival defects [9, 29]. All studies placed PRF membrane on the palatal mucosa after harvesting FGG from the palatal donor site. The follow-up period started on the first day after surgery and continued until 12 weeks after the operation (Table 1).

Platelet-rich fibrin characteristics of the studies included

This SR included studies using different protocols of PRF. Almost all studies used the following protocol 3000 rpm for 10 min [16, 18, 27, 30]. Further details about protocols used to prepare PRF are shown in the Table 2.

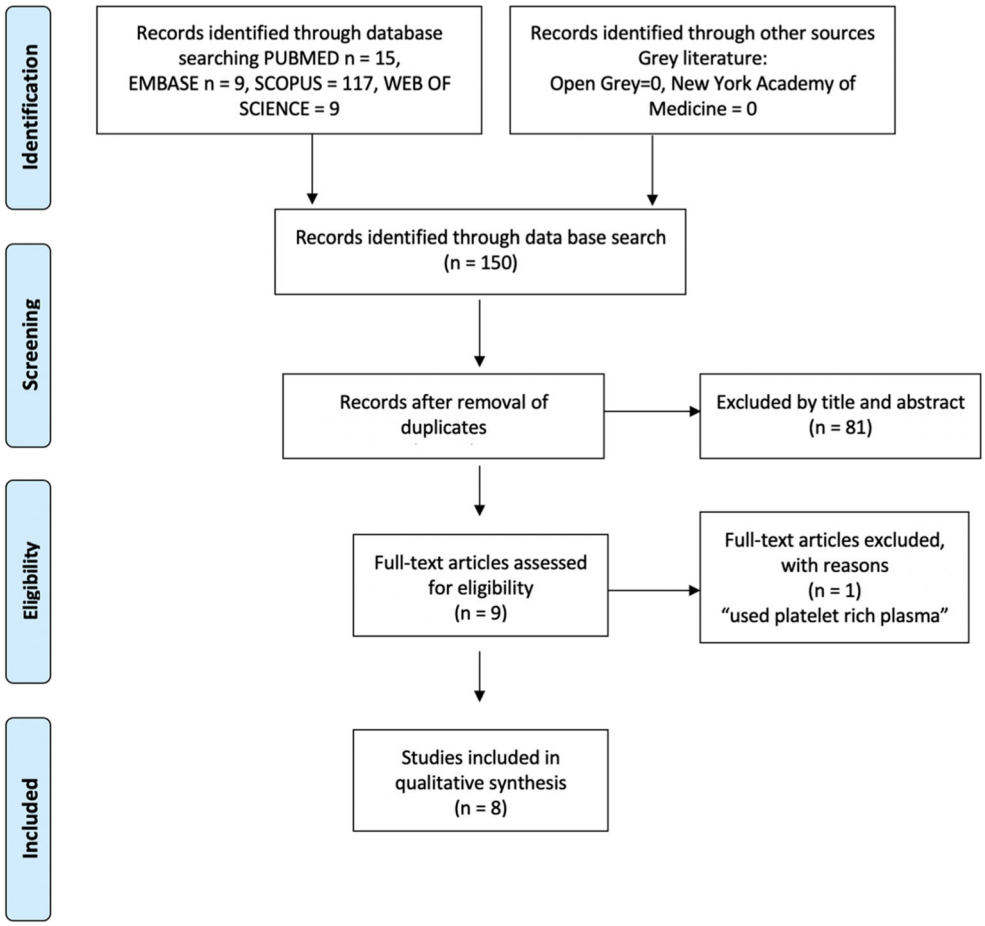

Fig. 1 PRISMA flow chart of manuscripts screened through the review process

Table 1 Main methodological characteristic of the studies included

Author/year	N	M/F age	Test group	Control group	Parameters recorded	Follow-up (weeks)	Evaluated outcome	Results	Summary of findings
Femminella et al. 2016 [18]	40	15/25 18–47	PRF (*n*=20)	Gelatin sponge (*n*=20)	CWE, BPW and post-surgical Pain	Up to 4	CWE: using peroxide test H2O2 Pain: (VAS) BPW: reported by patient	Week 2: 35% CWE for PRF and 10% for control group ($p = 0.003$) Week 3: 65% CWE for PRF and 15% for control group ($p = 0.001$) Pain: day 1–21 better results for PRF compared with control group ($p = 0.001$) BPW: no episodes of delayed bleeding were reported by any test or control patient during week 1	PRF produced significant clinical advantages in accelerating palatal wound healing and reducing the patient's morbidity.
Ustaoglu et al. 2016 [29]	40	/ -	PRF (*n*=20)	Wet gauze compression (*n*=20)	CWE, BPW and post-surgical Pain	Up to 3	CWE: using peroxide test H2O2 Pain: (VAS) BPW: reported by patient	Week 2: 68.7% CWE for PRF and 16.7% for control group ($p = 0.001$) Week 3: CWE was observed in all patients in both groups Pain: did not differ between the two groups during the first week ($p>0.05$) Day 1: 87.5% BPW for PRF group and 100% in the control group ($p <0.001$) Day 2: 12.5% BPW for PRF group and 66.7% in the control group ($p <0.001$)	PRF bandages accelerated wound healing at FGG donor sites, in addition, provided greater comfort by reducing postoperative bleeding
Ozcan et al. 2017 [19]	83	/ 21–48	PRF (*n*=42)	Wet gauze compression (*n*=41)	CWE, BPW and post-surgical Pain	Up to 4	CWE: using peroxide test H2O2 Pain: (VAS) BPW: reported by patient	Week 1: no CWE in any group Week 2: 85.7% CWE for PRF and 12.2% for control group ($p = .001$) Week 3: 100% CWE for PRF and 45.2% for control group ($p = .001$) Pain: day 1–14 better results for PRF compared with WG ($p = 0.0001$) Day 1: 0 % BPW for PRF group and 90.2 % in the control group ($p =.0001$) Day 5: 0% BPW for PRF group and 22 % in the control group ($p =.001$)	The use of PRF at the palatal donor site after FGG harvesting may provide significant benefits in terms of wound healing parameters and course of patients' postoperative recovery
Bahammam et al. 2018 [27]	24	14/10 21-48	PRF (*n*=12)	Untreated (*n*=12)	CWE and post-surgical Pain	Up to 8	CWE: using color photographs Pain: (VAS)	Week 3: the clinical photographs showed better tissue healing in terms of color match, contour, and texture in the PRF group Pain: day 3–7 better results for PRF compared with control group ($p <0.05$)	PRF palatal bandages significantly reduced postoperative pain and discomfort and facilitated wound healing after harvesting FGG

Table 1 (continued)

Author/year	N	M/F age	Test group	Control group	Parameters recorded	Follow-up (weeks)	Evaluated outcome	Results	Summary of findings
Sharma et al. 2019 [30]	20	5/15 -	PRF (*n*=10)	Collagen dressing (*n*=10)	CWE, BPW, and post-surgical Pain	Up to 4	CWE: using peroxide test H2O2 Pain: (VAS) BPW: reported by patient	18th day: 81% of wound area was reduced in the PRF group and 73% in the control group. 24th day: 92.4% of wound area was reduced in the PRF group and 92% in the control group (p >0.05) 30th day: CWE was observed in 100% of patients in both groups. Pain: day 1–30 no difference was observed between the groups (p > 0.05) BPW: no case of immediate bleeding in any of the groups was observed	PRF palatal bandages significantly accelerated palatal wound healing and reduced the patient's pain and discomfort
Patarapongsanti et al. 2019 [16]	18	7/11 45–78	PRF (*n*=18)	Oxidized regenerated cellulose (*n*=18)	CWE and post-surgical Pain	Up to 4	CWE: using peroxide test H2O2 Pain: (VAS)	Week 2: 89.89% CWE for PRF and 66.67% for control group (p = .228) Week 3: 100% CWE for PRF and 94.44% for control group (p = 1.00) Pain: day 1–7 better results for PRF compared with control group (p<0.05)	Both approaches showed comparable clinical outcomes in terms of CWE. Despite this, PRF was able to provide greater benefits, as it reduces patient morbidity and discomfort at the FGG donor sites
Sousa et al. 2020 [28]	25	9/16 19–65	PRF (*n*=14)	Gelatin sponge (*n*=11)	CWE and post-surgical Pain	Up to 12	CWE: using color photographs Pain: (VAS)	Week 2: 64.3% CWE for PRF and 9.1% for control group (p = 0.012) Week 4: 92.9% CWE for PRF and 90.9% for control group (p = 1.000) Week 12: CWE was observed in all patients in both groups Pain: day 1–7 better results for PRF compared with control group being significantly higher at the second day (p = 0.013)	Both approaches significantly accelerate palatal wound healing and reduce the patient's pain and discomfort
Kiziltoprak et al. 2020 [9]	24	/ 18–53	PRF (*n*=12)	Sterile tamponade (*n*=12)	CWE, BPW and post-surgical Pain	Up to 12	CWE: using peroxide test H2O2 Pain: (VAS) BPW: bleeding status was assessed as presence/absence of wet sterile gauze on the wound surface	Week 2: 41.7% CWE for PRF and 0 % for control group (p <0.05) Week 4: CWE was observed in all patients in both groups Pain: did not differ between the two groups during the first week (p>0.05) Day 3: 16.7% BPW for PRF group and 75% in the control group (p <0.05) Day 7: 0% BPW for PRF group and 8.3% in the control group (p >0.05)	PRF have positive effects on the healing process by accelerating wound healing and reducing postoperative morbidity

N population, *M/F* male female, *PRF* platelet-rich fibrin, *CWE* complete wound epithelization, *BPW* bleeding from the palatal wound, *FFG* free gingival graft, *VAS* visual scale analog

Free gingival graft harvesting

In 4 studies [16, 19, 27, 29], the grafts were harvested according to the surgical technique described by Sullivan and Atkin [31]. The other studies did not mention the technique that was used. The graft sizes and thicknesses were evaluated in seven studies [9, 16, 18, 19, 27–29], and all reported sizes that were comparable between the study groups. The thickness of the free gingival graft ranged from 1.5 to 2 mm [9, 16, 18, 19, 27–29].

Clinical outcome

Wound healing

All the studies included in this systematic review evaluated wound healing at the palatal donor site. Six studies [9, 16, 18, 19, 29, 30] evaluated the clinical aspects of healing by using the peroxide test [32]. One clinical study used the visual criteria (percentage) of wound closure [28]. Another study evaluated healing based on the degree of color match, tissue texture, and contour of the surgical area compared with the adjacent tissue [27]. The time interval in which healing was assessed varied between studies from the third day to twelfth week.

Six studies using PRF [9, 18, 19, 27–29] showed faster wound healing during the first 2 weeks than their different control groups sterile tamponade [9], gelatin sponge [18, 28], wet gauze compression [19, 29], and untreated [27] ($p<0.005$). Kiziltoprak et al. [9] treated 24 patients (12 test and 12 control groups). Five patients in the PRF group and none patient in the control group demonstrated complete healing at 2 weeks. In the same follow-up time, Ozcan et al. [19] treated 83 patients (42 test and 41 control groups). The authors demonstrated that the PRF group had complete healing in 36 patients in comparison with 5 patients in the control group. Ustaoglu et al. [29] treated 20 patients in the test group and 20 in the control group. They showed that 14 patients in PRF group and 5 in the control group had complete healing at 2 weeks. Souza et al. [28] treated 25 patients (14 test and 11 control groups). The authors demonstrated that the PRF group had complete healing in 64.3% patients in comparison with 9.1% patients in the control group. Femminella et al. [18] treated 20 patients in each group. The authors demonstrated that the PRF group had complete healing in 35% patients in comparison with 10% patients in the control group at 2 weeks.

Two studies that compared PRF vs control (collagen dressing (CollaCote®) [30] PRF vs oxidized regenerated cellulose [16] did not show statistical difference in the third week after surgery. Patarapongsanti et al [16] treated 18 patients in each group. All patients in the PRF group and 17 patients in the control group demonstrated complete healing at 3 weeks. In the same follow-up time, Sharma et al. [19] treated 20 patients (10 test and 10 control groups). The authors demonstrated that all patients in both groups had complete healing. On the other hand, in the same time interval of follow-up, four studies showed that group PRF had completed wound healing after harvesting FGG [9, 16, 19, 29] and 4 weeks post-surgery; all studies showed completed healing, and no differences were observed between PRF and their different control groups.

Patient reported outcome (pain)

The VAS was used to assess post-surgical pain among patients in all studies. The time interval in which pain was assessed varied between studies and was from 3 h to the fourth week after surgery. Five studies using PRF [16, 18, 19, 27, 28] showed lower pain levels than their different control groups (oxidized regenerated cellulose [16], gelatin sponge [18, 28], wet gauze compression [19], and untreated [27]) 7 days after the surgery ($p<0.05$). The mean pain scores in the PRF groups were 2.4 ± 0.2 [18] and 0 [19, 27, 28] respectively, and in the control groups, the scores were 4.6 ± 0.2 [18], 1 [19], 0.34 [27], and 1 [28], respectively. However, at the same time of follow-up, three studies showed comparable VAS scores without statistical difference [9, 29, 30]. Three studies showed that individuals in the PRF group showed no pain 5 days after harvesting FGG in comparison with control group [19, 27, 28].

Control of postoperative bleeding

The control of postoperative bleeding from the palate after FGG harvesting was reported in five clinical studies [9, 18, 19, 29, 30]. Three studies using PRF [9, 19, 29] showed lower prevalence of bleeding than the control groups (sterile tamponade [9] and wet gauze compression [19, 29]) on days 1 and 2 ($p \leq 0.001$). Two studies that compared PRF vs controls (collagen dressing [30] gelatin sponge [18]) did not report any case of immediate bleeding observed during the first week in any of the groups.

Risk of bias in individual studies

In general, 4 studies were classified as "low risk," 3 were classified with "some concerns," and only one study exhibited "high risk" of bias according to the authors' analysis. Adequate methods of sequence generation and allocation of participants were reported in 7 studies. All the studies described blinding of the patients and examiners, and all of them described how assignment to the intervention was measured. Only one study showed differences from baseline values between groups [9]. As regards deviations from intended interventions, 100% of the studies were classified with "low" risk of bias. Finally, 40% of studies reported the results in

Table 2 PRF protocols of included studies

Author, year	Brand of centrifuge	Protocol of PRF	Relative centrifugal force
Feminella et al. 2016	Intra-Spin, Intra-Lock	3000 rpm for 10 min	400 g
Ustaoglu et al. 2016	Unrelated	2800 rpm for 12 min	Unrelated
Ozcan et al. 2017	Hettich	2700 rpm for 12 min	Unrelated
Bahammam et al. 2018	Unrelated	3000 rpm for 10 min	400 g
Sharma et al. 2019	Unrelated	3000 rpm for 10 min	Unrelated
Patarapongsanti et al. 2019	Intra-Spin, Intra-Lock	3000 rpm for 10 min	400 g
Sousa et al. 2020	DUO Quattro; PRF Process, Nice, France	1500 rpm for 8 min	Unrelated
Kiziltoprak et al. 2020	PC-O2 Process for PRF, Nice, France	2300 rpm for 3 min	509.53 G

RPM revolutions per minute

accordance with the pre-specified plan. A summary, according to a specific graphic tool, is presented in Fig. 2.

Discussion

To the best of our knowledge, this is the first SR to report clinical and patient-centered outcomes after application of PRF at the palatal donor site for harvesting FGG. According to this systematic review, six studies showed that the PRF membrane was effective in improving wound healing during the first 2 weeks. Relative to patient-centered outcomes, five studies showed that PRF promoted less postoperative pain. Finally, five studies that evaluated bleeding showed that the PRF membrane improved control of the postoperative bleeding.

The FGG is widely used in periodontal and peri-implant plastic surgeries, with the epithelium tissue being removed from the palatal area [1, 33]. Despite the promising results of these plastic surgeries, most patients reported discomfort in the wounded palatal area [2, 34, 35]. Therefore, to minimize this discomfort, accelerate the healing process, and reduce delayed bleeding caused by the palatal wound during FGG harvesting, various methods, including use of the PRF membrane, have been proposed.

Soileau and Brannon (2006) reported that at least 9 weeks are necessary for palatal wound remodeling to have the appearance of being histologically complete, after FGG harvesting [36]. Six studies included in this systematic review evaluated palatal wound healing by the peroxide test [9, 16, 18, 19, 29, 30]. This test is based on the principle that if the epithelium is discontinuous, then H_2O_2 diffuses into the connective tissue; the enzyme catalase acts on H_2O_2 to release water and oxygen. This is shown clinically by the production of bubbles on the wound. If bubbles appeared, it meant that the surgical site was not completely epithelialized [32]. Our SR showed that use of PRF is a treatment strategy that can accelerate wound healing of the palatal mucosa after FGG harvesting and can reduce patient morbidity, such as pain. This result is in concordance with a recent SR where the use of PRF placed within the donor site of connective tissue graft leads to a statistically significant reduction in postoperative pain [37]. This faster epithelialization could possibly be related to PC-induced upregulation of cell growth, proliferation of fibroblasts and myofibroblasts, and type-I collagen synthesis leading to accelerated cascades in the early phase of healing [7, 38]. One clinical study showed results that were comparable between PRF and collagen dressing (control group) [30]. This could be explained because the collagen dressings were able to control bleeding and stabilize blood clots as well as protect the wound bed while accelerating the healing process [39].

In FGG, the donor site is an open wound that makes postoperative healing more painful and discomforting for the patients. In our study, the PRF group showed lower pain levels than control groups [16, 18, 19, 27, 28]. Although many studies indicated significant effects of reduction in pain attributable to PRF, it is still not known whether this was a result of accelerated wound healing or related to specific contents of the platelet concentrate [12]. The pain perceived after FGG harvesting has been shown to be positively correlated with the palatal wound depth, rather than the wound surface area [8, 35]. In seven studies included in our SR, the graft sizes and thicknesses were evaluated, and all of them reported comparable size between the study groups [9, 16, 18, 19, 27–29]. Only one study did not report the thickness of the grafts [30]. However, all surgeries were performed by a single operator, and this could have

Fig. 2 Summary of the risk of bias of the clinical trials included in the systematic review, according to the Cochrane risk-of-bias tool, RoB 2. Plus sign indicates yes; minus sign indicates no; question mark indicates not specified/unclear (some concerns)

minimized both the differences in healing between the test and control sites, and the postoperative pain levels between participants.

Only one study showed a high risk of bias, and the power of analysis was above 80% in five studies indicating that no or minor methodological flaws occurred in the studies included. Therefore, there were no or small deviations from the true effect estimation, providing confidence in the interpretation of the findings [40]. With regard to the limitations of this SR, it is important to note that there was heterogeneity among the studies included (e.g., different PRF protocols, different relative centrifugal forces (RCFs) or missing data related to PRF preparation, and different control groups among studies).

Parameters, such as centrifuged time, revolutions per minute (RPM), and type of centrifuge varied considerably between the studies included in this SR. A recent study showed that the characteristics of the centrifuge and centrifugation protocols have a very significant impact on the cells, growth factors, and fibrin architecture of an L-PRF clot and membrane [41]. On the other hand, some studies have described the importance of relative centrifugal forces in the biological properties of PRF. The RCF values are subject to significant changes depending on the rotor radius (distance between the tube and the rotor axis) [42, 43]. The studies included in this SR used different centrifugation devices. Therefore, it is important to understand that an increase in radius simply caused by changes in rotor angulations and rotor diameter has a dramatic effect on RCF values [43]. Other factors such as the number of PRF membranes placed on the palatal wound could change the actual number of growth

factors and cytokines released during the process, potentially affecting the proliferation of cells, and thus the healing efficacy of the PRF [44, 45]. Only one study included in this SR mentioned the number of PRF membranes; in this study, the authors placed a quadruple layer of PRFs [18].

Therefore, further well-designed studies with accurate protocols and standard PRF parameters are required in order to clearly understand the influence of PRF on wound healing.

Despite limitations, some observations on the applicability of the results obtained could be formulated. The application of PRF seemed to develop additional benefits in the palatal area after free gingival graft harvesting.

Conclusion

Within the limitations of this study, the collective evidence emerging from this SR may support the use of PRF membrane in the palatal area after free gingival graft harvesting could improve wound healing, postoperative discomfort (pain), and postoperative bleeding. The results of this review must be interpreted with caution, due to the low number of RCTs included and high degree of heterogeneity among the PRF protocols. Further well-designed RCTs with accurate protocol and standard PRF parameters are required in order to gain clear understanding of the influence of PRF on wound healing and patient-centered outcomes

Declarations

Ethics approval This article does not contain any studies conducted with human participants or animals, by any of the authors.

Informed consent For this type of study, formal consent is not required

Conflict of interest The authors declare no competing interests.

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