Efficacy of Platelet-Rich Fibrin in Alveolar Ridge Preservation Following Minimally Traumatic Tooth Extraction

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Abstract

AIM: The application of platelet-rich fibrin (PRF) in alveolar ridge preservation (ARP) has been shown to enhance treatment outcomes. The aim of this study is to systematically review the efficacy of PRF in the preservation of alveolar ridge following minimally traumatic tooth extraction.

METHODS: A comprehensive literature search was conducted with the publication date set to the past 10 years. A total of 26 controlled clinical trials met the inclusion criteria and were included for review. The outcome parameters analysed included post-operational morbidity, soft tissue healing, changes of alveolar dimension, and bone formation in the socket.

RESULTS: All included studies treated the test sites with PRF, and the control sites were left for spontaneous healing. The tooth extraction procedures were kept minimally traumatic. A pronounced post-extraction pain reduction effect was reported in the test sites, with corresponding fewer analgesic consumptions. PRF-treated sites demonstrated accelerated soft tissue healing. The applied PRF reduced bone atrophy and led to an appreciable quantity of new bone formation in the socket, thereby sustaining the bone volume.

CONCLUSION: PRF ameliorates immediate post-operational discomfort, improves soft tissue healing, and enhances bone tissue preservation and regeneration. Clinical application of PRF is effective and should be considered as a biomaterial for ARP following dental extractions.

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1 Introduction

Dental implants have been widely used in the past decades as a treatment modality for edentulous sites. They are alloplastic structures inserted into the alveolar bone to support a fixed or removable dental prosthesis (Oshida et al., 2010). Adequate bone dimension and quality, as well as soft tissue status at the implant-receiving site, are crucial for a functional and aesthetic prosthetic outcome (Misch, 2015). However, the alveolar ridge and soft tissue undergo prominent morphological changes following tooth loss. Rapid hard tissue reduction was observed in the first three to six months post-extraction period with a weighted mean of 3.79 mm horizontal bone loss and 1.24 mm vertical bone loss at six months (Tan et al., 2012). The horizontal dimension has the most pronounced bone resorption, followed by mid-facial and mid-lingual bone height reductions (Couso-Queiruga et al., 2021). Larger amounts of bone resorption can be expected in all dimensions of a molar site, compared with a non-molar site, except for mid-facial bone height changes. These extensive alterations of the bone and soft tissues not only pose a major challenge for dental implant placement but may also entail the need for an additional ridge augmentation procedure (Goyal et al., 2015). Alveolar ridge preservation (ARP) or socket preservation technique has been proposed to overcome these biological challenges. It is a predictable way to minimize tissue loss after a tooth extraction (MacBeth et al., 2017). Various biomaterials have been proposed and/or utilized in ARP including bone grafts, growth factors (GFs), enamel matrix derivatives, and autologous platelet concentrates (APCs) (Jamjoon and Cohen, 2015; Lee and Jeong, 2020; Annunziata et al., 2018).

APCs are biomaterials derived from the patient's whole blood. They contain various GFs and molecules that have anti-inflammatory effects and promote soft tissue healing (O'Sullivan and Ní Ríordáin, 2021). The potential regenerative and enhanced healing effect of APC on biological tissues has led to its introduction to several clinical applications in dentistry such as ARP, sinus augmentation, periodontal surgery, endodontic surgery, etc. (Al-Hamed et al., 2019). Platelet-rich plasma (PRP) is a first-generation platelet concentrate introduced by Marx et al. in 1998 to serve as a delivery medium and an amplifier for GFs (Marx et al., 1998). PRP has been shown to successfully facilitate wound healing and bone formation (Albanese et al., 2013). However, several drawbacks were observed, for example, the need for an anticoagulant (Karimi and Rockwell, 2019). A second-generation platelet concentrate, platelet-rich fibrin (PRF) or leukocyte-and platelet-rich fibrin (L-PRF), was developed by Choukroun et al. in 2001 to overcome these limitations (Choukroun et al., 2001). The multiple advantages of PRF include no biochemical additives, easy manipulation, slow release of GFs, great flexibility, and elasticity (Choukroun and Miron, 2017; Dohan et al., 2006). These features have led to the preference of PRF over PRP in clinical applications.

The application of APCs in ARP has been a popular research topic in recent years. Several systematic reviews have aimed to evaluate the efficacies of APCs such as PRP and PRF in the preservation of tissues at post-extraction sites, but the results were inconclusive (Annunziata et al., 2018; Moraschini and Barboza, 2015).

This study aims to systematically review and assess the efficacy of PRF in reducing post-extraction morbidity, aiding soft tissue healing, minimizing bone loss, and improving bone quantity in the alveolar ridge following minimally traumatic tooth extraction.

2 Methods

The stepwise approach of the PICOS process was adopted to formulate the search strategies. This strategy focuses on systemically healthy adults who require tooth extraction and examines the effects of applying PRF in the extraction socket compared to spontaneous healing. The primary outcome parameters evaluated include post-operational morbidity, soft tissue healing, changes in alveolar dimensions, and bone formation within the socket. The type of study used to obtain data are controlled clinical trials, utilizing either a split-mouth or parallel design.

The literature search combined a consultation with a previous systematic review and an electronic database search. A systematic review (Annunziata et al., 2018) on the efficacy of APCs in ARP was consulted. The electronic database search was conducted on 15 December 2021, in three databases: National Library of Medicine/PubMed, Cochrane CENTRAL (The Cochrane Central Register of Controlled Trials), and Google Scholar. An ad hoc search string "(platelet-rich fibrin OR PRF OR autologous platelet concentrate) AND (ridge preservation OR socket preservation OR alveolar preservation OR tooth extraction OR alveolar socket OR extraction socket)" was created. The publication date was limited to the past ten years. No language restriction was applied.

The studies included in this review consisted of controlled clinical trials that investigated the efficacy of PRF in preserving tissue at sites of human tooth extractions. These trials did not impose any restrictions based on the age, gender, or sample size of the subjects, provided that the individuals were systemically healthy and required one or more tooth extractions. Important inclusion criteria also stipulated that minimally traumatic extraction techniques be employed, and that follow-up periods were at least two months for the evaluation of hard tissue healing and a minimum of seven days for the assessment of soft tissue healing. The language of publication was not restricted, and all selected studies had to have been published within the last ten years.

In contrast, several types of studies and patient conditions were excluded to ensure the relevance and integrity of the findings. Specifically, studies involving the extraction of third molars, as well as those featuring patients with poor oral hygiene, heavy smokers, pregnant women, or individuals with medical conditions that could hinder the healing process—such as uncontrolled diabetes, immunosuppression, or those who had undergone radiation—were not considered. Additionally, animal studies, case reports, case series, and abstracts from journal supplement issues were excluded. Studies that lacked a control group with spontaneous healing or did not provide sufficient information pertinent to the topic were also not included in the review.

An initial search applying the search string yielded 268 studies in PubMed and 203 studies in Cochrane CENTRAL. After narrowing it down to clinical trials within the past ten years, a total of 51 and 203 articles were found, respectively. In Google Scholar, the initial search found 2,140 studies, and a total of 1,890 studies were published within the past ten years. Studies gathered from the initial search were screened by the titles and abstracts, which resulted in 14 studies from PubMed and 21 studies from Cochrane CENTRAL. In Google Scholar, 32 studies were selected after title and abstract screening of the first 1,000 hits sorted by relevance. Six articles were gathered from the consultation of the previous systematic review (Annunziata et al., 2018), all of which were also found within the electronic database search. Following the elimination of duplicated studies selected from the different databases and the consulted previous systematic review, a yield of 44 articles was obtained. Lastly, full-text articles were attentively assessed for eligibility following the inclusion and

exclusion criteria. A final number of 26 articles were selected. **Figure 1** illustrates the literature selection process.

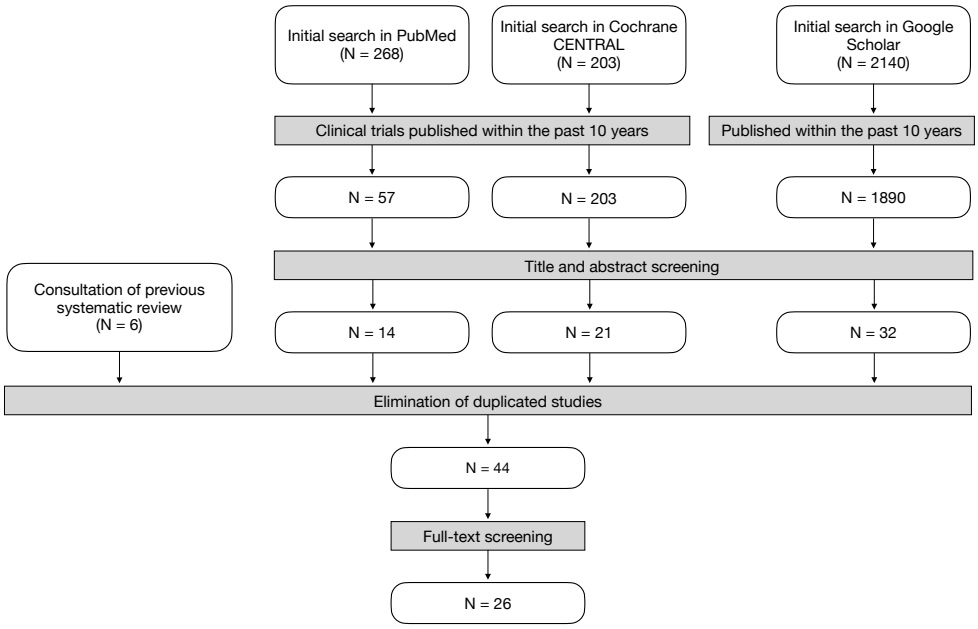

Figure 1. Flow chart of the article selection process.

2.1 Statistics

The qualitative methodology employed to systematically analyze the textual content of the included studies is comprised of descriptive statistucs, frequency analysis, and content analysis. It should be noted that, due to the narrative nature of this study, regression analysis and meta-analysis techniques were ineligible for the analytical framework.

3 Results

Of all included studies, 21 were randomized controlled trials (RCTs). Among them, seven had a split-mouth design, 13 had a parallel design, and one had a crossover design. The remaining five studies were controlled clinical trials (CCTs), of which two had a split-mouth design and three had a parallel design.

The follow-up period ranged from two months to six months for hard tissue healing, and from one week to three weeks for soft tissue healing. The number of participants ranged from 4 to 90. A total of 1262 extraction sockets in 865 patients from the 26 studies were evaluated in this systematic review.

All included studies treated the test sites with PRF or L-PRF, and the control sites were left for spontaneous healing. Sites or groups left for natural healing without any addition of biomaterials were referred to as control sites or control group (CG).

Other interventions performed in the included studies, which were not of interest for the present study, included freeze-dried bone allograft (FDBA), xenograft, PRF combined

with other materials such as FDBA, xenograft, bone marrow aspirate concentrate, flap, plaster of Paris, collagen plug, bone albumin, and titanium-prepared PRF (T-PRF). These intervention groups were not considered in this study. The basic information of the included studies is displayed in supplementary **Table S1**.

3.1 Details of the tooth extractions

The reasons for extraction in the included studies comprised crown and root fracture, pulp necrosis, endodontic failure, non-restorable caries, tooth with unfavourable prosthetic support, periodontal reasons, residual roots, orthodontic indications, trauma, root resorption, periapical granuloma, and hopeless teeth. Dental extractions were performed under aseptic conditions. In four studies, patients were asked to rinse with chlorhexidine gluconate mouthwash at the beginning of the appointment (Badakhshan et al., 2020; Clark, 2016; Kumar et al., 2018; Taha, 2019). In addition, one study scrubbed the extra-oral skin with 5% betadine solution (Kumar et al., 2018).

All studies kept the extraction procedure as minimally traumatic as possible to avoid damage to the alveolar walls and the surrounding soft tissue. Under local anaesthesia, the teeth were luxated with periotomes and/or luxators to achieve sufficient tooth mobility. Root-sectioning was performed on multi-rooted molars if required. Finally, the teeth were delivered with appropriate forceps. If present, sharp bony edges were smoothed with a bone rongeur or bone file. The sockets were debrided with a curette to eliminate any residual granulation tissue, and inspected to affirm the integrity of the socket walls. The resultant sockets were irrigated with sterile normal saline solution. Post-operative instructions were given along with the prescription of appropriate analgesic drugs and antibiotics.

Two studies performed the extractions with elevated mucoperiosteal flaps (Godwin Saji, 2016; Ivanova et al., 2021). One study in particular carried out the extraction with an extractor device (Fontes Martins et al., 2021), and one study did not specify the technique (Ahmed et al., 2019). All other studies (n = 22) performed simple, flapless extractions.

3.2 Preparation of platelet-rich fibrin

PRF is obtained by centrifuging blood at specific settings. The protocols for PRF preparation varied among the included studies. The relevant parameters of PRF preparation are summarised in **Table S2**.

An appropriate amount of blood was drawn from the patients via venipuncture in the cubital fossa, depending on the number and size of extraction sockets. The collected blood volume ranged from 5 ml (Mezal et al., 2019) to 80 ml (Temmerman et al., 2016). Blood collection tubes of different capacities and materials were used, all without anticoagulant, bovine thrombin, or any gelling agent. Five studies used glass tubes (Areewong et al., 2019; Clark, 2016; Ercan, 2018; Godwin Saji, 2016; Suttapreyasri & Leepong, 2013), four used glass-coated plastic tubes (Badakhshan et al., 2020; Canellas et al., 2019; Castro et al., 2021; Mourão et al., 2020), and one used plastic tubes (Temmerman et al., 2016). Other studies did not specify the type of tubes used.

Immediate transfer of the blood collection tubes into the centrifuge was required since no anticoagulant was used. Blood-containing tubes were positioned in opposite slots of the centrifuge to counterbalance each other. If necessary, a tube filled with water was placed in the slots to prevent imbalance. Various commercially available centrifuges were used, and a single centrifugation at room temperature was conducted for each blood sample. Blood samples were centrifuged at 3,000 rpm for 10 minutes in 12 studies (Ahmed et al., 2019;

Alzahrani et al., 2017; Clark, 2016; Du Toit et al., 2016; Kumar et al., 2018; Mezal et al., 2019; Saha, 2019; Sharma et al., 2020; Srinivas et al., 2018; Suttapreyasri & Leepong, 2013; Taha, 2019), or at 2,700 rpm for 12 minutes in 11 studies (Areewong et al., 2019; Badakhshan et al., 2020; Canellas et al., 2019; Castro et al., 2021; Ercan, 2018; Hauser et al., 2013; Marenzi et al., 2015; Mourão et al., 2020; Temmerman et al., 2016; Ustaoglu et al., 2019).

After centrifugation, three distinct layers formed within the tube: a top layer of platelet-poor acellular plasma (cloudy), a middle layer of PRF clot (yellow-opaque), and a bottom layer of red blood cell sediments. The PRF clot was removed using sterile tweezers or forceps and placed in a bowl or dappen dish. The red blood cells were separated from the PRF clot by gentle scraping or with scissors.

The clot was then either directly applied to the socket (Ahmed et al., 2019; Badakhshan et al., 2020; Clark, 2016; Du Toit et al., 2016; Fontes Martins et al., 2021; Godwin Saji, 2016; Kumar et al., 2018; Mezal et al., 2019; Saha, 2019; Srinivas et al., 2018; Suttapreyasri & Leepong, 2013), compressed in a specially designed box (Alzahrani et al., 2017; Canellas et al., 2019; Hauser et al., 2013; Mourão et al., 2020; Temmerman et al., 2016; Zhang et al., 2018), or compressed between sterile sponges/gauzes (Ercan, 2018; Ustaoglu et al., 2019) to generate a fibrin membrane. Alternatively, it was placed in a specially designed box or cylinder to form a fibrin plug (Areewong et al., 2019; Canellas et al., 2019).

3.3 Post-operational morbidity

The pain after tooth extraction was assessed in six studies using the 10-cm or 10-point Visual Analogue Scale (VAS) (Ercan, 2018; Kumar et al., 2018; Marenzi et al., 2015; Mourão et al., 2020; Temmerman et al., 2016; Ustaoglu et al., 2019).

In four studies, the VAS pain scores reported by the participants on the first day were significantly lower in the test group (TG) than in the CG (Ercan, 2018: $p < 0.05$, Marenzi et al., 2015: $p < 0.001$, Mourão et al., 2020: $p = 0.013$, Ustaoglu et al., 2019: $p = 0.047$). The difference became insignificant on the second day (Ercan, 2018: $p > 0.05$, Ustaoglu et al., 2019: $p = 0.054$). Marenzi et al. (2015) found the pain levels to decrease to zero and were nearly equal in both groups after four days. Mourão et al. (2020) only mentioned that the collection of questionnaires was at one-week follow-up and did not specify the timing of the pain score recording. The differences between the groups were significant ($p < 0.05$) in all four of these studies presenting averaged data and outcomes of respective statistical tests (shown in **Table 1**).

Table 1. The VAS pain scores.

Study	**Follow-up**	**VAS pain scores (mean ± SD)**		***p*-value**
		Test group	Control group	
Ercan 2018	1 d	3.20 ± 2.04	5.50 ± 1.50	***p*<0.05**
	2 d	0.47 ± 0.92	1.29 ± 1.49	NS
Marenzi et al. 2015	1 d	3.20 ± 0.30	4.50 ± 0.70	***p*<0.001**
Mourão et al. 2020	NR	4.00 ± 1.15	5.12 ± 1.08	***p*=0.013**
Ustaoglu et al. 2019	1 d	3.30 ± 2.07	5.11 ± 1.60	***p*=0.047**
	2 d	0.48 ± 0.92	1.01 ± 1.44	NS

Abbreviations: NR: not reported, NS: not significant

One study did not provide the averaged data of the pain score, but a brief description

was given instead (Kumar et al., 2018): None of the participants in the TG had pain, while four participants in the CG experienced pain at 24 hours, and two of them still had pain on the seventh day. The split-mouth study conducted by Temmerman et al. (2016) asked the participants to fill in the worst, average, and weakest pain experienced for the first seven days. Statistically significant differences were found between the groups on days three, four, and five for the worst and average amount of pain ($p < 0.005$). Excluding the two studies that did not report averaged outcome data (Kumar et al., 2018; Temmerman et al., 2016), the mean post-operational pain score ranged from 0.47 (Ercan, 2018) to 4 (Mourão et al., 2020) for the TG and from 1.01 (Ustaoglu et al., 2019) to 5.5 (Ercan, 2018) for the CG after an observation period of one day to one week.

Three studies documented the number of analgesics consumed after the tooth extraction (Ercan, 2018; Mourão et al., 2020; Ustaoglu et al., 2019), and the results are listed in **Table 2**. Mourão et al. (2020) reported a significantly higher number of analgesic consumptions by the participants in the CG than those in the TG. The timing of data collection was not specified in the study. In contrast, Ustaoglu et al. (2019) and Ercan (2018) found no significant difference in the number of analgesics taken by participants in the CG and TG at any period ($p > 0.05$), with the analgesic consumption being only slightly higher in the CG.

Table 2. Analgesic consumption.

Study	**Follow-up**	**Number of analgesics**		***p*-value**
		Test group	Control group	
Ercan 2018	1 d	0.87 ± 0.83	1.43 ± 1.09	NS
	2 d	0.07 ± 0.29	0.36 ± 0.74	NS
Mourão et al. 2020	NR	1.00 ± 1.15	1.75 ± 0.85	**p=0.014**
Ustaoglu et al. 2019	1 d	0.89 ± 0.84	1.47 ± 1.11	NS
	2 d	0.07 ± 0.33	0.32 ± 0.70	NS

Abbreviations: NR: not reported, NS: not significant

In summary, all five studies that performed statistical analysis reported significantly less pain after tooth extraction. The highest reported mean post-operational pain was 5.5 in the control sites and 3.3 in the test sites after one day, while the minimum pain score was 4.5 in the control sites and 3.2 in the test sites. Not all studies reporting pain also considered the number of analgesics taken. However, the decreased pain was also reflected in a consistently lower extent of analgesic consumption in all three studies reporting this outcome parameter, even though only one reached statistical significance.

3.4 Soft tissue healing

Soft tissue healing was assessed clinically in nine studies (Ahmed et al., 2019; Ercan, 2018; Marenzi et al., 2015; Mourão et al., 2020; Sharma et al., 2020; Srinivas et al., 2018; Suttapreyasri & Leepong, 2013; Travezan-Moreyra et al., 2017; Ustaoglu et al., 2019). In these studies, different indices were used for assessment, including the Landry Wound Healing Index (LWHI), complete wound epithelialization rate (CWE), clinical dimensions of socket orifice, and a modified Healing Index.

Seven studies adopted the LWHI to evaluate the extraction site based on tissue colour, response to touch, marginality of the incision line, and extent of the area (Ahmed et al.,

2019; Ercan, 2018; Mourão et al., 2020; Sharma et al., 2020; Srinivas et al., 2018; Travezan-Moreyra et al., 2017; Ustaoglu et al., 2019). The rating ranged from 1 to 5, corresponding to very poor, poor, good, very good, and excellent, respectively. The observation interval ranged from one day after the procedure (Ahmed et al., 2019) to two weeks (Ercan, 2018; Mourão et al., 2020; Sharma et al., 2020; Travezan-Moreyra et al., 2017; Ustaoglu et al., 2019).

The results are shown in **Table 3**. All seven studies reported a lower LWHI value in the CG than in the TG, with a minimum mean score of 2.137 in CG (Travezan-Moreyra et al., 2017) and 2.764 in TG (Ahmed et al., 2019). This difference between the CG and TG was found to be significant in four studies (Mourão et al., 2020: $p = 0.0138$, Sharma et al., 2020: $p < 0.05$, Srinivas et al., 2018: $p < 0.001$, Travezan-Moreyra et al., 2017: $p < 0.05$). The difference remained significant in the second week in two studies (Sharma et al., 2020; Travezan-Moreyra et al., 2017: $p < 0.05$), but became insignificant in one study (Mourão et al., 2020: $p = 0.2734$). One study did not record the LWHI in the second week (Srinivas et al., 2018). In two studies, the difference between groups was not significant after one and two weeks (Ercan, 2018; Ustaoglu et al., 2019: $p > 0.05$). One study found very good soft tissue healing in 86.7% of the control sites and 94.1% of the test sites but did not report the statistical significance (Ahmed et al., 2019).

Table 3. Soft tissue healing evaluated with LWHI.

Study	**Follow-up**	**LWHI (mean ± SD)**		***p*-value**
		Test group	Control group	
Ahmed et al. 2019	1 d	2.76*	2.47*	NR
	3 d	2.88*	2.73*	NR
	1 wk	3.94*	3.87*	NR
Ercan 2018	1 wk	3.53 ± 0.64	3.21 ± 0.69	NS
	2 wk	4.53 ± 0.52	4.36 ± 0.49	NS
Mourão et al. 2020	1 wk	3.81 ± 0.65	3.18 ± 0.54	**p=0.014**
	2 wk	4.75 ± 0.44	4.50 ± 0.51	NS
Sharma et al. 2020	3 d	3.43 ± 0.50	3.17 ± 0.38	**p=0.025**
	1 wk	3.93 ± 0.25	3.73 ± 0.08	**p=0.039**
	2 wk	4.83 ± 0.38	4.30 ± 0.09	**p=0.000**
Srinivas et al. 2018	1 wk	3.80 ± 0.40*	3.00 ± 0.52*	**p<0.001**
Travezan-Moreyra et al. 2018	1 wk	3.29 ± 0.57*	2.14 ± 0.56*	**p<0.05**
	2 wk	4.35 ± 0.52*	3.04 ± 0.56*	**p<0.05**
Ustaoglu et al. 2019	1 wk	3.58 ± 0.63	3.21 ± 0.66	NS
	2 wk	4.59 ± 0.51	4.38 ± 0.49	NS

Abbreviations: NR: not reported, NS: not significant

*Values calculated with data provided by the original study

Two of the seven studies that evaluated soft tissue healing with LWHI also clinically assessed the CWE using the H2O2 bubbling test (Ercan, 2018; Ustaoglu et al., 2019) (**Table 4**). If the epithelium was discontinuous, the applied 3% H2O2 would pass into the underlying connective tissue and react with the catalase to release water and oxygen, manifesting as bubbling on the surface. In both studies, significantly lower CWE was found in the CG compared to the TG after one and two weeks ($p < 0.05$). In the second week, 100% CWE was achieved in the TG in both studies, while only 35.7% and 40.7% of the control sites

attained CWE.

Table 4. CWE evaluated with the H2O2 bubbling test.

Study	Follow-up	H2O2 test (CWE in %) (mean)		*p*-value
		Test group	Control group	
Ercan 2018	1 wk	53.30	7.10	**$p<0.05$**
	2 wk	100	35.70	**$p<0.05$**
Ustaoglu et al. 2019	1 wk	54.90	10.10	**$p<0.05$**
	2 wk	100	40.70	**$p<0.05$**

One study assessed soft tissue quality and maturation using a modified version of the Healing Index originally designed to evaluate healing with primary closure following periodontal surgery (Marenzi et al., 2015) (**Table 5**). This index involved three scoring levels for four parameters: tissue colour, consistency of the healing tissue, bleeding, and suppuration. The final scoring scale ranged from 4 to 12, corresponding to excellent healing and severely impaired healing, respectively. PRF-treated sites always resulted in better values than the control sites at all follow-up periods, with the differences being significant after one and two weeks ($p < 0.05$).

Table 5. Soft tissue healing evaluated with Modified Healing Index.

Study	Follow-up	Modified Healing Index (mean ± SD)		*p*-value
		Test group	Control group	
Marenzi et al. 2015	3 d	4.8 ± 0.6	5.1 ± 0.9	NS
	1 wk	4.5 ± 0.5	4.9 ± 0.3	NS
	2 wk	4.2 ± 0.2	4.3 ± 0.3	**$p=0.01$**
	3 wk	4.1 ± 0.2	4.2 ± 0.2	**$p<0.001$**

Abbreviations: NS: not significant

In one study, the clinical dimensions of the socket orifice (M-D width and B-L width) were measured to evaluate soft tissue healing (Suttapreyasri & Leepong, 2013). The measurements immediately following the extraction showed no difference between the groups. After eight weeks, the PRF-treated sites had slightly narrower orifices (M-D: 1.76 ± 1.36 mm, B-L: 3.31 ± 0.9 mm) than the CG (M-D: 2.17 ± 1.65 mm, B-L: 3.92 ± 0.64 mm), but the difference lacked statistical significance ($p > 0.05$).

Overall, the nine studies consistently reported better soft tissue healing in PRF-treated sites over a follow-up period of one day to eight weeks. Eight studies performed tests of statistical significance, and the vast majority (7 out of 8) yielded significantly superior wound healing.

3.5 Clinical alveolar ridge dimensional changes

As with soft tissue, the bony structures around dental tissues undergo modification after tooth extraction. The pattern and extent of the dimensional changes can be evaluated either clinically or radiographically.

Four studies observed the change of alveolar ridge dimensions clinically (Alzahrani et al., 2017; Hauser et al., 2013; Kumar et al., 2018; Suttapreyasri & Leepong, 2013). All four

studies evaluated the change in the buccal-lingual alveolar bone width (**Table 6**), and one of them evaluated the change in the alveolar bone height alongside (Kumar et al., 2018).

Table 6. The alveolar bone width changes evaluated clinically. Measurements in mm.

1stAuthor, year	**Follow-up**	**Bone width in or % (clinical) (mean ± SD)** Test group	Control group	***p*-value**
Alzahrani, 2017	Measured at 5 mm apical to crest.			
	BL	11.94 ± 2.33	13.46 ± 3.13	NR
	1 wk	11.70 ± 2.37	13.01 ± 3.00	NR
	4 wk	11.33 ± 2.30	12.04 ± 2.50	NR
	8 wk	10.97 ± 2.23	11.54 ± 2.42	NR
	BL – 1 wk	2.09 ± 0.84% (0.24*)	3.26 ± 2.21% (0.45*)	NS
	BL – 4 wk	5.22 ± 0.80% (0.61*)	9.79 ± 6.02% (1.42*)	**p=0.012**
	BL – 8 wk	8.58 ± 1.73% (0.97*)	13.54 ± 6.57% (1.92*)	**p=0.036**
Hauser, 2013	Measured at approximately 4 mm apical to crest[1]			
	BL – 8 wk	0.48 % (0.06)	3.70% (0.43)	**p<0.05**
Kumar, 2018	Did not specify level of measurements			
	BL	9.70 ± 1.73	8.16 ± 1.87	NS
	6 m	6.70 ± 1.33	5.20 ± 1.59	NS
	BL – 6 m	3.00 ± 0.64	3.00 ± 0.83	NS
Suttapreyasri, 2013	At the most coronal prominent points[2]			
	BL – 1 wk	1.65*, 0.56*, 0.67*	3.07*, 0.74*, 0.68*	NR
	BL – 2 wk	2.29*, 1.18*, 0.80*	3.02*, 1.12*, 0.83*	NR
	BL – 4 wk	3.04*, 2.05*, 1.03*	3.65*, 1.85*, 1.03*	NR
	BL – 6 wk	3.82*, 2.43*, 1.32*	4.36*, 2.67*, 1.58*	NR
	BL – 8 wk	3.55*, 2.21*, 2.28*	3.62*, 3.39*, 0.95*	NR

Abbreviations: BL: baseline, NR: not reported, NS: not significant
*Values calculated with data provided by the original study
[1]distance between the most prominent points buccally and lingually
[2]buccally and lingually (W0), W0 – 3, W0 – 5.

The measurements of the alveolar bone width were obtained by directly using a caliper intra-orally in two studies (Hauser et al., 2013; Kumar et al., 2018). In the other two studies, measurements were done on the study casts acquired at each interval with the help of an acrylic jig or stent (Alzahrani et al., 2017; Suttapreyasri & Leepong, 2013). All measurements were done perpendicular to the long axis of the alveolus; however, the level at which the evaluation was performed varied. The level of measurement ranged from the alveolar crest (Suttapreyasri & Leepong, 2013) to five millimetres apical to the crest (Alzahrani et al., 2017; Suttapreyasri & Leepong, 2013).

The width reductions were found to be greater in the control sites in all four studies, with the exception of two measurements done by Suttapreyasri & Leepong (2013): TG 2.05 mm vs. CG 1.85 mm at 3 mm below the crest after one month, and TG 2.28 mm vs. CG 0.95 mm at 5 mm below the crest after two months. The loss of alveolar bone width was observed to be significantly greater in the CG than in the TG at four weeks in one study (Alzahrani et al., 2017: $p = 0.012$), and at eight weeks in two studies (Alzahrani et al., 2017: $p = 0.036$; Hauser et al., 2013: $p < 0.05$). On the contrary, Kumar et al. (2018) reported an insignificant difference in the loss of alveolar bone width between the two groups at six

months.

Suttapreyasri & Leepong (2013) evaluated the alveolar bone width by measuring the buccal and lingual contour individually. They reported a significantly higher resorption of the buccal contour in the CG (1.81 ± 0.88 mm) than in the TG (1.07 ± 0.31 mm) at the first week ($p = 0.031$). No other differences in the buccal and lingual contour changes between the two groups were found to be significant at any follow-up period.

Kumar et al. (2018) evaluated the alveolar bone height by measuring the vertical distance between the buccal crest and the cemento-enamel junction of the tooth mesial to the extraction socket intra-orally with a caliper. The height reduction was greater in the CG (3.3 ± 0.61 mm) than in the TG (3.0 ± 0.8 mm) after six months, though the difference was not significant (**Table 7**).

Table 7. The alveolar bone height changes evaluated clinically. Measurements in mm.

Study	**Follow-up**	**Bone height (clinical) (mean ± SD)**		***p*-value**
		Test group	Control group	
Kumar et al. 2018	BL	8.50 ± 1.20	8.43 ± 1.13	NS
	6 m	5.50 ± 1.04	5.00 ± 0.86	NS
	BL – 6 m	3.00 ± 0.80	3.30 ± 0.61	NS

Abbreviations: BL: baseline, NS: not significant

Altogether, the clinical analysis of all five studies revealed that extraction sites treated with PRF exhibited less reduction in alveolar height and width. Significantly more bone width loss was observed in the CG by half of the studies reporting this outcome parameter after a period of one to eight weeks (2 of 4).

3.6 Radiological alveolar ridge dimensional changes

Eight studies recorded post-extraction alveolar bone dimensional changes using either cone beam computed tomography (CBCT) or intra-oral periapical radiograph. Two studies assessed only the vertical bone height (Hauser et al., 2013; Suttapreyasri & Leepong, 2013), while six studies assessed both the vertical and horizontal bone dimensions (Badakhshan et al., 2020; Canellas et al., 2019; Castro et al., 2021; Taha, 2019; Temmerman et al., 2016; Zhang et al., 2018). Vertical bone height was measured on the buccal, lingual, mesial, and distal aspects of the tooth extraction sockets, and the results are summarised in **Tables 8-11**.

Six studies assessed bone height on the buccal and lingual aspects. The reported mean buccal bone height loss ranged from 0.2 ± 0.8 mm (Castro et al., 2021) to 3.79 ± 0.9 mm (Badakhshan et al., 2020) in the CG and from 0.1 ± 1.6 mm (Temmerman et al., 2016) to 2.41 ± 0.8 mm (Taha, 2019) in the TG after a follow-up period of three to six months. The CG had significantly higher values of buccal bone height loss in three studies (Badakhshan et al., 2020: $p < 0.001$, Canellas et al., 2019: $p = 0.02$, Temmerman et al., 2016: $p < 0.001$). In contrast, buccal bone reduction was found to be significantly higher in the test group by Taha (2019) at three months ($p \leq 0.05$).

For the lingual side, the mean vertical resorption ranged from 0.7 ± 0.8 mm (Temmerman et al., 2016) to 3 ± 1.17 mm (Badakhshan et al., 2020) in the control group and from 0.3 ± 1.2 mm (Temmerman et al., 2016) to 1.46 ± 0.7 mm (Taha, 2019) in the test group after a follow-up period of three to six months. A significant difference was reported by only one of all six

Table 8. The buccal alveolar bone height loss evaluated radiographically. Measurements in mm (mean ± SD).

Study	Follow-up	Buccal vertical bone loss (XR)		*p*-value
		Test group	Control group	
Badakhshan et al. 2020	3 m	2.00 ± 2.24	3.79 ± 0.90	**$p<0.001$**
Canellas et al. 2019	3 m	0.70 ± 0.70	1.39 ± 1.20	**$p=0.02$**
Castro et al. 2021	3 m	0.20 ± 1.20	0.20 ± 0.80	NS
Taha 2019*	3 m	2.41 ± 0.80	0.79 ± 0.60	**$p \leq 0.05$**
	6 m	1.71 ± 0.50	1.92 ± 0.90	NS
Temmerman et al. 2016	3 m	0.10 ± 1.60	1.60 ± 1.20	**$p<0.001$**
Zhang et al. 2018	3 m	1.60 ± 1.46	2.80 ± 1.81	NS

Abbreviations: NS: not significant

*Taha (2019) further divided each group into two subgroups. Analyses were performed at 3 months in one subgroup and at 6 months in the other.

Table 9. The lingual alveolar bone height loss evaluated radiographically. Measurements in mm (mean ± SD).

Study	Follow-up	Lingual vertical bone loss (XR)		*p*-value
		Test group	Control group	
Badakhshan et al. 2020	3 m	1.36 ± 0.57	3.00 ± 1.17	**$p<0.001$**
Canellas et al. 2019	3 m	0.67 ± 0.90	1.24 ± 1.15	NS
Castro et al. 2021	3 m	1.10 ± 0.90	1.00 ± 0.90	NS
Taha 2019*	3 m	1.46 ± 0.70	0.95 ± 0.79	NS
	6 m	0.96 ± 0.52	1.12 ± 1.20	NS
Temmerman et al. 2016	3 m	0.30 ± 1.20	0.70 ± 0.80	NS
Zhang et al. 2018	3 m	1.00 ± 0.71	2.05 ± 1.29	NS

Abbreviations: NS: not significant

*Taha (2019) further divided each group into two subgroups. Analyses were performed at 3 months in one subgroup and at 6 months in the other.

Table 10. The mesial alveolar bone height loss evaluated radiographically. Measurements in mm (mean ± SD).

Study	Follow-up	Mesial vertical bone loss (XR)		*p*-value
		Test group	Control group	
Badakhshan et al. 2020	3 m	2.05 ± 1.14	3.75 ± 1.67	**$p<0.001$**
Hauser et al. 2013	8 wk	1.21 ± 0.40	0.77 ± 0.17	NR
Suttapreyasri 2013	1 wk	1.53 ± 0.16	1.70 ± 0.29	NS
	2 wk	1.76 ± 0.20	1.94 ± 0.26	NS
	4 wk	2.01 ± 0.28	2.42 ± 0.42	NS
	6 wk	2.17 ± 0.44	2.57 ± 0.40	NS
	8 wk	2.22 ± 0.51	2.82 ± 0.65	NS

Abbreviations: NR: not reported, NS: not significant

Table 11. The distal alveolar bone height loss evaluated radiographically. Measurements in mm (mean ± SD).

Study	Follow-up	Distal vertical bone loss (XR)		*p*-value
		Test group	Control group	
Badakhshan et al. 2020	3 m	1.46 ± 0.78	2.78 ± 0.96	**$p<0.001$**
Hauser et al. 2013	8 wk	0.76 ± 0.25	2.07 ± 0.81	NR
	1 wk	1.07 ± 0.16	1.41 ± 0.29	NS
	2 wk	1.28 ± 0.21	1.74 ± 0.34	NS
Suttapreyasri 2013	4 wk	1.55 ± 0.22	1.87 ± 0.34	NS
	6 wk	1.60 ± 0.19	1.71 ± 0.49	NS
	8 wk	2.08 ± 0.09	2.10 ± 0.50	NS

Abbreviations: NR: not reported, NS: not significant

studies (Badakhshan et al., 2020).

Three studies evaluated bone height reduction on the mesial and distal aspects with a follow-up period from one week to three months. All but one study (Hauser et al., 2013) reported higher mean vertical resorption on both the mesial and distal walls in the control group, and the difference between the groups reached statistical significance in one study (Badakhshan et al., 2020: $p < 0.001$). On the contrary, Hauser et al. (2013) found a higher value of mesial vertical bone resorption in the test sites, though the p-value was not reported.

Six studies analysed alveolar bone width alterations (**Table 12**). The level at which measurements were taken extended from the bone crest (Badakhshan et al., 2020; Zhang et al., 2018) to five millimetres below the crest (Canellas et al., 2019; Castro et al., 2021; Temmerman et al., 2016). It can be deduced from the data that the more coronal the measurement level, the greater the width reduction will be. All but two of the values reported by the six studies showed more bone width loss in the control group than in the test group. The two exceptions were found by Castro et al. (2021) at crest -3 mm level after three months and by Taha (2019) at six months. These differences were not statistically significant.

Three studies observed a significantly lower width reduction in PRF-treated sites at one and three millimetres below crest (Badakhshan et al., 2020: $p < 0.001$, $p < 0.001$; Canellas et al., 2019: $p = 0.001$, $p = 0.005$; Temmerman et al., 2016: $p < 0.001$, $p = 0.007$). Furthermore, significantly less width loss was also reported by Badakhshan et al. (2020) at crest level ($p < 0.001$) and by Temmerman et al. (2016) at crest -5 mm ($p = 0.02$).

The most pronounced width resorption was observed by Temmerman et al. (2016) in the control group at 1 mm below crest (5.4 ± 4.4 mm), and the least amount of width loss was reported by Badakhshan et al. (2020) in the control group at 3 mm below crest (0.3 ± 0.25 mm).

In summary, three of six studies reported significantly less buccal bone height reduction in sites treated with PRF, while the majority of studies (5 of 6) found no significant differences between the groups in lingual bone height changes. With regard to the ridge width change, the vast majority of the values reported revealed less resorption when PRF was applied. Of the six studies that reported this parameter, three noted a significantly lower loss in PRF-treated sites at various bone levels after three months.

Table 12. The alveolar bone width loss evaluated radiographically. Measurements in mm (mean ± SD).

1stAuthor, year	Follow-up	LoM[1]	Horizontal bone loss (XR)		*p-value*
			Test group	Control group	
Badakhshan, 2020	3 m	crest	0.92 ± 0.68	2.08 ± 1.03	**$p<0.001$**
		1	0.63 ± 0.43	1.39 ± 0.50	**$p<0.001$**
		3	0.30 ± 0.25	1.78 ± 1.19	**$p<0.001$**
Canellas, 2019	3 m	1	0.93 ± 0.90	2.27 ± 1.20	**$p<0.001$**
		3	0.85 ± 0.80	1.67 ± 1.10	**$p=0.005$**
		5	0.67 ± 0.50	1.08 ± 1.00	NS
Castro et al. 2021	3 m	1	2.20 ± 1.00	2.20 ± 1.10	NS
		3	1.80 ± 1.70	1.70 ± 0.80	NS
		5	1.20 ± 0.80	1.40 ± 0.80	NS
Taha, 2019*	3 m	NR	1.48 ± 0.90	1.49 ± 0.60	NS
	6 m		2.24 ± 1.06	2.03 ± 0.70	NS
Temmerman, 2016	3 m	1	2.40 ± 2.30	5.40 ± 4.40	**$p<0.001$**
		3	0.60 ± 0.70	1.20 ± 1.10	**$p=0.007$**
		5	0.40 ± 0.50	0.50 ± 0.50	**$p=0.02$**
Zhang et al. 2018	3 m	crest	1.05 ± 0.78	2.08 ± 1.67	NS

Abbreviations: F/U: follow-up period, NR: not reported, NS: not significant

*Taha (2019) further divided each group into two subgroups. Analyses were performed at 3 months in one subgroup and at 6 months in the other.

[1]Level of measurement. Distance from crest in mm.

3.7 Radiographical analysis of the socket fill

The quantity of new bone formation within the empty socket after a tooth extraction can be assessed either radiographically with the aid of computer software or histologically under microscopes after sample processing.

Five studies evaluated the percentages of bone fill in the post-extraction sockets, and the follow-up period ranged from one week (Alzahrani et al., 2017) to six months (Kumar et al., 2018; Saha, 2019). The imaging techniques used were either CBCT or intra-oral periapical radiographs. Three studies converted the radiographs into squares or pixels to calculate the area with bone fill (Alzahrani et al., 2017; Kumar et al., 2018; Saha, 2019), while two studies took the highest point of viewable mineralized bone as a reference to analyse the amount of bone fill (Castro et al., 2021; Temmerman et al., 2016). The area or height of the bone fill at the follow-up appointments was compared with the initial extraction socket area or height to obtain the percentages of bone fill (**Table 13**).

Higher mean bone fill percentages were observed in the TG than in the CG by four studies. Moreover, the inter-group differences were significant in three studies after an observation period of one week to three months (Alzahrani et al., 2017; Castro et al., 2021; Temmerman et al., 2016). Contrarily, one study recorded similar levels of bone fill in the CG and TG at six months (Kumar et al., 2018: TG $73.76 \pm 0.14\%$ vs. CG $74.3 \pm 0.13\%$, $p > 0.05$). One study in particular reported bone fill values at six weeks, three months, and six months after the extraction (Saha, 2019). Test sites yielded higher amounts of mean bone fill at the first follow-up appointment (Saha, 2019: TG $40.3 \pm 13.9\%$ vs. CG $28.4 \pm 9.4\%, p > 0.05$), but on average slightly more bone was formed in the control sites at

Table 13. Bone fill percentages in post-extraction sockets.

Study	Follow-up	Bone fill (%) (mean ± SD)		*p*-value
		Test group	Control group	
Alzahrani et al. 2017	1 wk	74.05 ± 1.66	68.82 ± 1.07	**p=0.012**
	4 wk	81.54 ± 3.33	74.03 ± 1.22	**p=0.00**
	8 wk	88.81 ± 1.53	80.35 ± 2.61	**p=0.017**
Castro et al. 2021	3 m	85.20 ± 22.90	67.90 ± 19.20	**p=0.005**
Kumar et al. 2018	6 m	73.76 ± 0.14	74.30 ± 0.13	NS
	6 wk	40.30 ± 13.90	28.40 ± 9.40	NS
Saha 2019	3 m	56.30 ± 17.40	60.90 ± 9.20	NS
	6 m	79.60 ± 6.70	79.60 ± 4.80	NS
Temmerman et al. 2016	3 m	94.70 ± 26.90	63.30 ± 31.90	**p=0.004**

Abbreviations: NS: not significant

the second follow-up (Saha, 2019: TG $56.3 \pm 17.4\%$ vs. CG $60.9 \pm 9.2\%, p > 0.05$).

To summarize, three of the five studies reported significantly higher percentages of bone fill in the PRF-treated sites. The other two found similar results in both groups. In the control sites, the highest mean bone fill percentage was reported by Alzahrani et al. (2017) at two months ($80.35 \pm 2.61\%$), and the least amount of bone fill was reported by Saha (2019) at six weeks ($28.4 \pm 9.4\%$). In contrast, the test sites had a maximum reported mean bone fill of $94.7 \pm 26.9\%$ at three months (Temmerman et al., 2016) and a minimum of $40.3 \pm 13.9\%$ at six weeks (Saha, 2019).

3.8 Histomorphometric analysis of the socket fill

Five studies investigated the new bone formation ((**Table 14**)) at the extraction site with histomorphometric analysis after a period of two months (Areewong et al., 2019) to six months (Fontes Martins et al., 2021). Prior to dental implant placement, bone core biopsies were harvested from the center of the socket using a trephine bur of 2-3 mm internal diameter and 6-10 mm length. Bone samples were retrieved from the trephine and immediately fixed in 10% formalin (Areewong et al., 2019; Ivanova et al., 2021), 4% paraformaldehyde (Fontes Martins et al., 2021), or 70% ethanol fixatives (Du Toit et al., 2016). The containers were couriered for laboratory preparations.

In three studies, specimens were decalcified in various solutions (Canellas et al., 2019; Fontes Martins et al., 2021; Ivanova et al., 2021), while the specimens remained undecalcified in one study (Du Toit et al., 2016). The histological processing of the specimens encompassed dehydration, infiltration, and embedding. The embedding media used included methyl methacrylate (Areewong et al., 2019), resin (Du Toit et al., 2016), and paraffin blocks (Fontes Martins et al., 2021; Ivanova et al., 2021). The blocks were sectioned into slices and stained with toluidine blue-basic fuchsin (Areewong et al., 2019), hematoxylin-eosin (Canellas et al., 2019; Fontes Martins et al., 2021; Ivanova et al., 2021), or methylene blue-basic fuchsin (Du Toit et al., 2016). The samples were viewed under microscopes and images were captured for further analysis with image processing software.

All five studies reporting this outcome parameter found higher percentages of new bone formation in the TG than the CG. Among them, the highest amount of new bone formation was $60.79 \pm 9.72\%$ (Ivanova et al., 2021) in the TG and $47.9 \pm 18.1\%$ (Du Toit et al., 2016)

Table 14. Percentages of new bone formation in post-extraction sockets.

Study	Follow-up	% of New bone formation		*p*-value
		Test group	Control group	
Areewong et al. 2019	2 m	31.33 ± 18.00	26.33 ± 19.63	NS
Canellas et al. 2019	3 m	55.96 ± 11.97	39.69 ± 11.12	***p*<0.001**
Du Toit et al. 2016	3 m	50.70 ± 13.30	47.90 ± 18.10	NS
Fontes Martins et al. 2021	6 m	54.20 ± 4.31	40.60 ± 5.98	***p*<0.05**
Ivanova et al. 2021	4 m	60.79 ± 9.72	39.04 ± 10.89	***p*<0.001**

Abbreviations: NS: not significant

in the CG, while the least amount was $31.33 \pm 18\%$ (Areewong et al., 2019) in the TG and $26.33 \pm 19.63\%$ (Areewong et al., 2019) in the CG. Three studies found the differences to be statistically significant (Canellas et al., 2019: $p < 0.001$, Fontes Martins et al., 2021: $p < 0.05$, Ivanova et al., 2021: $p < 0.001$).

Overall, PRF-treated sites yielded more new bone formation than the control sites in all of the studies, and statistical significance was reached in more than half (3 of 5) of the studies evaluating this parameter histologically.

4 Discussion

PRF has increasingly been used as an autologous regenerative material to promote soft and hard tissue healing. Being a relatively new application, only a few reviews have studied the effect of PRF, and no consensus has been reached on its real benefit in fresh extraction sockets. This systematic review was conducted to investigate the efficacy of PRF in the preservation of the alveolar ridge following minimally traumatic tooth extraction. A total of 26 studies that examined the application of PRF to fresh extraction sockets were selected for analysis. All included studies had a control group in which sockets were left for natural healing.

All aspects of the procedures are of utmost importance to the analysed parameters. Fourteen studies did not report the reasons for extraction. The inclusion criteria of atraumatic extraction ensured that no additional factors could extensively impact the analysis outcome. Various commercially available centrifuge devices and dissimilar PRF-preparation protocols were adopted by the included studies. Although the effects of the heterogeneous PRF-preparation details could not be precisely recognized based on the findings of this study, it should be mentioned that centrifugal settings and blood collection tube types were proven to substantially influence the resulting PRF composition (Tsujino et al., 2019). Moreover, factors such as the patient's age, nutritional status, and genetic susceptibility can affect the characteristics of PRF (Liu et al., 2019).

4.1 Post-operational morbidity

The analysis of the included studies demonstrated that PRF largely ameliorated post-extraction discomfort, which also reduced the demand for analgesic medications. This pain-reducing effect was especially evident on the first post-operative day, during which the pain score ranged from 4.5 to 5.5 for the control sites, and the values declined to 3.2 to 3.3 for the test sites. All six studies reported consistent results. Previous studies have

suggested that PRF induces tissue healing, and reduces pain and inflammation (Muñoz et al., 2016; Zhu et al., 2021). These properties can be ascribed to the fact that PRF provides a dense fibrin network and releases a significant load of various growth factors (GFs). The GFs and leukocytes present in PRF have a powerful impact on the overall healing cascade in which they stimulate the transition of the wound healing process from the inflammatory phase to the proliferative phase (Bielecki et al., 2012). Eventually, the activation of pain receptors ceases due to faded pro-inflammatory signals.

It should be mentioned that the study design of the included studies could be a possible source of bias. Of the four studies assessing post-extraction pain, two did not address the blinding situation (Ercan, 2018; Mourão et al., 2020). In the split-mouth study by Marenzi et al. (2015), the single-blinded design was considered ineffective since patients could essentially see the treatment performed in their own mouths.

The observed results in the current study are in line with two other in vivo studies that evaluated the effects of PRF in stimulating soft tissue healing and reducing post-operative pain following the surgical removal of impacted third molars (Da Silva et al., 2021; Nourwali, 2021). The application of different APCs such as PRP (Boztug et al., 2021), A-PRF (Starzynska et al., 2021), and concentrated growth factor (CGF) (Kamal et al., 2020) in the medical field also revealed comparable results. Post-extraction morbidity, such as pain and inflammation, may affect the surrounding tissue healing, as well as the patient's quality of life. The marked pain-reducing effect of PRF should be highlighted when considering its application in surgical procedures.

4.2 Soft tissue healing

In the current review, an overall trend of better soft tissue healing was observed in all nine studies that evaluated this parameter. Specifically, seven studies reported significant differences, one study reported a non-significant difference, and one study did not perform tests of significance.

Ercan (2018) and Ustaoglu et al. (2019) adopted two different methods for assessment. Both studies reported similar results in the test and control groups when assessing soft tissue healing by LWHI, while significantly better effects were found in the TG when performing the H_2O_2 bubbling test. Essentially, CWE assessment with the H_2O_2 test yields a yes-or-no result, with even the slightest production of bubbles representing incomplete wound epithelialisation. Inspecting the reported data, more than half of the test sites achieved CWE after one week, and wound epithelialisation was completed in all test sites after two weeks. This implies that even when healing was not so amply improved that LWHI resulted in significant differences, there was definitely a different form of healing, particularly in the aspect of epithelialisation. This phenomenon evidently indicated that PRF accelerates soft tissue wound healing.

Suttapreyasri and Leepong (2013) measured the dimensions of the socket orifice for soft tissue healing evaluation. The measurement was conducted at week eight, which is significantly later than the usual one to five weeks required for an extraction wound to completely epithelialize (Pippi, 2017).

To summarise, based on our results, the placement of PRF is clinically helpful with respect to soft tissue healing. This phenomenon can be explained by the regenerative effect of PRF, as underlined by previous studies (Petrescu et al., 2021; Ding et al., 2021). Miron et al. (2017) examined the effects of PRF on soft tissue wounds in a variety of medicinal and dental settings. In soft tissue defects, PRF was found to release a series of GFs, increase

cell proliferation, induce angiogenesis, and possess anti-inflammatory and anti-microbial potentials. These characteristics make PRF an effective biomaterial in the augmentation of wound healing. Furthermore, early and uneventful soft tissue healing protects the underlying bony tissue that is still in the process of remodelling. In comparison to bone grafts, the most widely utilised ARP material, PRF provides the additional benefit of facilitated wound healing. Our findings are in accord with the results obtained by two reviews on the healing effect of PRF in maxillary sinus augmentation and burns (Ortega-Mejia et al., 2020; Pallua et al., 2010).

4.3 Hard tissue dimensional changes

In this review, both clinical and radiographical evaluations in all but one study coherently revealed less loss of alveolar bone height and width in sockets with PRF added. The differences in ridge width and buccal bone height reduction between groups were significant in half of the studies examining these parameters, while that of mesial, distal, and lingual bone height loss was only significant in one study. Based on our results, PRF could reduce the dimension of alveolar ridge resorption by up to 3 mm, which is considered clinically relevant.

Contrasting results were observed by Taha (2019) in the 3-month subgroup, where the TG exhibited more vertical bone loss than the CG. Moreover, the difference between groups reached statistical significance on the buccal side. In the same study, results of the 6-month subgroup showed more bone loss in the natural healing sites. When looking at the average bone loss of the 3-month and 6-month groups collectively, similar results were demonstrated for the test and control sites. Reviewing the study details, its distinct results compared to the other studies might be due to the amount of PRF applied into the socket. Taha (2019) used only one clot in each socket, whereas Canellas et al. (2019) and Temmerman et al. (2016) placed four to eight units of PRF into each socket, and the TGs in both studies exhibited significantly less bone loss than the control sites. An obvious source of imprecision in Taha's study is the small sample size and an even smaller number of subjects after further subdividing each group into two. Furthermore, no power analysis was performed to calculate the minimum sample size.

Three studies evaluated the vertical dimensions at the mesial and distal aspects. Among them, one study (Hauser et al., 2013) encountered difficulties in producing overlapping periapical radiographs. Ultimately, only three patients were included for analysis in each group. Badakhshan et al. (2020) reported a non-normal distribution of the CG data, which led to the use of a statistical test with lower power.

As for the horizontal ridge dimension, the inter-group differences were more pronounced at the crest, and diminished with the apical movement of the measurement points. This observed trend suggested that PRF was more effective in preventing bone width reduction at the crest level, which could be attributed to the pattern of physiological alveolar atrophy where the most considerable bone loss occurs at the most coronal region. The lack of a sufficiently high number of included studies renders the protective effect of PRF on horizontal, mesial, and distal vertical bone resorption inconclusive.

Overall, the prevention of bone height reduction was more effective on the buccal than on the lingual aspect. This can be attributed to the bone resorption pattern after tooth extractions, in which the buccal aspect is commonly more easily resorbed than the lingual due to its composition of bundle bone (Farmer & Darby, 2014). Moreover, Farmer & Darby (2014) observed a doubled amount of bone resorption at the mid-buccal point as opposed to the mesial and distal. Buccal and lingual bone height measurements were taken at the

mid-points in all included studies analysing this parameter.

The relatively faster bone resorption on the mid-buccal aspect might be prevented early on in the remodeling process by the application of PRF into the fresh socket. The demonstrated effects of PRF reducing bone atrophy can be attributed to its various cytokine and growth factor contents (Francisco et al., 2020). The biochemical process of stimulated bone regeneration and repair compensates and leads to overall reduced bone atrophy.

Various types of bone graft materials are routinely used for ARP. A clinical trial by Azangookhiavi et al. (2020) compared the effect of FDBA and PRF in ARP. Both materials yielded optimal outcomes of ridge preservation, and a statistically insignificant difference was found between the groups. Thakkar et al. (2016) investigated the combined use of demineralised freeze-dried bone allograft with PRF in extraction sockets and demonstrated that the combination better preserved the ridge width than demineralised freeze-dried bone allograft alone. The reason could be that PRF alone serves as a placeholder and a reservoir of growth factors, but it might not deliver sufficient mechanical strength. Hence, the addition of a mineral-containing graft to PRF would be a compelling alternative.

Interestingly, previous research on the placement of PRF in third molar sockets has yielded debatable results. Anwandter et al. (2016) presented results in favour of PRF in ridge preservation, while Aravena et al. (2021) reported inconclusive data. To summarise, it remains difficult to quantify the effect of PRF on alveolar ridge dimensions from our findings. Nonetheless, it is certain that PRF does have a positive impact on the preservation of ridge dimensions.

4.4 New bone formation in the extraction socket

Both radiographic and histological analysis methods revealed similar results in this study. That is, sites treated with PRF exhibited a better quantity of new bone formation in the socket. The inter-group differences were statistically significant in half of the studies. The demonstrated effects of PRF can be explained by several biochemical processes. PRF possesses both osteoinductive and osteoconductive properties: osteoinductive by the release of multiple GFs, and osteoconductive by serving as a framework for new bone development (Naik et al., 2013).

Li et al. (2018) conducted an in vitro study to investigate the effect of PRF exudates on human periodontal ligament cells. It was demonstrated that PRF enhances the process of periodontal tissue regeneration. Liu et al. (2019) also suggested that the PRF scaffold favours and promotes osteogenesis. In a naturally healing extraction socket, the empty space becomes occupied with a coagulum, which is later replaced by proliferating connective tissue via the activity of fibroblasts (Cardaropoli et al., 2003). Eventually, the connective tissue transforms into bone tissue, concluding the healing of the socket. The fibrin matrix and GFs released by the PRF applied in sockets promote more efficient cell migration and proliferation, thereby accelerating the bone regeneration process. It is also possible that the applied PRF membranes acted as barriers to maintain the space and allow the ingrowth of bone-forming pre-osteoblasts along with the new vasculature.

In particular, Ivanova et al. (2021) adapted the tension-free mucoperiosteal flap over the post-extraction socket to achieve primary wound closure, and they reported a highly significant 21.75% difference in new bone formation between the groups. Alzahrani et al. (2017) and Saha (2019) assessed the amount of new bone formation at various time points, and an increasing bone mass can be observed over the course of time. This progressive increase has been illustrated by Vieira et al. (2015) in experimental research in mice. Clark

et al. (2018) histomorphometrically evaluated osteogenesis in fresh extraction sockets filled with A-PRF, A-PRF + FDBA, FDBA, or natural healing. Sockets treated with A-PRF alone yielded more vital bone than sites treated with the combination of A-PRF and FDBA, followed by sites treated with FDBA alone.

Radiographic assessment allows the visualization of new bone formation within the socket, while histomorphometric analysis enables quantitative evaluation of bone micro-architecture (Ma et al., 2020). Both techniques can undoubtedly provide an overview of the bone tissue quantity within the socket. However, it must be acknowledged that periapical radiographs and sections of CBCT images are merely two-dimensional representations of a three-dimensional structure. With the retrieval of bone core biopsies and the subsequent histological processing, calculation of the definite bone quantity is made possible. Nevertheless, this quantification is still confined to the actual trephined portion. Whether or not it can be applied to the entire extraction socket as a whole remains unspecified.

The result of this study is in accordance with a pilot study evaluating new bone formation in sinus floor augmentation with injectable-PRF-soaked collagen plug (Gulsen & Dereci, 2019). The appreciable quantity of osteogenesis in turn sustains the bone volume in the socket, thereby reducing the necessity of an often-needed ridge augmentation procedure in a non-preserved post-extraction socket prior to dental implant placements.

Heterogeneity of the measuring methods used by the included studies rendered the comparability between studies challenging. The lack of a sufficient number of included studies for some parameters made it difficult to draw conclusions on their clinical relevance. Future investigations should emphasize the standardization of PRF-preparation protocols and the assessment measures to ensure the power and reliability of reviews.

Conclusions

In conclusion, the analysis of the included studies suggested that the clinical application of PRF into fresh sockets following atraumatic tooth extraction is beneficial for later dental implant placement. PRF was proven to significantly ameliorate immediate post-operative discomfort and enhance soft tissue healing. It could also reduce alveolar bone loss, with the most evident effect observed on the buccal aspect. The increased quantity of new bone formation is favourable for future tooth replacement procedures. The autograft property, simple handling, and low cost make PRF a suitable material of choice for alveolar ridge preservation. Based on our results, it is recommended to apply PRF to the post-extraction socket as the sole ARP biomaterial or in combination with bone grafts for ARP to achieve reduced post-operational morbidity, improved soft tissue healing, and enhanced bone preservation and regeneration.

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Ethical approval

No ethical approval was required for this study as it did not involve human participants, animal subjects, or sensitive data. This study falls under the category of data collection without participant identification.

Consent for publication

Not applicable.

Authors' contributions

The author(s) declare that all the criteria for authorship designated by the International Committee of Medical Journal Editors have been met. More specifically, these are: (a) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (b) Drafting the work or revising it critically for important intellectual content; AND (c) Final approval of the version to be published; AND (d) Agreement 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.

Competing interests

The author(s) declare that there are no competing interests related to this work.

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