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Does platelet-rich fibrin reduce negative postoperative outcomes in postextraction sockets?

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Abstract

Background and aim. Nowadays increasing numbers of clinical trials produce evidence that PRF may indeed reduce postoperative pain, swelling and other negative outcomes of invasive tooth extractions. However, despite the evidence in the literature, controversies remain on PRF's clinical efficiency and postextraction socket (PS) preservation in comparison with blood clots filled in PS. The aim of this study is to quantitatively evaluate the influence of platelet-rich fibrin with leukocytes in postextraction sockets on postoperative pain and swelling outcomes.

Materials and methods. The literature search was conducted in PubMed and ScienceDirect databases. Only split-mouth randomized clinical trials adhering to eligibility criteria were included. Postoperative pain and swelling data were extracted to quantitatively evaluate the effect on different periods: 1st, 3rd, 7th postoperative days.

Results. 5 studies have satisfied all eligibility criteria and been included in this study. Only 3rd postoperative day in pain evaluation statistically significant result favors PRF been noticed. Swelling evaluation could not be analyzed quantitatively because of different facial swelling measurements used between articles. Despite that, 4 of 5 articles showed statistically significant results favors PRF in the 1-4 postoperative days period.

Conclusion. Within the limitations of our study, it seems that PRF shows significant results in a reduction of postoperative pain and swelling outcomes on the most acute inflammation healing period. Despite that,

to decide whether or not PRF is relevant in clinical practice, more split-mouth randomized clinical trials with low risk of bias and the same swelling evaluation approach should be done.

Keywords: platelet-rich plasma [MeSH], post-operative pain [MeSH], socket preservation, post-operative swelling.

1. Introduction

Platelet-rich fibrin (PRF) is one of the available blood-derived products generally used to promote wound healing and coagulation (1). Ordinarily, PRF is extracted from patients' peripheral blood and through slow centrifugation fibrin scaffolding is created containing white blood cells, growth factors and other proteins, that all together promote wound healing (1,2). PRF applications are widely used in dentistry, especially in implant dentistry, alveolus surgery or tooth extractions (1–3). Arguably, third molar extractions tend to be associated with a relatively increased risk of complications after surgery, such as postoperative pain, trismus, swelling, nerve injury, bleeding, alveolar osteitis and overall compromised socket healing (4). Management of these complications or preventing them is of paramount importance in dental practices. Increasing numbers of clinical trials produce evidence, that PRF may indeed reduce postoperative pain, swelling and other negative outcomes of invasive tooth extractions (5,6). However, despite the evidence in the literature, controversies remain on PRF's clinical efficiency in reducing negative postoperative outcomes in comparison with blood clots filled in PS (4–7). Therefore, the aim of this study is to quantitatively evaluate the influence of platelet-rich fibrin (containing leukocytes) in postextraction sockets on postoperative pain and swelling outcomes.

2. Materials and methods

This study was conducted in accordance with PRISMA and Cochrane methodological recommendations for systematic reviews and meta-analysis (8,9). A research protocol and focus research question was developed based on the relevant population, intervention, comparison and outcome (PICO): does the usage of PRF in postextraction socket enhance the reduction of postoperative pain and swelling in comparison with a regular blood clot? A systematic literature search was conducted in PubMed Medline and ScienceDirect databases with the following keywords: "Platelet-rich fibrin", "PRF", "dental extraction", "socket preservation", "postextraction", "molar surgery". The search was expanded by checking for potential additional papers in the reference lists of relevant papers. Relevant studies were included in the analysis based upon the pre-defined inclusion criteria: publications available for full text and written in the English language, (P) healthy 18-70 years old patients, (I) split-mouth randomized controlled trial publications comparing PRF and (C) blood clot in postextraction sockets and (O) with at least one of these outcomes had to be evaluated in the article to be considered acceptable: postoperative pain measured in Visual Analogue Scale (VAS), postoperative facial swelling. The exclusion criteria were as follows: patients with any influential factors in wound healing, e. g. smokers, animal, retrospective, non-randomized studies, systematic reviews, case reports. Articles identified through literature search were subjected independently to inclusion and exclusion criteria. The inclusion of the articles was based on the article's relevancy and study's eligibility. Each included article was independently reviewed by two reviewers. Disagreements in terms of publications' eligibility for analysis, data collection process, risk of bias were resolved by consensus with the

expertise of the supervising experienced researcher. Data from articles were extracted in the form of variables according to the aim of this systematic review. The following data was obtained from the included articles:

- "Author(s)" – the corresponding author.
- "Year of publication" – the year in which the study was published.
- "Patients" - describes the number of patients who participated in the study as a case or control group.
- “Follow-up” – describes the sequence of post-operative follow-up dates.
- “VAS” – primary outcome measure recorded at each follow-up according to VAS.
- "Postoperative swelling” – describes the postoperative swelling at each follow-up in regards to the outcome measurement in each study.

For randomized prospective clinical studies quality assessment, we used a revised Cochrane risk of bias tool (RoB 2) (10). Relevant data, as stated previously, was collected and organized into a Microsoft excel file. Statistical analysis was performed using Review Manager 5.4 software to generate forest plots. Heterogeneity between the results of the selected studies was assessed using the I^2 test. Heterogeneity was evaluated according to Cochrane Collaboration recommendations. Since heterogeneity was present in all studies ($I^2 > 0$), a random effect model was used to perform a meta-analysis. Data is presented as mean with standard deviation, confidence interval selected at 95%.

3. Results

During the primary literature search, we identified 615 records. 587 publications left after duplicates were removed. During the first phase of literature analysis, titles and abstracts were reviewed and a total of 571 articles were excluded. The remaining 16 full-text articles were analyzed and 11 studies were excluded, as it is showcased in Figure 1. Ultimately, 5 studies have satisfied all eligibility criteria. 4 studies were evaluated to have an overall high (11,12) or some concern (13,14) and only 1 article low (15) risk of bias, as shown in Table 1. Pain evaluation results showed: (a) the 1st and 7th postoperative days (PDs) non statistically significant result favors PRF, respectively, mean difference = -0.51, P 95% CI: -1.06 to 0.04 and mean difference = -0.65, P 95% CI: -1.33 to 0.03; (b) 3rd day statistically significant result favors PRF mean difference = -1.05, P 95% CI: -2.01 to -0.10; (c) high heterogeneity levels were noticed on the 1st, 3rd, 7th PDs pain evaluations (I^2=82%, 92% and 96%). All these previous results are reflected in forest plots (Figure 2). Swelling evaluation could not be analyzed quantitatively because of different facial swelling measurements used between articles. Despite that, 4 of 5 articles showed statistically significant results favors PRF in the 1-4 PDs period (11–13,15) and only 1 article showed statistically significant result favors to PRF during the 4-7 PDs timespan (11).

Tables

Table 1. Clinical studies quality assessment (RoB 2).

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Ozgul 2015	-	-	-	+	+	-
	Asutay 2016	-	+	+	+	+	-
	Daugela 2018	+	+	+	+	+	+
	Kapse 2018	-	-	X	+	+	X
	Gupta 2020	-	-	X	-	-	X

Judgement:

X High

- Some concerns

+ Low

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Figures

Figure 1. Prisma flow diagram.

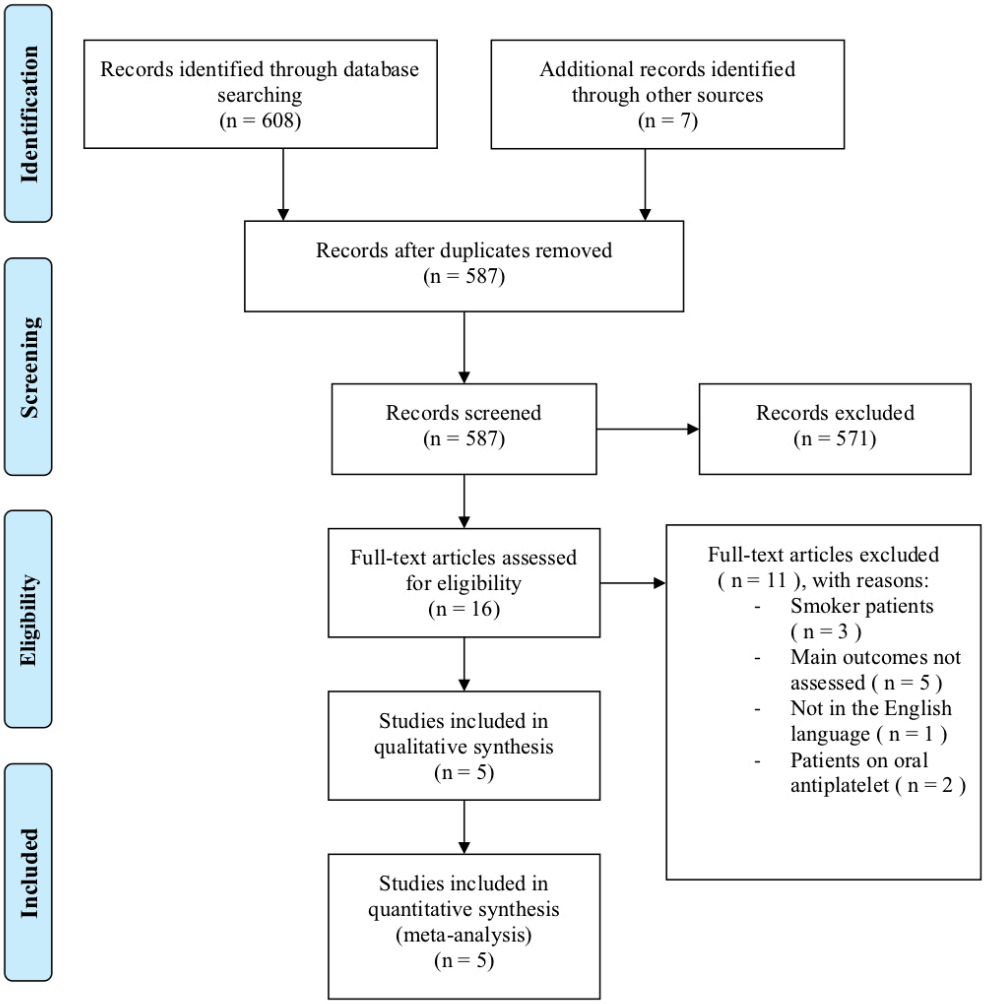
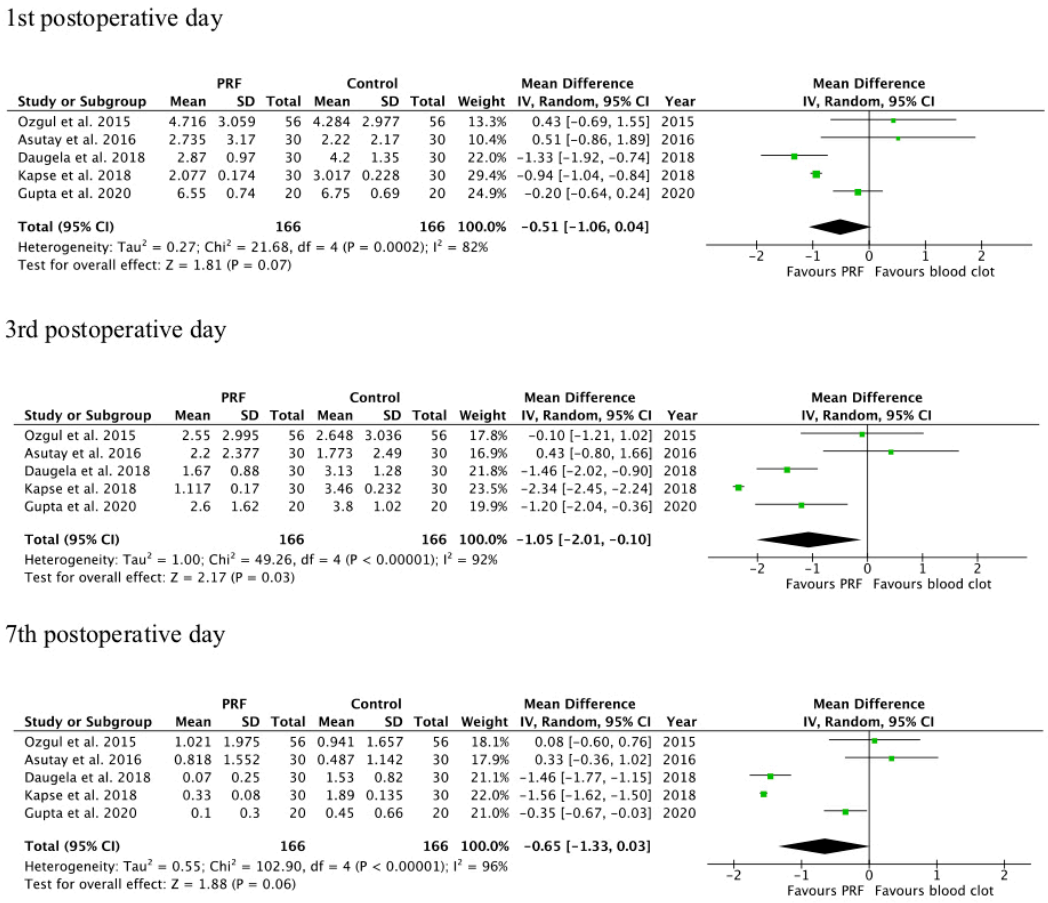


Figure 2. Random effects forest plots. Comparison of pain levels 1st, 3rd, 7th postoperative days between PRF versus blood clot filled postextraction sockets.



4. Discussion

In this systematic review we have found that PRF has a positive influence on postoperative pain reduction in postextraction sockets on the most acute inflammation healing period. Although the clinical efficacy of PRF is still a topic of controversy in dentistry, more evidence is emerging supporting the PRF use in third molar extraction surgeries.

PRF use in the context of tooth extraction is thought to generate a network of fibrin similar that of blood clot. PRF generally consists of platelets and growth factors that are enmeshed into the fibrin matrix through slow centrifugation (16–18). This fibrin matrix creates a scaffolding to enhance cell migration and differentiation (19,20). It is also known that the fibrin matrix releases growth factors over a period of 7-14 days to promote angiogenesis, these growth factors include transforming growth factor (TGF-b), vascular endothelial growth factor

(VEGF) and many other growth factors: platelet-derived growth factor (PDGF), and insulin-like growth factor (16–20). Furthermore, PRF also contains leukocytes and cytokines (such as interleukin (IL-4; IL-6; IL-1A), tumor necrosis factor), which tend to contribute to anti-infectious and tissue healing properties of the PRF (16–20). Therefore, PRF generally is thought to contribute to angiogenesis, tissue healing and wound cicatrization; and it can be hypothesized that PRF may reduce negative postoperative complications or outcomes.

In this study, quantitative analysis of postoperative swelling could not be performed due to methodological differences between the studies. However, qualitative analysis revealed that PRF does reduce swelling during the first 4 PDs of the third molar extraction healing process (11–13,15). Only one study stated otherwise (14), however, a recent systematic review also concluded that PRF had a positive effect on reducing postoperative swelling (5) but conclusions remain contradictory in other reviews and meta-analyses (4,6,7). On the other hand, it should be noted, that same as in our study, evidence could not be summarized decisively due to lack of methodologically homogeneous studies for meta-analysis, indicating the need for high-quality studies (5,7).

Regarding quantitative pain evaluation, our results indicate that the use of PRF reduce postoperative pain, however a significant result was detected only on the third day after surgery. Similar results were observed in other systematic reviews, in which pain reduction was detected when PRF had been used (4–7), although authors agreed that more studies were needed to reach a definitive conclusion.

Therefore, it is difficult to accurately estimate PRF efficiency in pain reduction, as results seem to be inconclusive. This may be related to several factors. Firstly, pain reporting may be influenced by the split-mouth evaluation, patients may have had difficulty in accurately distinguishing pain from site to site, also pain expression is the entirely subjective parameter. Another point to consider is the presence of leukocytes in the PRF. The statement that leukocytes included in platelet concentrate could negatively affect the healing process could be found in the scientific literature (21). Therefore, as an alternative for platelet-rich fibrin, PRGF (platelet concentrate without leukocytes) should be investigated in future studies for the purpose to expect a better outcome.

There are some limitations in this study. Firstly, merely one of five studies have been evaluated as low risk of bias. Secondly, postoperative swelling evaluation could not be assessed quantitatively due to different facial swelling measurements between included studies. Thirdly, a high heterogeneity level between studies been noted. Lastly, this systematic review would have qualified for highest standards of systematic reviews if it had been registered in the international register of systematic reviews and meta-analyses (PROSPERO).

Despite that, this article has some strengths as well. Firstly, inclusion criteria strictness - only split-mouth, randomized clinical trials have been included, thus, high-quality evidence is presented in this article. Secondly, patients with any influential factors in wound healing were excluded, Figure 1 shows that 3 articles had been excluded for the reason of included patients who were smokers and 2 articles had been excluded

due to the patients receiving anticoagulant therapy.

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