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Abbreviations

PRF: platelet-rich fibrin; L-PRF: leukocyte-platelet-rich fibrin; A-PRF: advanced platelet-rich fibrin I-PRF: injectable platelet-rich fibrin; P-PRF: leukocyte-poor platelet-rich fibrin; KTW: keratinized tissue width; GT: gingival thickness; CTG: connective tissue grafts; PRP: platelet-rich plasma; PDGF: platelet-derived growth factor TGF: transforming growth factor; rpm: rotations per minute; IL-1 β: Interleukins 1 beta; IL-8: Interleukins 8; IL-1Ra: interleukin 1Ra; MCP-1: monocyte chemoattractant protein-1; VEGF: vascular endothelial growth factor; RCT: randomized controlled clinical trial; CAF: coronally advanced flap

Mini Review

A Mini-review on the Impact of Platelet-Rich Fibrin on the Thickness and Width of keratinized Mucosa

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Abstract

Objectives

The present mini-review compares the effect of different forms of platelet-rich fibrin (PRF) utilized for soft tissue management on width and depth of keratinized mucosa.

Materials and methods

The Pubmed database was screened in January 2022 to find randomized controlled clinical trials examining the effect on soft tissue thickness and width by plateled-rich fibrin (PRF). In the preliminary search the following keywords were used in combination with the keyword „PRF“: “AND mucosa”, “AND keratinized mucosa”, “AND socket preservation”, “ AND recession”,and “implants”.

Results

During the literature search on Pubmed, 39 papers were found. After the initial evaluation 17 full texts were read and analyzed, eight articles that met the inclusion criteria were selected for comparison and literature review. All of the studies showed that platelet-rich fibrin (PRF) resulted in a significant increase in keratinized tissue width (KTW) and gingival thickness (GT).

Conclusion

Platelet-rich fibrin offers a valuable tool for soft tissue optimization, for example, prior to implantation or for periodontal surgery. Especially in patients with anatomical limitations, they may offer an alternative to connective tissue grafts (CTG). However, the heterogeneity of study protocols is high, making direct correlations and especially millimeter comparisons difficult. The interested practitioner should therefore carefully check which PRF type was used. One should be aware that the different PRF types each represent a different blood product.

Introduction

The use of autologous platelet and fibrin concentrates in oral and maxillofacial surgery is clinically established for decades now and has sometimes been the subject of controversial debates. The first generation of platelet concentrates was platelet-rich plasma (PRP) and growth factor-rich plasma. In the second generation, L-PRF and A-PRF were developed. L-PRF stands for leukocyte-platelet-rich fibrin. From this, advanced platelet-rich fibrin was developed. This second-generation products have the advantage of not requiring anticoagulants or bovine thrombin [2]. The regenerative potential of platelets was initially introduced in 1974 by Ross et al.(2) It was proposed that platelet-derived growth factor (PDGF) serves as growth factor with influence on fibroblasts, smooth muscle cells, and glial cells [2]. To date the presence of a variety of growth factors with different biological effects on wound healing and stabilization have been described for the second generation platelet-rich fibrin concentrates [3]. There are positive effects of PRF on the cellular level: a higher number of leukocytes and a fibrin mesh. This fibrin mesh leads to the important migration of cells, which are necessary for wound healing. Some other advantages over first-generation products are that they can be easily and cost-effectively be produced chairside and they bond faster building a complex physiological fibrin matrix that lead to a highly flexible three-dimensional mesh [1].

Depending on the manufacturing and product parameters e.g. centrifuge type, time required for preparation, platelet concentration, quality of leukocytes, preparation density and degree of polymerization, the following classification of different PRF types can be found in recent publications: [4]

P-PRF (pure platelet-rich Fibrin): Such as Fibrinet™ (Royal Biologics) [5]: Pure PRF (P-PRF) or leukocyte-poor PRF does not contain leukocytes and has a high-density fibrin network [6]. However, its strong fibrin matrix allows a handling like xenogenous derived membranes and is often applied in periodontal surgery. The main drawbacks of P-PRF are its higher costs and a complex production procedure compared to L-PRF [6]

L-PRF (leukocyte-rich Fibrin): Such as described by Choukroun et al. compares preparation formulas that led to a high-density fibrin network which contains leukocytes [4,7]. It is not possible to use this PRF-gel in an injectable form.. However, because of their strong fibrin matrix, they can likewise be handled like xenogenous derived membranes and can be applied for the treatment of periodontal bony defects, ridge preservation, sinus-floor elevation, in implant surgery, and to create L-PRF bone blocks [7]. Numerous publications report its useful effects in oral and maxillofacial [9], periodontal [10], otologic [11], and plastic surgery [12]. An example of a L-PRF clot and a matrix manufactured from it is seen in Figure 1.

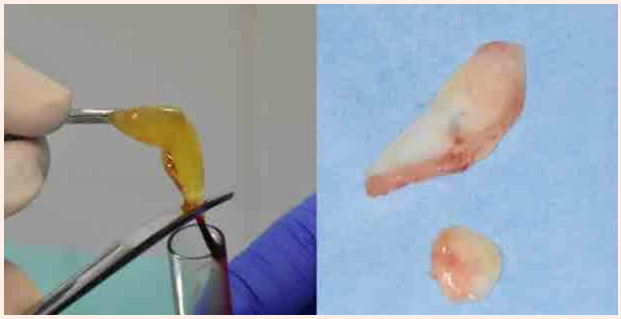

Figure 1: Left side a L-PRF clot is liberated from attached red blood clotting. Right side shows a PRF matrix that can be used as a biological membrane for recession covering or optimization for keratinized mucosa after tooth extraction.

A-PRF (advanced platelet-rich Fibrin): A-PRF + fibrin matrix showed a more porous structure, allowing more space for trapped platelets and immune competent cells. It is suggested to present a higher and more sustained release of growth factors, compared to L-PRF [13-16]. However a recent publication favors L-PRF with advanced histological and mechanical properties compared to A-PRF [17].

I-PRF (injectable platelet-rich Fibrin): Injectable PRF mainly promotes increased levels of collagen type-1, and increased levels of various growth factors (e.g., PDGF, TGF-β). It leads to increased fibroblast migration and collagen expression. The liquid form of this PRF type allows an injection (for example with sterile needle) [18,19].

T-PRF (Titanium prepared platelet-rich Fibrin): Conventional PRF is filled in glass tubes during blood collection. This glass could be a disadvantage compared to the titanium-coated surfaces, as it is hypothesized that titanium may lead to better platelet activation. The advantage of T-PRF is that epithelial cell adhesion and migration is improved compared to conventional PRF types [3,20].

Materials and Methods

The Pubmed database were searched in January 2022 to find randomized controlled clinical trials investigating the effect of plated-rich Fibrin (PRF) on thickness and width of keratinized mucosa.In the preliminary search the following keywords were applied: „PRF“: “AND mucosa”, “AND keratinized mucosa”, “AND socket preservation”, “AND recession“, “AND implant”. The selection included all studies presented in the English language. The review process included search and selection of interesting publications (identification, screening, eligibility of included studies). Within the selection process, all articles were selected by abstract and title. Abstracts were initially read by two independent researchers to identify potentially eligible full-text papers. All authors discussed and agreed upon which articles met the inclusion criteria and which articles were to exclude.

Inclusion criteria:

- Study design : Randomized controlled trials RCTs
- Population : Studies on humans
- Intervention : Test and control group differ in the presence of PRF
- Time of publication : Latest 5 years (January 2017 to January 2022)

Types of outcome:

- Keratinized tissue width (KTW) in mm
- Gingival thickness (GT) in mm

Exclusion criteria:

- no RCT
- no exact data (in millimeter) for KTW and GT
- Allogeneic material in combination with PRF

The baseline values of KTW and GT were screened and compared to the values at the evaluation time points. As an own outcome of this study, the differences of the indicated averages and median values were formed to determine the gain or loss of the KTW and GT. The data is shown in Table 2-3. We did not perform our own statistical analysis. Instead, the authors' significance calculations were presented.

Results

A literature search on Pubmed, was conducted and a total of 39 papers were found eligible for further investigation. Papers unrelated to the topic were ignored and duplicate papers were eliminated. The titles and abstracts were furthermore screened according to the inclusion and exclusion criteria. All articles that met the inclusion criteria and did not have an exclusion criterion in the abstract were read in full. This initial evaluation amounted to 17 papers. After these 17 full texts were read and analyzed, 8 articles that met the criteria as stated above were included for this mini-review [21-28]. Three articles investigated the width and thickness of the keratinized mucosa after implantation and five articles investigated changes of the keratinized mucosa after recession coverage (Miller Class I and II). All eight studies were randomized controlled clinical trials (RCT) from 2017 to 2019.

We evaluated the PRF protocols of the different RCTs and their reported effects on the change of keratinized mucosa as follows:

Turer et al. investigated I-PRF in 2020 [21], Hartlev et al. investigated A-PRF 24, two studies investigated L-PRF [22,26], two other studies investigated T-PRF [25,27], and two studies did not explicitly mention which exact type of PRF was involved [23,28]. A concise listing of the different PRF types and their exact manufacturing protocol can be found in Table 1.

Table 1: An overview of the research data over the last 5 years.

Author	Year	n	Month	Study	Test Group	Control Group	PRF	Tubes	rpm	min	g
Culhaoglu et al.	2017	63	6	RCT	CAF+PRF	CAF+CTG	L-PRF	-	2700	12	-
Kuka et al.	2017	52	12	RCT	CAF+PRF	CAF	-	glass	3000	10	-
Turer et al.	2019	72	6	RCT	CAF+CTG+PRF	CAF+CTG	I-PRF	-	700	3	60
Uzun et al.	2018	114	12	RCT	PRF	CTG	T-PRF	titanium	2700	12	-
Öncü et al.	2017	60	6	RCT	CAF+PRF	CAF+CTG	-	glass	2700	12	-
Ustaoglu et al.	2020	30	3	RCT	PRF	CTG	T-PRF	titanium	2700	12	-
Hartlev et al.	2021	27	24	RCT	AB+PRF	BB+collagen	A-PRF	glass	1300	14	208
Temmerman et al.	2018	8	1.5	RCT	PRF	FGG	L-PRF	glass	2700	12	408

Abbreviations: n: number of examined test sides in total; PRF: Platelet-Rich Fibrin; RPM: Rotations Per Minute; Min: Minutes; g: Centrifugal Force; RCT: Randomized Clinical Trial; CAF: Coronally Advanced Flap; CTG: Connective Tissue Grafts: AB: Autologous Bone; BB: Bovine Bone; FGG: Free Gingival Graft; - : Not Mentioned in the Study.

Five Studies investigated the effects of PRF in Miller classes I and II [21,22,23,27,28]: A summary of the height and width of the keratinized mucosa is comprised in Table 2 & 3.

Table 2: Keratinized Tissue Width (KTW) in mm and their gain with time in mm.

Author	Indication	Control Group			Test Group		
		T_0	T_1	diff.	T_0	T_1	diff.
Culhaoglu et al.	Miller class I	3.05	5.29*	2.24*	4.43	4.86*	0.43
Kuka et al.	Miller class I	2.95	3.60*	0.65	2.60	3.30*	0.70
Turer et al.	Miller class I and II	2.00	4.00*	2.00	2.00	4.8*	2.8*
Uzun et al.	Miller class I and II	3.50	4.25*	0.75	2.81	4.78*	1.97*
Öncü et al.	Miller class I and II	2.60	4.33*	1.73*	2.70	3.80*	1.10
Ustaoglu et al.	implants	3.56	3.83*	0.27	3.12	3.21*	0.09
Hartlev et al.	implants	-	3.40	-	-	3.15	-
Temmerman et al.	implants	5.00	4.00*	-1.00	4.50	3.25*	-1.25

Abbreviations: T_0: Pre-Operative KTW in mm; T1: KTW at evaluation time in mm; Diff: Difference in mm (T_1-T_0); *: significant.

Table 3: Gingival thickness (GT) in mm and their gain with time in mm.

		control group			test group		
Author	Indication	T_0	T_1	diff.	T_0	T_1	diff.
Culhaoglu et al.	Miller class I	1.61	2.35*	0.74*	1.75	1.86*	0.11
Kuka et al.	Miller class I	0.73	0.80*	0.07	0.78	1.31*	0.53*
Turer et al.	Miller class I and II	0.9	1.6*	0.7	0.80	1.7*	0.9
Uzun et al.	Miller class I and II	1.32	1.85*	0.53*	1.21	1.34*	0.13
Öncü et al.	Miller class I and II	0.69	0.85*	0.16	0.69	0.99*	0.3*
Ustaoglu et al.	implants	2.35	2.93*	0.58	2.24	2.62*	0.38
Hartlev et al.	implants	-	-	-	-	-	-
Temmerman et al.	implants	-	-	-	-	-	-

Abbrevations: T_0, pre-operative GT in mm; T1, GT at evaluation time in mm; diff., difference in mm (T_1-T_0); *, significant.

Turer et al. examined Miller class I and II recession coverage using coronally advanced flap (CAF), connective tissue graft (CTG), and I-PRF compared to a group in which I-PRF was omitted. After six months post-op, KTW and GT were again investigated using a probe. They concluded that both study groups had significantly increased KTW and GT post-operatively. The group using I-PRF had a significantly higher gain in KTW than the control group. In contrast, the control group had a slightly higher gain in GT (control: 0.9 mm vs. test: 0.7 mm), however, the latter result was statistically not significant [21].

Culhaoglu et al. investigated recession coverage of PRF + coronally advanced flap (PRF+CAF) in the test group versus coronally advanced flap + connective tissue graft (CAF + CTG) in the control group [22]. In contrast to Turer et al. they concluded that KTW achieved significantly higher gains in the control group (CAF + CTG). Likewise, the gain of GT in the control group was also significantly higher than in the PRF group. However, both groups achieved significant gains in KTW, leading the authors to conclude that PRF may serve as an appropriate alternative to the gold standard of CTG in recession coverage [22].

Kuka et al. focused on the same study objective like Culhaoglu et al., however, the control group only had a coronally advanaced flap (CAF) for recession coverage [23]. Within the test group, PRF + CAF were applied. The study presented the test group (PRF + CAF) being significantly superior to the control group in both KTW and GT gain [23].

Uzun et al. compared PRF and connective tissue graft (CTG) for recession coverage in Miller classes I and II [27]. Both groups were able to provide clinically satisfactory recession coverage. In fact, KTW was significantly higher in the test group (PRF) than in the control group (CTG). However, GT had significantly higher gains within the control group. Like Culhaoglu et al. before, Uzun et al. also concluded that PRF could serve as a sufficient alternative to the invasive procedure of raising a CTG [27].

Öncü et al. compared PRF and connective tissue graft (CTG) for recession coverage in Miller classes I and II but with different results as Uzun et al. [28]. Herein, the gain in KTW was significantly higher in the control group, whereas the gain in GT was significantly higher in the PRP group this time. However, both study groups produced significant gains in KTW and GT compared to the baseline [28].

A total of three papers investigated the keratinized mucosa changes (KTW + GT) in conjunction with implant insertion:

Hartlev et al. investigated PRF + autogenous bone material at timepoint of implantation compared to a bovine bone material + collagen membrane. They gave report that the mean width of the keratinized tissue around the implant was 3.15 mm in the PRF group and 3.40 mm in the control group. The difference between the groups was 0.25 mm but no statistical difference could be detected [24].

Ustaoglu et al. examined the KTW and GT after implantation by PRF versus implantation by CTG [25]. They found higher KTW and GT in both groups three months after implantation. The control group had higher gains, although these were not statistically significant. The authors concluded that PRF could be a minimally invasive alternative to the well-established CTG [25].

Temmerman et al. investigated KTW and GT after implantation by PRF versus a free gingival graft (FGG) in the control group. In the test group, T-PRF was applied instead of L-PRF. The outcome presented significantly higher KTW and GT values after six weeks in both groups. The gain in KTW was also significant in both groups compared to the baseline measurements. However, the control group had higher values compared to the T-PRF group but remained statistically not significant. Moreover GT was not part of the investigation [26].

Discussion

The aim of this mini review was to evaluate the outcome of randomized clinical trials of the last five years that investigated the biological effect of PRF with regard to width and thickness of keratinized mucosa. All studies showed that PRF resulted in an increase in KTW and GT. Moreover, in some studies, PRF was even statistically superior compared to the control group [21,23,27]. PRF could therefore be assumed as a time- and cost-effective alternative for patients who have a deficit in their KTW and GT but are unwilling to have a CTG. Apart from costs, the two most important factors that bother patients the most with CTG are a high donor site morbidity with pain and long reconvalescence as also a prolonged operating time. Furthermore, in cases, with particularly large and extensive recession coverings, a CTG may come to its anatomical limits. Especially in these cases PRF alone or in combination with a xenogenous derived collagen matrix may offer a sufficient alternative. Although there are a rising number of publications that cover the application of PRF for soft tissue management, typical problems of clinical studies increasingly emerge. A major limitation factor is the diversity of different PRF protocols. Most authors did not even report the exact centrifugal force, although according to Ghanaati et al. this aspect is crucial for the composition and the biological effects of the underlying PRF [29]. The latter aspect reveals an ongoing point of discussion: most available publications to date show a significant biological effect of PRF on the particular study objective but the exact biological and physical characteristics of the different PRF types are not well understood and reported to date. The different PRF types show highly different characteristics of the PRF clot, the underlying fibrin matrix, the cell types as also the growth factors contained. This clearly indicates that different PRF types represent completely different blood products, an aspect which must be considered in future clinical studies. Otherwise a useful comparison is impossible. Furthermore, the studies investigated KTW and GT at inconsistent time points over a large time span (6 weeks to 24 months), which also prohibits adequate interstudy comparability. Apart from these two aspects of heterogeneity the direct comparison of KTW and GT increment in millimeter is furthermore denied from a statistical point of view – both are sometimes

reported as median, sometimes reported as mean values. Hence, we present the basically detectable biological effect of gain in KTW and GT as individual and absolute values which are listed per study in Table 2 & 3.

Conclusion

An increasing number of randomized controlled clinical trials give report of a sufficient gain of keratinized mucosa both in width and thickness, when PRF is applied. Since PRF is a safe, fast and cost-effective chairside method further reports will follow soon. Especially, since PRF shows very promising results when compared to the free connective tissue craft, which has per se a significant higher donor morbidity. For better comparison of gain in millimeters future studies should include a proper report of PRF type, manufacturing method, applied devices as also the evaluation time points. The practitioner should be aware of the fact that different PRF types are different blood products that may lead to different biological effects, thus, an adequate research must be performed upfront to find a method that will achieve the desired results.

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