Does the Choice of Preparation Protocol for Platelet-Rich Fibrin Have Consequences for Healing and Alveolar Ridge Preservation After Tooth Extraction? A Meta-Analysis

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Purpose: Multiple preparation protocols for platelet-rich fibrin (PRF) are in use today, and clinical results are often heterogeneous. This study analyzes the impact of the chosen PRF preparation protocol on *1)* wound healing and *2)* alveolar ridge preservation.

Methods: For this systematic review and meta-analysis, eligible studies were identified in PubMed and Cochrane databases. Included were randomized controlled and controlled clinical trials with healthy patients treated with PRF after atraumatic tooth extraction compared to untreated socket(s), reporting at least one of the following outcome variables: pain, swelling, soft tissue healing, alveolar osteitis risk, horizontal and vertical bone loss, socket fill, and new bone formation. Main predictor variable was relative centrifugal force (RCF) comparing high RCF (high PRF), intermediate RCF (standard [S-PRF]), low RCF (advanced PRF), and various RCF settings (concentrated growth factor preparation [CGF]). The type of centrifugation tubes (silica-coated plastic and glass) was a secondary predictor. Weighted or standardized mean differences, risk ratio and corresponding 95% confidence intervals were calculated.

Results: Forty studies published between 2012 and 2022 were selected. The pooled effects of all outcomes were significant against untreated sockets. Within the subgroups high PRF or advanced PRF had the lowest efficacy for many outcome parameters. Pain reduction (in visual analog scale units) was highest for S-PRF (−1.18 [−1.48, −0.88], $P < .00001$) and CGF (−1.03 [−1.16, −0.90], $P < .001$). The risk ratio of alveolar osteitis (0.09 [0.01, 0.69], $P < .02$) and soft tissue healing (standardized mean difference = 2.55 [2.06, 3.03], $P < .001$) were best for CGF. No subgroup differences were found for bone-related outcomes. No meaningful analysis of the tube material effect was possible.

Conclusion: This study confirms that PRF is associated with reduced postoperative complications but indicates that preparation protocol influences clinical outcomes. S-PRF and CGF protocols appear to be superior for several outcome parameters.

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Platelet-rich fibrin (PRF) has gained popularity in recent years as a therapy to both reduce various complications after tooth extractions, such as pain, edema, trismus, and alveolar osteitis, and to aid in preserving alveolar ridge dimensions. PRF is an autologous material derived from the patient's blood[1] and was originally developed by Choukroun et al as a second-generation platelet concentrate.[2] It is formed by gradual fibrin polymerization during centrifugation and does not require anticoagulants or activators. PRF consists of a fibrin matrix with embedded platelets, circulating stem cells, and leukocytes.[1-3] Preserving the activity of the embedded cells is crucial, as both leukocytes and platelets are important players in wound healing processes.[4,5] They are responsible for the activation and release of biomolecules that can stimulate cell recruitment, proliferation, remodeling, and differentiation of cells involved in the wound healing process.[6] The simplicity of preparation is an advantage of PRF and has contributed to its rise in popularity, but the clinical research to date has shown a controversial effect of PRF on wound healing parameters as well as on the preservation of the alveolar ridge. Several reviews[7-9] aim to increase the level of evidence, but clear conclusions are still lacking due to the limited number of included studies and heterogeneity among studies.

A major source of this heterogeneity can be found in the employed PRF preparation protocols. Here multiple modifications were made, especially during the last decade, and even protocols initially held to be identical can differ in potentially critical details. These are, in particular, the relative centrifugal force (RCF) and the material of the centrifuge tubes. Recent in vitro research has shown that both factors significantly influence the size and stiffness of the fibrin network, the content and distribution of platelets and leukocytes, and the release of growth factors by these cells.[10-14] This significantly impacts the quality of the fibrin clots obtained and thus potentially the clinical efficacy of different PRF preparations.

Special emphasis must be placed on the fact that not the rotations per minute (rpm) are important for the quality of the obtained clot but instead the actual RCF.[11] The RCF value depends on the specific combination of used rpm and centrifuge rotor so similar rpm can result in different RCF values. Thus the original protocol of 3,000 rpm for 10 minutes[3] always results in high RCF values, while the current standard protocol of 2,700 rpm for 12 minutes usually gives a range of intermediate ones. A so-called advanced protocol is based on yet lower RCF values, and a fourth protocol variation that uses a preset sequence of four centrifugation speeds includes both intermediate and high RCF values (known as concentrated growth factor instead of PRF preparation). The tube materials used for PRF preparation are glass, silica-coated plastic, or simple plastic tubes.

It is the purpose of this study to determine if differences in PRF preparation protocol are a potential cause for the observed heterogeneity of PRF benefit in clinical studies. The hypothesis is that different preparation protocols with varying RCF values and different centrifugation tube materials impact PRF quality and thus ultimately clinical PRF efficacy.

To test this hypothesis, we performed a meta-analysis of PRF efficacy with protocol type as the main predictor variable. We analyzed subgroup effects of the four protocols described above. The used centrifuge tubes were considered as secondary predictors. The specific aims of this study were to determine which clinical outcomes are potentially affected by the two predictor variables, and if there is any protocol type or tube material which benefits patients to a larger and more reliable degree.

Materials and Methods

This systematic review and meta-analysis was structured and performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[15] The search strategy of this thesis was designed after defining the population, intervention, comparison, outcomes, study design elements (Table 1). With the aim of elucidating potential sources for observed heterogeneity in the clinical application of PRF the central question was the following: are there any differences in the impact of PRF on bone and general healing parameters depending on the applied preparation protocol as well as type of centrifugation tubes used? The following preparation protocol subgroups were assigned: *1)* high (H-PRF)—high centrifugation forces with RCF values above 850 g, *2)* intermediate (S-PRF)—intermediate centrifugation forces with RCF values between 650 and 708 g, *3)* low force subgroup (A-PRF)—low centrifugation forces with RCF values between 198 and 214 g, and *4)* concentrated growth factor (CGF)—all studies performed with specific Medifuge protocol using several alternating RCFs.

ELIGIBILITY CRITERIA

Included were randomized controlled trials or controlled clinical trials with the following inclusion criteria: healthy patients treated with PRF after tooth extraction compared to patients left for natural healing and reporting at least one of the outcome parameters listed in Table 1. Excluded were all other treatments used to promote healing after extraction (eg, fibrin glue, platelet-rich plasma, plasma rich in growth factors, enamel matrix derivative, or recombinant growth

Table 1. PICOS FRAMEWORK APPLIED AS BASIS FOR THE SYSTEMATIC SEARCH

Criterion	Details
Population (P)	systemically healthy patients with simple or surgical tooth extraction
Intervention (I)	addition of H-PRF, S-PRF, A-PRF, or CGF
Comparison (C)	extraction sockets left to natural healing without any intervention
Outcomes (O)	*1)* for general healing: pain, swelling, soft tissue healing indices, development of alveolar osteitis *2)* for bone healing: vertical and horizontal bone resorption, new bone formation, socket fill
Study design (S)	randomized or controlled clinical trials

Abbreviations: A-PRF, advanced relative centrifugal force values; CGF, concentrated growth factor; H-PRF, high relative centrifugal force values; S-PRF, standard relative centrifugal force values; PICOS, population, intervention, comparison, outcomes, study design.

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factors). Also excluded were studies on periodontal intrabony and furcation defects, periodontal plastic surgery, palatal cleft, or surgery in combination with sinus augmentation. Studies comparing PRF to other bone substitutes without a control group of empty sockets were also disregarded. Articles representing reviews or based on prospective and retrospective cohort studies and case-series, studies including fewer than five sockets per group, in vitro studies, animal studies, and studies not published in English were also not considered.

SEARCH STRATEGY

For a systematic and comprehensive search in the databases PubMed, the Cochrane Library, Embase, combinations of the following search terms were used: "platelet-rich fibrin" or "PRF" with "tooth extraction", and "post extraction", "extraction sockets", "bone regeneration", "bone healing", "soft tissue healing", "wound healing" and "alveolar osteitis". Additional studies were identified by hand searching the reference lists of the included studies and relevant reviews and by citation screening. The search was independently conducted by two authors (A.A. and C.W.B.) from March 2021 to December 2021, with the last search performed on December 10, 2021.

SCREENING AND SELECTION OF STUDIES

Titles and abstracts obtained were independently screened by two authors (A.A. and C.W.B.). If sufficient information was not provided, the full-text article was obtained. After the removal of duplicates, full-text versions of all the eligible hits were examined independently by both the reviewers. The final selection of publications was based on the pre-established eligibility criteria. Any inconsistencies were resolved by open discussion to achieve a consensus. In case a disagreement was not resolved, the third author (S.B.) was consulted. The inter-rater reliability between the two main reviewers was determined by kappa value using a free online calculator (GraphPad Software, Inc, La Jolla, CA, http://graphpad.com/quickcalcs/kappa1.cfm).

DATA EXTRACTION AND QUALITY ASSESSMENT

The risk of bias was evaluated using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2)[16] based on these domains: random sequence generation, allocation concealment, blinding of patients, study personnel and blinding of outcome assessment, completeness of data, selective reporting of outcomes, and other bias. The latter was used if no study registration protocol was shown, since this meant that the primary outcomes of interest could not be identified and the completeness of publication could not be judged. The risk level ratings assigned to the described domains were either high, low, or unclear.

The overall risk of bias was categorized as follows: *a)* low risk, if five areas of the study are judged as low risk, *b)* some concerns, if the study is judged as unclear risk in at least one area, and *c)* high risk, if at least one domain was judged to be high risk or if multiple domains were judged to have unclear risk. This was considered to be particularly relevant for the categories blinding and the description of the exact protocol (assessed in the category others). Inter-rater reliability for the risk of bias assessment was calculated similarly to study selection and expressed by means of the kappa value.

Information on used protocol details was extracted from published articles. If such information, in particular on applied RCF, was not available, the authors were contacted via email or technical information from respective centrifuges were used for own calculations.

Data were extracted independently by two investigators (A.A. and C.W.B.). Analysis was based on eight different outcome parameters, in each case comparing untreated healing (empty sockets) to PRF-assisted healing. For some outcome parameters,

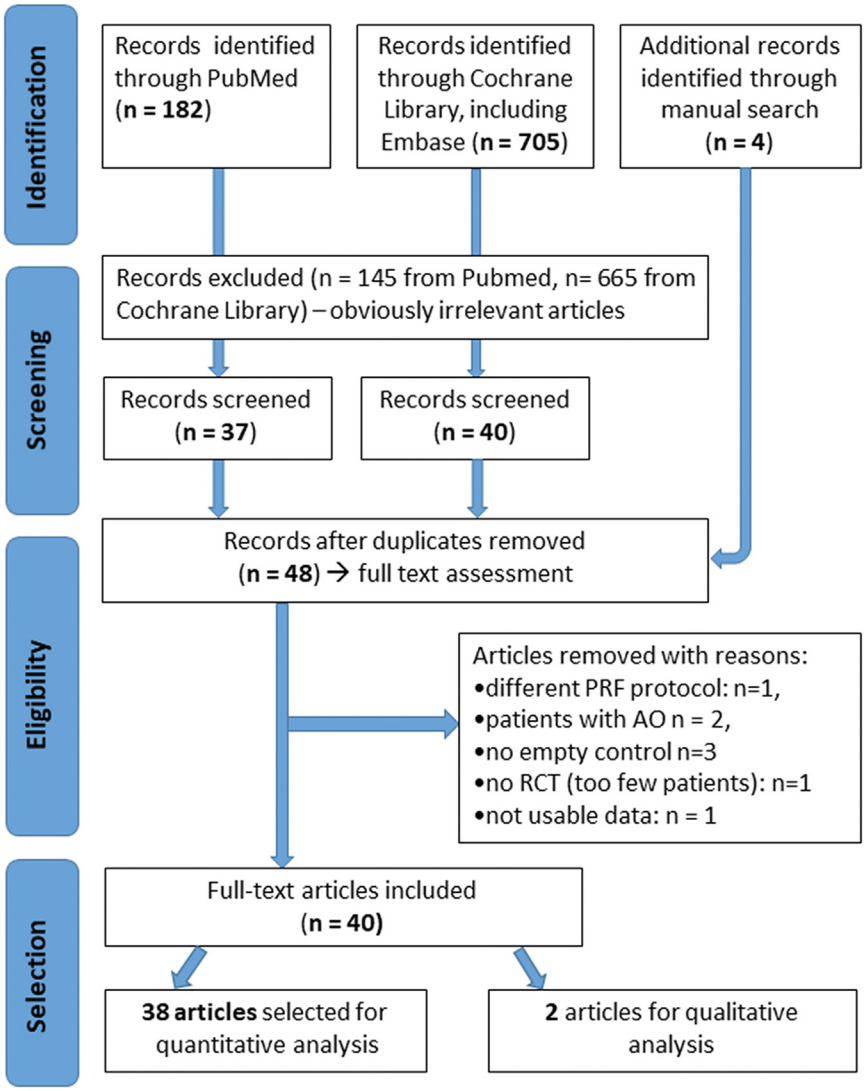

FIGURE 1. Schematic representation of the study selection process.

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transformation of the original published data was necessary for the following reasons:

All included studies used the visual analog scale (VAS) to assess pain, with the majority applying scores from 0 to 10. Studies with scores from 0 to 100 were transformed to fit into this scale so that mean differences (MDs) between both groups could be calculated in score units referring to a scale from 0 to 10. For the parameter swelling the evaluation method varied consistently among studies. A majority of studies reported outcomes for 3 lines: from the tragus to the pogonion, from the tragus to the corner of the mouth, and from the lateral corner of the eye to the angle of the mandible. Others presented data for only 2 lines assessed as vertical and horizontal swelling. For this reason, an average swelling was calculated as a new summary parameter. If data for day 2 was not provided, it was calculated as an average of day 1 and day 3 data.

Soft tissue healing was assessed in the selected studies by means of three different healing scores. The majority of the studies reported their data according to Landry[17] (score 1 to 5 with best healing in level 5). Other studies used either the modified healing index (score 4 to 12) according to Mozzati et al[18] or the new socket wound healing index (score 0 to 4). As these two indices assign the best healing to the lowest score, the respective data were multiplied with a factor of -1 to calculate the pooled effect according to chapter 9.2.3.2 of the Cochrane handbook.

Data for horizontal bone resorption were reported in original studies either for specific positions (buccal, lingual, mesial or distal) at three different heights or

Table 2. DESCRIPTION OF STUDY CHARACTERISTICS

First Author/yr	Study Type	EM	Location of Sockets	PRF-Protocol (Classification, rpm, time, Centrifuge Type, RCF, tube Type)	Blood in ml/ Number, Type of Applied Material per socket	Number of Patients/Sockets in: PRF	Number of Patients/Sockets in: Control	Sex of Patients	Mean age ± SD or Range (yr)	Smoking Status	Outcomes Extracted (with Respective Follow-up)
Afat/2018[34]	RCT parallel	T	MTM	**H-PRF**: 3,000 rpm, 10 min, ElectroMag 615P, **905 g***, **sc plastic**	2 × 10 ml, 1 plug & 1 membrane	20 Pt. 20 Skt.	20 Pt. 20 Skt.	38 F, 22 M	(18-30)	all NS	pain (1 d, 3 d, 7 d), swelling (2 d, 7 d)
Afat/2019[35]	RCT parallel	T	MTM	**H-PRF**: 3,000 rpm, 10 min, ElectroMag 615P, **905 g***, **sc plastic**	2 × 10 ml, 1 plug & 1 membrane	20 Pt. 20 Skt.	20 Pt. 20 Skt.	38 F, 22 M	22.3; (18-30)	all NS	soft tissue healing (7 d, 14 d), development of AO (PO)
Al-Hamed/ 2016[36]	RCT Mostly parallel	T	MTM	**H-PRF**: 3,000 rpm, 10 min, 80-1, RCF: NM, **glass**	1 × 5 ml 1 plug	24 Pt. 25 Skt.	23Pt. 25 Skt.	37 F, 13 M	T: 25.8 ± 6.72 C: 24.68 ± 7.4	NM	pain (3 d, 7 d), soft tissue healing (7 d), development of AO (PO)
Alzharani/ 2017[37]	RCT parallel	NT	NM	**H-PRF**: 3,000 rpm, 10 min, Hermle**, 865 g,** tubes: NM	2 × 10 ml 2 membranes	12 Pt. 12 Skt.	12 Pt. 12 Skt.	15 F, 9 M	37.8 (25-50)m	all NS	horizontal bone resorption, socket fill (2 m)
Aravena/ 2021[38]	RCT split-mouth	NT	max. third molar	**S-PRF**: 2,700 rpm, 12 min, Intra-Spin, **708 g**, **glass**	8 × 10 ml, 4 - 6 membranes	16 Pt. 16 Skt.	16 Pt. 16 Skt.	56% F	24.75	all NS	horizontal & vertical bone resorption (3 m), soft tissue healing (7d)
Areewong/ 2019[39]	RCT parallel	NT	premolar & max. anterior	**S-PRF**: 2,700 rpm, 12 min, Intra-Spin, **708 g**, **sc plastic**	1 × 10 ml 1 plug	18 Pt.	18 Pt.	21 F, 15 M	50 ± 67; (22-73)	no HS	New Bone Formation (2 m)
Asmael/ 2018[40]	RCT split-mouth	T	multiple extractions	**H-PRF**: 3,000 rpm, 10 min, Xiangtian 80-1, **1008 g**, **glass**	1 x 5 - 10 ml 1 plug	20 Pt. 20 Skt.	20 Pt. 20 Skt.	20 M	44.2; (18-72)	all S	soft tissue healing (7 d), development of AO (PO)

Table 2. Cont'd

First Author/yr	Study Type	EM	Location of Sockets	PRF-Protocol (Classification, rpm, time, Centrifuge Type, RCF, tube Type)	Blood in ml/ Number, Type of Applied Material per socket	Number of Patients/Sockets in: PRF	Number of Patients/Sockets in: Control	Sex of Patients	Mean age ± SD or Range (yr)	Smoking Status	Outcomes Extracted (with Respective Follow-up)
Asutay/ 2017[22]	RCT split-mouth	T	MTM	**S-PRF**: 2,700 rpm, 12 min, Centrifuge, RCF and tubes: NM	1 × 10 ml 1 plug	30 Pt. 30 Skt.	30 Pt. 30 Skt.	24 F, 6 M	20.32; (18 - 29)	all NS	pain (1 d, 3 d, 7 d), swelling (2 d, 7 d), development of AO (PO)
Baslarli/ 2015[41]	RCT split-mouth	T	MTM	**H-PRF**: 3,000 rpm, 10 min, Centrifuge, RCF: NM, **glass**	1 × 9 ml 1 membrane	20 Pt. 20 Skt.	20 Pt. 20 Skt.	13 F, 7 M	23.9; (19-34)	all NS	development of AO (PO)
Bilginaylar/ 2016[20]	RCT, partial split-mouth	T	MTM	**H-PRF**: 3,000 rpm, 10 min, ElectroMag M415P, **905 g***, **sc plastic**	1 × 10 ml 1 plug	20 Pt. 20 Skt.	20 Pt. 20 Skt.	23 F, 17 M	(18-31)	all NS	pain (1 d, 3 d, 7 d), swelling (2 d, 7 d)
Canellas/ 2020[42]	RCT parallel	NT	non-molar	**S-PRF**: 2,700 rpm, 12 min, Intra-Spin, **708 g, sc plastic**	6 × 9 ml 4 plugs, 2 membranes	24 Pt. 24 Skt.	24 Pt. 24 Skt.	27 F, 21 M	(17-65)	all NS	horizontal & vertical bone resorption (3 m), new bone formation (3 m)
Castro-a/ 2021[30]	RCT, split mouth	NT	max. & mand. anterior	**S-PRF**: 2,700 rpm, 12 min, Intra-Spin, **708 g**, **sc plastic**	4 × 9 ml 2 -3 membranes	20 Pt. 20 Skt.	20 Pt. 20 Skt.	15 F, 6 M	NM	3 S 17 NS	horizontal & vertical bone resorption (3 m)
Castro-b/ 2021[30]				**A-PRF**: 1,300 rpm, 8 min, DUO Process, **207 g**†, **glass**	4 × 10 ml 2 -3 membranes	20 Pt. 20 Skt.	20 Pt. 20 Skt.				
Clark/2018[31]	RCT parallel	NT	non-molar	**A-PRF**: 1,300 rpm, 8 min, Centrifuge: NM, **200 g**, **glass**	1 × 10 ml, 1 plug & 1 collagen dressing	10 Pt. 10 Skt.	10 Pt. 10 Skt.	22 F, 18 M	58	all NS	horizontal & vertical bone resorption (15 w), Vital Bone Formation (15 w)

Daugela/ 2018[43]	RCT split-mouth	T	molar	**S-PRF**: 2,800 rpm, 12 min Hettich EBA 20, **761 g**, **sc plastic**	2 × 10 ml 2 plugs	34 Pt. 34 Skt.	34 Pt. 34 Skt.	20 F, 14 M	22.76 ± 2.02	all NS	pain (1 d, 3 d, 7 d), soft tissue healing (3 d, 7 d, 14 d)
De Almeida Barros Mourão/ 2020[44]	RCT parallel	NT	max. & mand posterior, no third molar	**S-PRF:** 2700 rpm, 12 min, Intra-Spin, **708 g, sc plastic**	4 × 10 ml 2 membranes	16 Pt. 16 Skt.	16 Pt. 16 Skt.	19 F, 13 M	37; (19-57)	all NS	pain (PO), soft tissue healing (7 d)
Eshghpour/ 2014[45]	RCT split-mouth	T	MTM	**H-PRF:** 3,000 rpm, 10 min, Labofuge 400R, RCF & tubes: NM	1 × 10 ml 1 plug	78 Pt. 78 Skt.	78 Pt. 78 Skt.	33 F,45 M	25; (18-35)	all NS	development of AO (PO)
Eshghpour/ 2018[46]	RCT split-mouth	T	MTM	**H-PRF**: 3,000 rpm, 10 min, Centrifuge, RCF and tubes: NM	1 × 10 ml 1 plug	118 Pt. 118 Skt.	118 Pt. 118 Skt.	69 F, 49 M	23.9	all NS	Development of AO (PO)
Gnatek/ 2019[47]	RCT split-mouth	NT	NM	**CGF** Medifuge protocol: Medifuge MF200, **692, 547, 692**, **855g**, **unspecified plastic tubes**	9 ml tubes 1 or more plugs up to alveolar ridge (+1 membrane if needed)	20 Pt. 20 Skt.	20 Pt. 20 Skt.	NM		NM	pain (1 d, 7 d in NRS-groups)
Gülşen/ 2017[48]	RCT split-mouth	T	MTM	**H-PRF**: 3,000 rpm, 10 min**,** NUVE NF 200, **1016 g, sc plastic (+ silicone)**	3 × 10 ml 3 membranes	30 Pt. 30 Skt.	30 Pt. 30 Skt.	9 F, 21 M	(17–27)	NM	pain (1 d, 7 d), Swelling (2 d, 7 d)
Hauser-a/ 2013[49]	RCT parallel	17 NT	premolar	**S-PRF**: 2,700 rpm, 12 min, Progress PC02, **650 g**, **sc plastic**	4 × 8 ml, 4 membranes	9 Pt. 9 Skt.	8 Pt. 8 Skt.	14 F, 9 M	47 (22-75)	NM	horizontal bone resorption (2 m), new bone formation (2 m)
Hauser-b/ 2013[49]		6 T, 8 NT			4 × 8 ml, 4 membranes	6 Pt. 6 Skt.	8 Pt. 8 Skt.				
Ivanova/ 2021[50]	RCT parallel	T	no third molar	H-PRF (according to Choukroun) further details: NM	NM	30 Pt.	30 Pt.		30 F,		

Table 2. Cont'd

First Author/yr	Study Type	EM	Location of Sockets	PRF-Protocol (Classification, rpm, time, Centrifuge Type, RCF, tube Type)	Blood in ml/ Number, Type of Applied Material per socket	Number of Patients/Sockets in: PRF	Number of Patients/Sockets in: Control	Sex of Patients	Mean age ± SD or Range (yr)	Smoking Status	Outcomes Extracted (with Respective Follow-up)
Kapse/2019[25]	RCT split-mouth	T	MTM	**H-PRF**: 2,700 rpm, 12 min, REMI R-4C DX, **1100 g***, **glass**	1 × 10 ml, 1 plug	30 Pt. 30 Skt.	30 Pt. 30 Skt.	17 F, 13 M	25.47 (18-40)	NS during study	pain (1 d, 3d, 7 d), swelling (1 d, 3 d, 7 d)
Koyuncu 2020-1[51]	RCT split-mouth	T	MTM	**CGF**: Medifuge, **692, 547, 692, 855g**, **sc glass**	2 × 9 ml 2 (?) plugs	60 Pt. 60 Skt.	60 Pt. 60 Skt.	39 F, 21 M	25.82 (18-35)	all NS	pain (1 d, 3 d, 7 d), swelling (3 d, 7 d), soft tissue healing (3 d, 7 d), development of AO (PO)
Koyuncu 2020-2[52]	RCT split-mouth	T	MTM	**CGF**: Medifuge, **692, 547, 692, 855g**, **sc glass**	2 × 9 ml 2 (?) plugs	70 Pt. 70 Skt.	70 Pt. 70 Skt.	44 F, 26 M	25.86; (18–35)	all NS	development of AO (PO)
Kumar/ 2015[53]	RCT parallel	T	MTM	**H-PRF**: 3,000 rpm, 10 min, Centrifuge, RCF and tubes: NM	1 × 5 ml 1 plug	16 Pt. 16 Skt.	15 Pt. 15 Skt.	NM	26.1; (19-35)	NM	swelling (1 d),
Kumar/ 2018[54]	RCT, partly split-mouth	NT	anterior	**H-PRF**: 3,000 rpm, 10 min, Centrifuge, RCF and tubes: NM	1 × 10 ml 1 plug	NM 30 Skt.	NM 30 Skt.	40 F, 20 M	44.4; (18-60)	NM	horizontal & vertical bone resorption (6 m)
Ma/2021[55]	RCT parallel	NT	molar and premolar	**CGF**: Medifuge, **692, 547, 692, 855g**, **sc plastic**	2 × 9 ml, 1 plug + 1 membrane	23 Pt. 23 Skt.	23 Pt. 23 Skt.	18 F, 28 M	43.98 ± 13.8	no HS	horizontal & vertical bone resorption (3 m), Vital Bone Formation (3 m)
Makki-a/ 2021[32]	RCT parallel	17 NT, 23 T	max., mand. posterior	**S-PRF**: 2,700 rpm, 12 min, Medifuge, **692 g**, **glass**	1 × 10 ml 1 membrane	20 Pt.	20 Pt.	31 F	(18-60)	NM	soft tissue healing (7 d, 14 d)
Makki-b/ 2021[32]		17 NT, 23 T		**A-PRF**: 1,500 rpm, 14 min Medifuge, **214 g**, **glass**	1 × 10 ml 1 membrane	20 Pt.	20 Pt.	29 M			

Marenzi/ 2015[56]	RCT split-mouth	NT	canine, premolar and molar	**S-PRF**: 2,700 rpm, 12 min Intra-Spin, **708 g, sc plastic**	2-6 x 9 ml, 1 plug (condensed)	26 Pt. 54 Skt.	26 Pt. 54 Skt.	17 F, 9 M	53 ± 4	no HS	pain (1 - 3 d), soft tissue healing (7 d, 14 d)
Martins/ 2021[26]	RCT parallel	T	max. anterior	**S-PRF**: rpm: NM, 12 min, Centribio 80-2D, **400 g**†, tubes: NM	1 x 8-10 ml 1 plug	5 Pt. 5 Skt.	5 Pt. 5 Skt.	NM	47.13; (31-66)	all NS	percentage of mineralized tissue
Nourwali/ 2021[57]	CCT parallel	T	MTM	**H-PRF**: 3,000 rpm, 10 min, UNICO power spin, **1028 g**, tubes: NM	1 × 10 ml 1 membrane	10 Pt.	10 Pt.	NA	(18-40)	NM	soft tissue healing (14 d), swelling (2 d)
Ozgul/2015[58]	RCT split-mouth	T	MTM	**H-PRF**: 3,000 rpm, 10 min, Centrifuge and RCF: NM, **sc plastic**	1 × 10 ml 1 membrane	56 Pt. 56 Skt.	56 Pt. 56 Skt.	33 F/23 M	(18- 28)	NM	pain (1 d, 3 d, 7 d), swelling (1 d, 3 d, 7 d),
Ritto/2019[59]	RCT split-mouth	T	MTM	**S-PRF**: 2,700 rpm, 12 min, Centrifuge and tubes: NM, **400 g**†	2 × 10 ml 2 plugs	20 Pt. 20 Skt.	20 Pt. 20 Skt.	12 F/8 M	21.8; (16–29)	all NS	pain (1 d, 3 d, 7 d),
Suttapreyasri/ 2013[60]	RCT split-mouth	NT	max. & mand. premolar	**H-PRF**: 3,000 rpm, 10 min, Hettich EBA 20, **865 g**, **glass**	1 × 10 ml 1 plug	8 Pt. 10 Skt.	8 Pt. 10 Skt.	5 F, 3 M	22.26 ± 2.44	NM	soft tissue healing (1, 2 w), horizontal & vertical bone resorption (2 m)
Temmerman/ 2016[61]	RCT split-mouth	NT	Incisors, canines, premolar	**S-PRF**: 2,700 rpm, 12 min, Intra-Spin, **708 g, sc plastic**	8 × 10 ml 2-5 plugs, condensed	22 Pt. 22 Skt.	22 Pt. 22 Skt.	7 F, 15 M	54 ± 11	all NS	pain (3 d, 7 d), horizontal & vertical bone resorption (3 m), socket fill (3 m)
Torul-a/ 2020[23]	RCT parallel	T	MTM	**A-PRF**: 1,300 rpm, 14 min, DUO process, **198 g, glass**	1 × 10 ml, 1 plug	25 Skt.	25 Skt.	52 F, 23 M	22.13; (18-40)	all NS	pain (1 d, 3 d, 7 d), swelling (2 d, 7 d)
Torul-b/ 2020[23]				**CGF**: Medifuge, **692, 547, 692, 855g**, **sc plastic (Vacutainer)**	1 × 10 ml, 1 plug	25 Skt.	25 Skt.				

Table 2. Cont'd

First Author/yr	Study Type	EM	Location of Sockets	PRF-Protocol (Classification, rpm, time, Centrifuge Type, RCF, tube Type)	Blood in ml/ Number, Type of Applied Material per socket	Number of Patients/Sockets in: PRF	Number of Patients/Sockets in: Control	Sex of Patients	Mean age ± SD or Range (yr)	Smoking Status	Outcomes Extracted (with Respective Follow-up)
Trybek/ 2021[62]	CCT parallel	T	MTM	**S-PRF**: 2,700 rpm, 12 min, EBA-200, **701 g**, tubes NM	2 × 10 ml, 1 plug & 1 membrane	45 Pt.	45 Pt.	62 F, 28 M	(18-37)	all NS	pain (1 d, 3 d, 7 d), swelling (2 d, 7 d),
Unsal/2018	RCT split-mouth	T	MTM.	**H-PRF**: 3,000 rpm, 10 min, Nuve NF 200, **1016 g*, sc plastic**	1 × 10 ml, 1 plug	50 Pt. 50 Skt.	50 Pt. 50 Skt.	33 F, 17 M	23.96; (15-43)	NM	pain (1 d, 3 d, 7 d), development of AO (PO)
Uyanik-a/ 2015[21]	RCT split-mouth	T	MTM	**H-PRF**: 3,000 rpm, 10 min, ElectroMag M415P, **905 g***, **sc plastic**	1 × 10 ml 1 plug	10 Pt. 10 Skt.	10 Pt. 10 Skt.		22.5 (19-31)	all NS	swelling (2 d, 7d)
Uyanik-b/ 2015[21]		NT				10 Pt. 10 Skt.	10 Pt. 10 Skt.				
Zahid/2019[24]	RCT split-mouth	NT	MTM	**A-PRF**: 1,300 rpm, 13 min, DUO PROCESS FOR PRF, **207 g‡**, **A-PRF tubes (sc plastic)**	2 × 10 ml 2 membranes	10 Pt. 10 Skt.	10 Pt. 10 Skt.	10 F	24	all NS	pain (1 - 7 d), swelling (1 - 7 d)

Abbreviations: DP, deviating protocol or unclear condition; EM, extraction method; F, female; HS, heavy smokers, M, male; mand., mandibular; max., maxillary; MTM, mandibular third molar; NT, non-traumatic; NRS, numeric rating scale; NS, non-smokers; OP, original protocol with correct centrifugation force; PO, postoperatively; Pt, patients; RCF, relative centrifugal force; RCT, randomized clinical trial; S, smokers, sc: silica coated, Skt: sockets; T, traumatic.

* Values calculated via data from centrifuge manufacturers.

† Value reported in article refers probably to position of clot, ~708 g when referenced to the bottom.

‡ Value according to Miron et al 2020.[14]

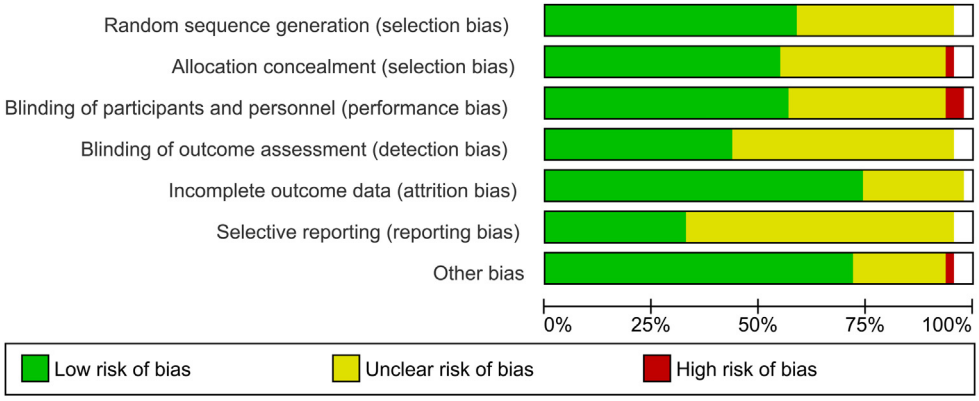

FIGURE 2. Risk of bias assessment.

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unspecifically at the midbuccal positions. To combine data from all studies, midbuccal values were pooled with averaged values from the mesial/distal or buccal/lingual measurements at the position 3 mm below the crest.

For all parameters mentioned above, the pooled standard deviation (SD) was calculated as the weighted mean of the respective individual SDs. If outcome parameters were published as median and range, respective values for mean were estimated according to Hozo et al[19] applying the formula (a+ 2m + b)/4 up to n = 25 or using the median itself as the best estimator for n > 25, and SD was calculated by R/4 (m = median, a = minimum, b = maximum, n = size of the sample, R = range).

The quality of evidence for selected outcomes was assessed as recommended by the GRADEpro software (version 3.6). The employed criteria were study design, limitations, inconsistency, indirectness, imprecision, and other considerations. The quality of evidence was rated as either high, moderate, low, or very low.

STATISTICAL ANALYSIS

Statistical analyses were conducted using RevMan software, version 5.3 (Cochrane collaboration). Weighted MDs were calculated for all variables with similar units, while standardized mean differences (SMDs) were reported for continuous variables using different units in the original studies. For alveolar osteitis (AO) the risk ratio (RR) is shown as pooled effect. Additionally, 95% confidence intervals were calculated for all pooled effects of subgroups and total effects. The heterogeneity of the studies was assessed using the Cochran's Q test as well as by the I^2 statistic. For high heterogeneity (at $I^2 > 50\%$) the random effects model according to Der Simonian and Laird was applied, whereas for lower heterogeneity the fixed effects model was chosen. The publication bias was evaluated by visual inspection of the symmetry of the funnel plots for parameters including data for eight or more studies.

Results

SELECTION OF STUDIES

Applying the above mentioned search terms resulted in 6912 articles in PubMed and 953 articles in the Cochrane Library. After applying filters ("last 10 years", "clinical studies" and "human") in PubMed, the number was reduced to a total of 182. Clinical trials within the last 10 years accounted for 705 hits in the Cochrane Library. Screening resulted in 37 hits for the PubMed collection and 40 for the Cochrane Library. Four further articles were manually added after checking the reference list of related studies. After eliminating duplicates, 48 articles remained for full-text analysis and were assessed for eligibility. Eight were excluded for the reasons given in Figure 1. Inter-rater reliability was very high with a kappa value of 0.83. The complete list of included studies with the most important study characteristics is presented in Table 2.

STUDY CHARACTERISTICS

The 40 selected studies focused on different objectives. The reduction in pain and improvement of healing after tooth extractions, particularly after third molar extractions, was analyzed in 24 studies. In another 14 studies, the primary goal was to promote alveolar ridge preservation in nonmolar positions, and 2 studies focused on the risk of development of AO. For all analyzed outcome factors, the control always consisted of empty sockets left to natural healing after tooth extraction. The number of included patients per study group ranged from 5 to 118. Studies

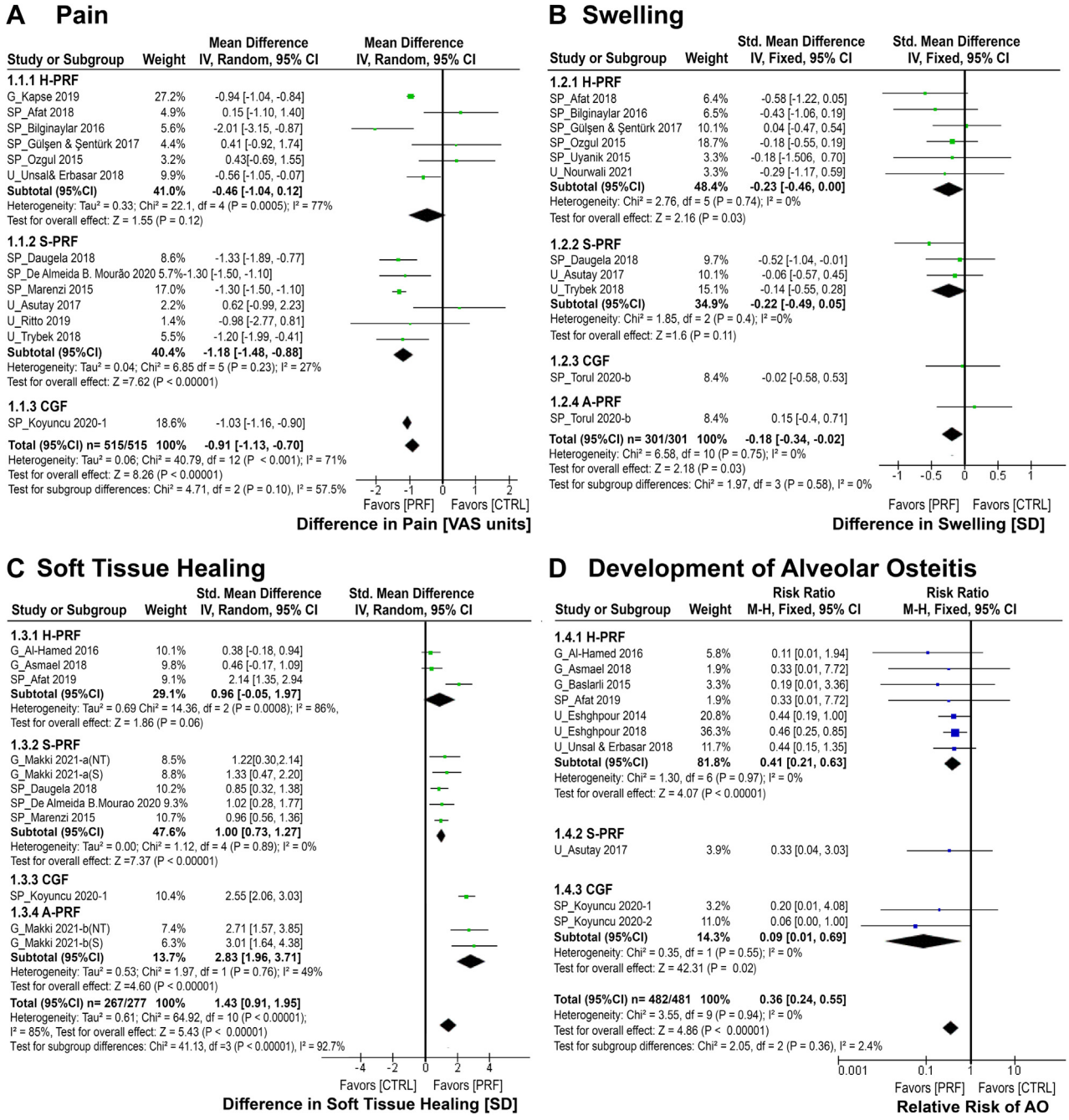

FIGURE 3. Forest plots showing the assessment of different outcome parameters related to overall healing events after application of PRF compared to empty sockets, subgrouping according to used protocol: *A*, Pain at 1 d after tooth extraction, *B*, Swelling at 2 d after tooth extraction, *C*, Soft tissue healing at 7 d after tooth extraction, *D*, Development of alveolar osteitis (postoperatively).

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with a critically low number of patients automatically received a lower weight in the statistical analysis.

A graph presenting the summary of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases identified in each study is shown in Figure 2, whereas individual assessment of each study is presented in Figure S1 in the supplement. In one study[20] a high risk was identified in two categories, namely in allocation concealment and in blinding of the patients, and another study[21] had a high risk due to missing blinding. In a third study[22] a high risk was allocated in the category "other bias" as the study protocol was not sufficient to determine applied centrifugal force, hence subgroup allocation might be wrong. In many studies information on several study details was incomplete, resulting in a

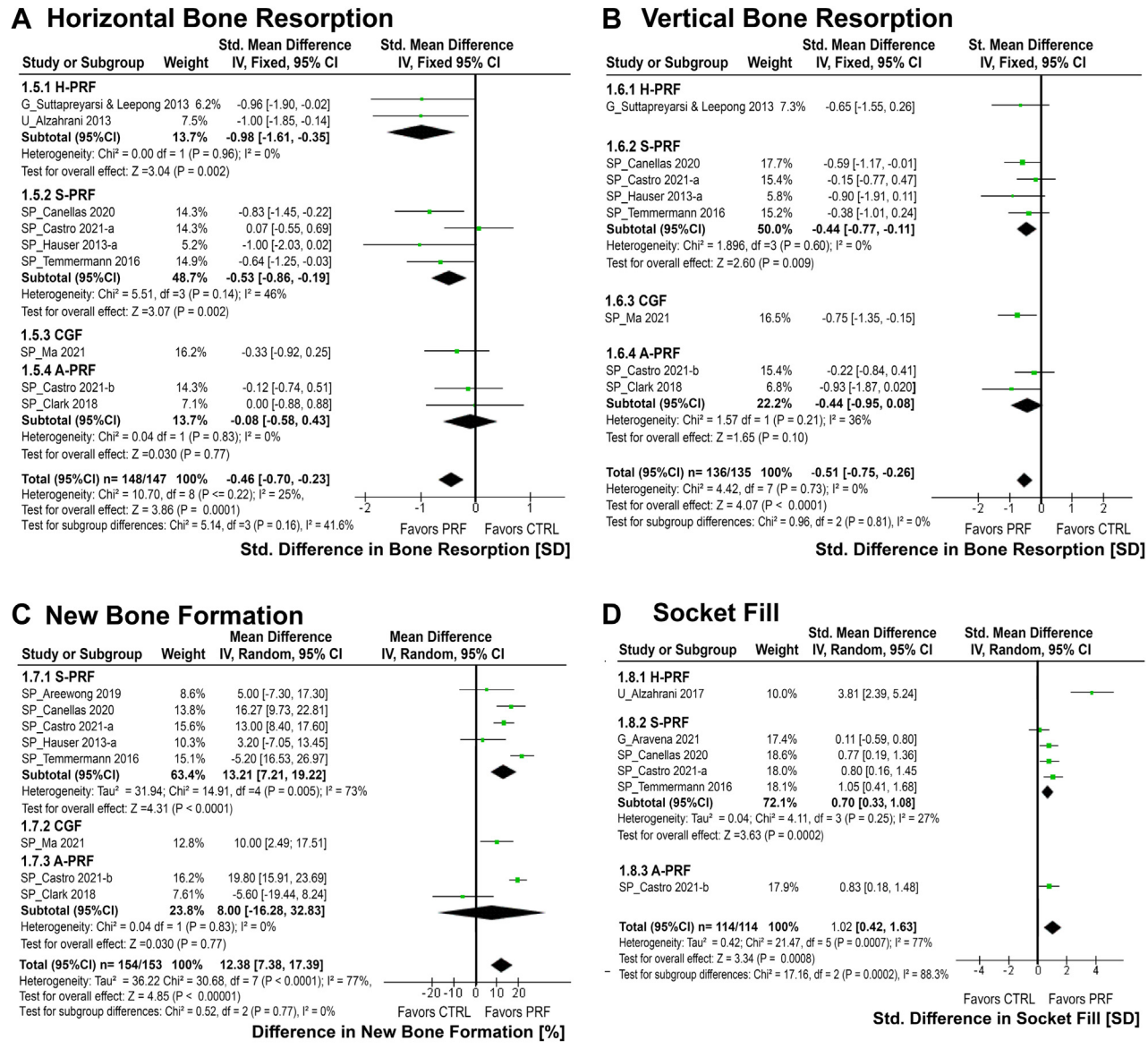

FIGURE 4. Forest plots showing the assessment of various bone healing related outcomes after application of PRF compared to empty sockets, subgrouping according to used protocol: *A*, Horizontal bone resorption in the buccolingual position, *B*, Vertical bone resorption in the midbuccal position, *C*, New bone formation, *D*, Socket fill. (All included data were determined 2 to 4 months after tooth extraction.).

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high percentage of studies with an unclear risk of bias. This was true in particular for the reporting bias, as only a minority of studies was registered. For this reason, identification of missing outcomes was not possible.

QUANTITATIVE OUTCOME SYNTHESIS

For all included outcome parameters both the total effect of PRF as well as subgroup effects depending on PRF preparation protocol (H-PRF, S-PRF, A-PRF, or CGF) are presented.

Quantitative analysis of tube material subgroups was not meaningful due to the low number of studies in each group. Instead, information on the used material is provided by the letter preceding the study name (G for glass, SP for silica-coated plastic, and U for unknown) and will be considered separately at the end of the chapters on general healing and bone healing, respectively.

CLINICAL OUTCOMES FOR GENERAL HEALING

Clinical outcomes for general healing included in this study consisted of pain, swelling, soft tissue healing, and the frequency of AO development.

Pain

Pain was reported in 17 studies using the VAS scale for assessment; outcomes from studies determined in

other categories were not regarded. Data were frequently reported for multiple time points, and the three most common ones were included in the meta-analysis: day 1, day 3, and day 7 after extraction. At day 1 (Fig 3A) and over all included PRF protocols, the use of PRF had a highly significant overall effect ($P < .00001$) on pain reduction by −0.91 VAS units [-1.13, -0.70]. Differentiating by protocol, the pain reduction was significant with comparable values in the S-PRF and CGF group (S-PRF: −1.18 [−1.48, −0.88], CGF: −1.03 [−1.16, −0.90]). The H-PRF group, on the other hand, showed a markedly lower and nonsignificant effect with −0.46 VAS units [−1.04, 0.12] and $P = .12$. The two A-PRF studies could not be included in the quantitative analysis as one[23] did not provide SD data and the other[24] no detailed data but only outcomes of significance tests. Despite the great differences between S-PRF and CGF to H-PRF, the χ^2 test for subgroup differences showed no significant effect of the protocol type ($P = .10$). However, if the CGF subgroup–which contained only one study–was disregarded, a significant difference between remaining H-PRF and S-PRF was identified ($P = .03$).

On day 3 after extraction, all observed trends were similar to day 1 (Fig S3 in supplement). Pain levels were reduced over time as expected, but the overall effect for PRF was still highly significant ($P < .0001$), with pain being reduced by 0.78 VAS units [−1.13, −0.42]. Within the subgroups, pain reduction compared to control was significant for all three groups, and differences among the subgroups were also significant. While the effects for S-PRF and H-PRF were comparable, the overall highest reduction was seen for the single CGF study −1.30 [−1.39, −1.21]. After 7 days there was still a slight pain reduction, but the total effect was no longer significant with −0.50 [−1.10, 0.11] and a P-value of .11. The differences between the subgroups had diminished.

Swelling

As the method of analysis varied consistently among the included studies, the pooled data are presented as SMDs. The pooled effect is calculated for 11 studies and shown in Figure 3B. One study (Kapse et al[25]) was excluded from calculation because their extremely low data variability resulted in large heterogeneity of the meta-analysis, but another calculation including this study is given in the supplement (Fig S4). At day 2 after extraction (11 studies), there is a very small but significant overall effect of PRF on swelling ($P = .03$) with −0.18 [−0.34, −0.02] units of SD. This effect was more pronounced on day 3 (6 studies) with −0.55 [−0.90, −0.20], $P = .002$ (Fig S5) but was based on a different selection of studies. Finally, on day 7 (9 studies), no more significant overall effect was seen with −0.14 [−0.39, 0.12], $P = .55$ (Fig S6). Significant differences depending on preparation protocol can only be seen on day 3 (Fig S5), where the CGF group showed substantially lower swelling with −1.08 [−1.46, −0.69) compared to H-PRF and S-PRF, but no data was available for A-PRF for this time point.

Soft Tissue Healing

Similar to swelling, the methods for assessing the parameter soft tissue healing were heterogeneous. For this reason, SMDs were calculated as pooled effects. The overall effect after 7 days was strong and highly significant ($P < .00001$) with an SMD of 1.43 SD [0.91, 1.95], showing a clearly improved soft tissue healing.

In the individual S-PRF, CGF, and A-PRF groups there was a significant positive effect on soft tissue healing ($P < .00001$), but not for H-PRF (Fig 3C). Further, the χ^2 test on subgroup differences revealed a significant impact of the protocol type ($P < .01$). The size of the subgroup effects was comparable for H-PRF (0.96 SD [−0.05, 1.97]) and S-PRF (1.0 SD [0.73, 1.27]), considerably higher for CGF with 2.55 SD [2.06, 3.03], and overall highest for A-PRF with 2.83 SD [1.96, 3.71].

After two or more weeks the healing scores improved in all groups. The total effect compared to controls was still significant ($P < .001$) with 0.74 SD [0.39, 1.10] and favored the application of PRF, but no more impact of the protocol type was found at this late stage (Fig S7).

Frequency of AO development

The overall trend showed a considerable and significant ($P < .00001$) risk reduction by 64% with a RR of 0.36 [0.24, 0.55] (Fig 3D).

Among the different protocols, the lowest RR was determined in the CGF subgroup with 0.09 [0.01, 0.69], while subgroup effects for H-PRF with a RR of 0.41 [0.21, 0.63] and S-PRF with 0.33 [0.04, 3.03] were quite comparable. Nonetheless, the differences between the protocol types were not significant due to the low absolute frequency of this condition.

In summary, the overall pooled effects of all four parameters related to general healing revealed a significant benefit in the application of PRF versus empty socket, although the effect in case of swelling was rather small. Among all protocol types, H-PRF consistently showed the lowest effects. For pain the outcomes for S-PRF and CGF were comparable, while for the development of AO and soft tissue healing the CGF protocol had the best overall outcomes.

Very few of the included studies specified tube materials. As a consequence, the impact of this variable on the majority of the outcome parameters could not be investigated. Meaningful comparisons were possible mainly in the H-PRF group. Here glass tubes

Table 3. SUMMARY OF FINDINGS

Impact of PRF Application on Different Aspects of Soft Tissue and Bone Healing after Tooth Extraction

Patients	Patients with Tooth Extraction - Third Molar or Non-molar Positions
Settings	Outpatient care
Intervention	PRF (different types of preparation)
Comparison	Empty socket (no PRF)

Outcomes	Illustrative comparative risks of PRF groups vs control group, (95% CI)	Relative effect (95% CI)	No. of patients (PRF/control) and studies	Quality of evidence (GRADE)	Comments
Outcomes for general healing (postoperational morbidity)					
Pain M: VAS F: 1 - 7 d	1 d: Mean pain (MD) **was 0.91 VAS units lower** [1.13 to 0.70 lower]	NA	515/515 (13 studies)	⊕⊕⊖⊖ low	Patients not blinded in several studies, heterogeneity between different **PRF-protocols**, imprecision, publication bias for 7 d
	7 d: Mean pain (MD) was **0.50 VAS units lower** [1.10 lower to 0.11 higher]	NA	365/365 (5 studies)	⊕⊖⊖⊖ very low	
Swelling M: ruler, score, or 3D-analysis F: 2 - 7 d	2 d: Mean swelling (SMD) was **0.18 SD lower** [0.34 to 0.02 lower],	NA.	301/301 (11 studies)	⊕⊕⊕⊖ moderate	Blinding of examiner unknown in several studies, publication bias for 7 d
	7 d: Mean swelling (SMD) **was 0.14 SD lower** [0.39 lower to 0.12 higher]	NA	255/255 (8 studies)	⊕⊕⊖⊖ low	
Soft tissue healing M: different scores F: 7 - 14 d	7 d: Mean soft tissue healing was **1.43 SD higher** [0.91 to 1.95 higher]	NA	267/277 (11 studies)	⊕⊕⊕⊖ moderate	Heterogeneity between different **PRF-protocols**
	14 d: Mean soft tissue healing was **0.74 SD higher** [0.39 to 1.10 higher]	NA	197/197 (9 studies)	⊕⊕⊕⊖ moderate	
Alveolar osteitis M: visual observation	NA	0.36 [0.24, 0.55]	482/481 (10 studies)	⊕⊕⊖⊖ low	Imprecision (few studies with sufficient high number of patients), potential impact of **PRF-protocol**
Outcomes for bone healing related parameters					
Horizontal bone resorption (bucco-lingual at 3 mm) M: caliper, or radiographic F: 2 - 4 m	Mean horizontal bone resorption in buccolingual position at 3 mm depth (SMD) was **0.46 SD lower** [0.70 to 0.23 lower]	NA	148/147 (9 studies)	⊕⊕⊕⊖ moderate	Potential impact of **PRF-protocols**
Vertical bone resorption M: radiographically, or casts/stents F: 2 - 4 m	Mean vertical bone resorption (SMD) was **0.51 SD lower** [0.75 to 0.26 lower]	NA	136/135 (8 studies)	⊕⊕⊕⊖ moderate	Indirectness (average of buccal and lingual position, obtained via different methods)
New bone formation M: CBCT or histology F: 2 - 4 m	2 - 4 m: Mean new bone formation (MD) was **12.38% higher** [7.38 to 17.39 higher]	NA	154/153 (8 studies)	⊕⊕⊕⊖ moderate	Imprecision
Socket fill M: radio graphically or CBCT F: 2 - 4 m	2 - 4 m: Mean socket fill (SMD) was **1.02 SD higher** [0.42 to 1.63 higher]	NA	114/114 (6 studies)	⊕⊕⊕⊖ moderate	Imprecision (H-PRF subgroup based on one study with unclear risk of bias)

Abbreviations: CI, confidence intervals; CBCT, Cone-beam computed tomography systems; F, follow-up period; H-PRF, high relative centrifugal force values; M, methods; MD, mean differences; NA, not applicable; PRF, platelet-rich fibrin; SMD, standardized mean differences; SD, standard deviation; VAS, visual analog scale.

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showed a slight trend to less pain on day 3 and reduced the relative risk to develop AO, while silica-coated plastic tubes resulted in better soft tissue healing. Tube material had no effect on soft tissue healing the S-PRF group.

CLINICAL OUTCOMES FOR BONE HEALING

Parameters included in this study for the assessment of bone resorption and healing were horizontal bone resorption, vertical bone resorption, new bone formation, and socket fill.

Horizontal bone resorption**:** As assessment methods were very heterogeneous, respective data were transformed to obtain averaged midbuccal horizontal bone resorption (Fig 4A) and expressed as SMDs. At 2 to 4 months after extraction, the effect over all the nine studies was significant with -0.46 [−0.70, −0.23] SD and $P = .0001$ (Fig 4A).

With regard to the different protocols, large effects on bone preservation were found for H-PRF with -0.98 SD [−1.61, −0.35] followed by S-PRF with −0.53 SD [−0.86, −0.19], both with $P = .002$. In contrast, no beneficial effect of PRF was seen for CGF or A-PRF. However, subgroup differences were not significant ($P = .16$).

Vertical Bone Resorption

The effect over all the eight studies was highly significant ($P < .0001$) and comparable to the averaged effect in the horizontal direction with −0.51 [−0.75, −0.26] SD (Fig 4B). There were nearly no differences between the four different protocols and consequently the *P*-value was markedly above the threshold for significance ($P = .81$).

New Bone Formation

Although different assessment methods were applied, new bone formation was consistently reported as bone volume/total volume‘. Hence, the pooled effect could be presented as MD in % of new bone to total bone (Fig 4C). Data collected exclusively for vital bone resorption are separately shown in the supplement in Figure S9. Over all the eight included studies, the pooled effect of PRF revealed a highly significant benefit ($P < .0001$) with 12.38% [7.38, 17.39] more bone formation compared to the control after 2 to 4 months**.**

The highest new bone formation was observed for S-PRF with 13.21% [7.21, 19.22] and $P < .0001$. For CGF (only one study) a comparably high value of 10.0% [2.49, 17.51] was obtained. The two included A-PRF studies had contradictory outcomes, resulting in a nonsignificant subtotal of 8.0% and a very broad confidence interval [-16.28, 32.83] with $P = .83$. Interestingly, the only H-PRF study (Martins et al[26]) reported new bone formation only after 6 months (Fig S8) and found significantly more bone than in the control with 13.6% [7.14, 20.06].

Socket Fill

Socket fill data were based on a variety of analysis methods and reported in % of initial socket size or as absolute volumetric data. Thus the meta-analysis was performed again by calculating SMDs. For the period of 2 to 4 months, the effect over all studies was 1.02 SD [0.42, 1.80] with $P = .0008$.

Comparison between subgroups was problematic as the only included H-PRF study had an extremely high SMD of 3.81 [2.39, 5.24]. This was due to low variability rather than actual socket fill differences, as the absolute increase was only moderate (H-PRF 88.8%, control 80.3%). In contrast, the data for S-PRF were quite homogeneous and resulted in a large and significant effect of 0.70 SD [0.33, 1.08] with $P = .002$. The only other study applying A-PRF was comparable with 0.83 SD [0.18, 1.48].

In summary, the pooled overall effect of PRF was always highly significant in the four bone-related outcome variables. Considering the impact of protocol type, a slight but not significant trend was identified only in horizontal bone resorption.

The impact of tube material is difficult to analyze for bone related outcomes as all A-PRF preparations used the specifically recommended glass, while nearly all S-PRF studies used silica-coated plastic tubes. The only S-PRF study with glass tubes reported only data on socket fill with considerably lower effects compared to silica-coated plastic.

Discussion

The main aim of this meta-analysis was to determine if different preparation protocols influence the clinical efficacy of PRF preparations. This assessment was based on eight different outcome variables that compare untreated healing to PRF-assisted healing, enabling us to draw conclusions on general aspects of healing as well as on bone healing. Not all potentially relevant protocol aspects could be taken into consideration as not all are given with enough consistency and detail, thus the focus here was on differences in centrifugation force and tube material.

EFFECT OF PREPARATION PROTOCOL–CENTRIFUGATION FORCE

The included studies were categorized as H-PRF, S-PRF, and A-PRF, with an additional subgroup CGF for all studies performed with a specific Medifuge protocol using a sequence of intermediate RCFs.

No obvious effect of protocol could be found for swelling as well as for nearly all parameters related

to bone healing. There were indeed differences depending on protocol type in the remaining general healing categories of soft tissue healing, pain, and prevention of AO. CGF was the overall most effective protocol here, with the best soft tissue healing (together with A-PRF), the best pain reduction (together with S-PRF), and the best reduction of AO. However, clear and consistent positive effects were also obtained for S-PRF. The effect in the H-PRF group, on the other hand, was both lower and not significant against the control in these three healing outcomes due to the high variability in the studies. The data for A-PRF subgroup were quite inconsistent, if available at all.

While the CGF results look promising, care must be taken for CGF and A-PRF as only a critically low number of studies could be included. In this context, the good performance of S-PRF may be more reliable as more data were available here. The results of the meta-analysis are further distorted by the fact that the outcome parameters of interest were not consistently investigated by all included studies. This is the case for pain and AO as well as for many parameters related to bone healing, as S-PRF was the typically chosen protocol type here.

Of interest is the difference observed between the original PRF protocol[2] classified as H-PRF and the newer modified S-PRF. The S-PRF had both higher consistencies in most outcome parameters and better results in pain and soft tissue healing. Here the lower centrifugation force (between 650 and 708 g compared to ~900 to 1100 g for H-PRF) may lead to more retained platelets and leucocytes and a higher viability of those entrapped cells. There is no clinical or in vitro study known so far that directly compares H-PRF with S-PRF, but publications comparing S-PRF with A-PRF[27] or H-PRF with A-PRF[28] clearly demonstrate that the lower centrifugation force leads to a more homogeneous cell distribution in the clot and a more prolonged release of growth factors. This should make S-PRF the protocol to be preferred over H-PRF.

The consistently good or even superior outcomes for CGF can be explained by its similarity to S-PRF, as the employed centrifugation force is also in the intermediate range during the first three centrifugation steps this protocol uses (692 g, 547 g, and 692 g), with only the last step using 855 g. Hence, the initial clotting step and fibrin fibril formation are expected to be comparable to the S-PRF protocol. The higher RCF applied only in the last step may lead to a higher percentage of entrapped cells in an already well-established fibrin network. It is possible that many clinicians do not consider this protocol due to the need for a specific centrifuge with preprogrammed centrifugation steps, and also, perhaps due to the somewhat confusing name "concentrated growth factor" preparation. But despite the different nomenclature, it is essentially a PRF preparation, and it is possible to program the required centrifugation steps into other programmable high-quality centrifuges.

For the fourth protocol that uses the lowest centrifugation force, A-PRF, only limited and controversial information is available. Based on the markedly lower centrifugation force, the forming fibrin network is less expressed and more loosely packed than for the other protocols.[29] This requires a more detailed adjustment of the centrifugation time to induce clotting at an optimal time point and retain a sufficiently high number of cells. Here in particular, the tube material effect on clotting onset has to be taken into consideration. Centrifugation time in the included studies was either 8 minutes[23,30,31] or 13 to 14 minutes,[24,32] but for no outcome parameter a direct comparison within or between studies was possible to assess the effect of long versus short centrifugation time. Interestingly, significant effects of A-PRF on soft tissue healing[32] and pain[24] were seen only in the studies with a longer centrifugation time.

Another critical point that was not directly addressed in this meta-analysis but became apparent as a potential confounder was the overall quality of the centrifuge in terms of vibrations. Only recently, Dohan Ehrenfest et al[29] demonstrated the impact of centrifuge vibrations on the formation of the fibrin network as well as on the vitality of retained cells, which were massively affected by the used centrifuge type. As higher RCF is commonly achieved by increasing rpm, the vibrations would in this case indeed play a much greater role and hence might additionally contribute to a decreased efficacy of H-PRF compared to S-PRF. While most S-PRF studies were performed using IntraSpin or Hettich centrifuges, many H-PRF studies used simple tabletop machines, which may also contribute to higher vibration levels.

EFFECT OF PREPARATION PROTOCOL–TUBE MATERIAL

Reliable conclusions on the impact of tube material cannot be drawn from this meta-analysis, mainly due to the fact that a high percentage of included studies did not specify what tubes were used even upon personal inquiry. Among those few studies with a detailed description, the distribution was very heterogeneous: the majority of S-PRF was prepared with the IntraSpin centrifuge set using the included silica-coated plastic tubes. In contrast, nearly all A-PRF preparations were obtained with glass tubes as recommended for this protocol type. A comparison between glass and silica-coated plastic tubes was possible only for H-PRF, showing slightly improved outcomes for glass. Glass is known to provoke a strong clot activation and accelerate coagulation onset. This may explain the better outcomes as for high centrifugation forces,

more cells will be found in the region where the fibrin clot forms. Miron et al[14] documented in their in vitro study that S-PRF plugs prepared in glass tubes were indeed more than twice as heavy as those obtained with silica-coated plastic. This indicates that glass may be advantageous for PRF preparations at higher centrifugation forces.

OVERALL BENEFIT OF PRF

The clinical effect of PRF is still discussed controversially, and though a number of reviews have addressed the issue,[7-9,33] clear conclusions are still lacking. This is due in part to a limited number of studies meeting the inclusion criteria, but mainly because of too much study heterogeneity. If different measurement methods or scores were used in the studies, we calculated the SMDs to combine the data into one pooled value. This allowed us to reassess the current evidence to allow for a better judgment on the overall efficacy of PRF.

The pooled outcome measures of all 8 outcome parameters showed a significant effect in favor of PRF compared to empty controls at selected time points after tooth extraction (Table 3). To the best of our knowledge, this is the first time such a clear effect could be shown. However, the effect on bone healing outcomes was not as large as on general healing ones.

In conclusion, PRF seems to be a suitable and cost-effective method to improve healing events after tooth extraction. Preparation protocol appears to affect the efficacy of the PRF preparation, which may contribute to the heterogeneity observed between studies. Protocols with intermediate RCF values such as S-PRF and CGF seem to be more beneficial than those with higher RCF values like H-PRF. For S-PRF at least, clear and consistent positive effects have been reported. Protocols with very low RCF values such as A-PRF, on the other hand, may face some issues in reliably producing a stable network of thick fibrin fibrils. All in all, a recommendation for S-PRF or CGF produced in high-quality centrifuges can be made.

While there are strong hints from in vitro research that the centrifuge tube material can be of high importance, the details available from the included studies were not sufficient for respective subgroup analyses. For this reason, clear descriptions of each preparation detail should be included in every publication, as they could further clarify the role of several factors. We hope to have increased awareness of this important fact.

Supplementary Data

Supplementary data associated with this article can be found in the online version, at 10.1016/j.joms.2023.01.004

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