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Review Article

Effect of platelet rich fibrin on stability of dental implants: A systematic review and meta-analysis

Shaheda Tabassum[1], Subash Chandra Raj[1]*, Hemamalini Rath[2], Asit Kumar Mishra[1], Annuroopa Mohapatra[1], Kaushik Patnaik[1]

[1]Department of Periodontics, SCB Dental College and Hospital, Cuttack, Odisha, India, [2]Department of Public Health Dentistry, SCB Dental College and Hospital, Cuttack, Odisha, India

Address for correspondence:
Subash Chandra Raj, Department of Periodontics, SCB Dental College and Hospital, Cuttack - 753 007, Odisha, India.
Phone: +91-9437008298.
E-mail: drsubash007@gmail.com

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ABSTRACT

Objective: The aim of the study is to provide a systematic review of the potential evidence for the effect of platelet rich fibrin (PRF) on stability of dental implants.

Methods: A systematic review was performed based on the Preferred Reporting Items for Systematic review and Meta-analysis. An extensive and comprehensive electronic search was carried out from January 2000 to March 2021, independently by author in PUBMED, Cochrane Central Register of Controlled Trials, Google Scholar, Scopus, Embase, and Web of Science irrespective of publication status, date, or language. For any registered ongoing or completed but unpublished trial, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and Cochrane Oral Health's Trials Register websites were searched. Randomized, controlled, and clinical trials which assessed the stability of implant with and without use of PRF using Osstell device by radiofrequency analysis were selected.

Results: The electronic and manual search yielded 630 studies. In all the eight included studies implant stability was measured using same ISQ units by Osstell device. Meta-analysis was carried out in six studies that had similar comparisons and reported the same outcomes at same time interval. Random effect models have shown pooled mean difference of 4.49 (95% CI 1.22–7.76) for 1-week post-insertion, 3.65 (95% CI 2.21–5.09) for 4-week post insertion, 3.25 (95% CI 0.03–6.47) for 8-week post-insertion, and 2.79 with 95% CI of 0.48, 5.10 for 12-week post-insertion.

Conclusions: The present systematic review suggests that PRF is effective in improving secondary implant stability with certain limitations and displays possible implication for clinical practice.

Keywords: Platelet Rich fibrin,Implant stability,Radiofrequency analysis, Dental implants

Introduction

The conventional replacement for lost teeth has been removable and fixed partial or full dentures. The need for a fixed, esthetic, and functional restoration makes dental implants a reliable alternative. Today, dental implants are used to support fixed prosthesis or removable partial-dentures.

Implant stability is essential for the long-term success of implant treatment. It can be divided into primary and secondary types. Primary stability is achieved at implant surgery and is determined by the implant design, the surgical technique, and the density of the bone. Secondary stability is dependent on the tissue response to the implant surgery and an ultimate bone healing.[1] A wide range of articular events and various signaling proteins mediate and regulate the healing process of both hard and soft tissues, respectively. It is known that platelets play a crucial role not only in hemostasis, but also in the wound healing process.[2] Choukroun *et al*. 2000, developed the production protocol of Platelet rich fibrin (PRF), attempted to accumulate platelets and released cytokines in a fibrin clot.[3]

There are various protocols used to produce platelet concentrates which lead to different products with different characteristics. There are four principal classes of platelet derivatives based on the content of leukocytes and the architecture of fibrin. These are pure platelet-rich plasma, leukocyte and platelet-rich plasma (L-PRP), pure PRF (P-PRF), and leukocyte and PRF (L-PRF). PRF is a second-generation platelet concentrate developed by Choukroun and defined as an autologous L-PRP material.[4]

PRF is inexpensive and quick to prepare and does not require any anticoagulant for preparation.[5] This material provides and stimulates neo angiogenesis.[6] Strong fibrin mesh of PRF prevents it from dissolving fast after application and permits

gradual release of growth factors such as platelet-derived growth factor, insulin like growth factor, vascular endothelial growth factor, and transforming growth factor that enhances both angiogenesis and osteoblastic proliferation and differentiation.[7,8]

PRF is considered as a healing biomaterial and it has a robust stimulating effect on various aspects of healing of soft and osseous tissue including angiogenesis, immune control, and harnessing the circulating stem cells.[9-11] PRF efficacy in optimizing and preserving the existing osseous structure and gingival architecture across peri-implant tissue needs to be corroborated. Oncu and Alaaddinoglu in 2015 observed that PRF application appeared to increase implant stability during the early healing period, as evidenced by higher implant stability quotient (ISQ) values and they stated that simple application of this material seems to provide faster osseointegration.[6]

The purpose of this systematic review is to assess the stability of dental implant with and without the use of PRF using Osstell device by radiofrequency analysis.

Methods

According to the preferred reporting items for systematic review and meta-analysis (PRISMA) statement, the study protocol was designed before the start of review. Based on PRISMA guidelines, the population, intervention, comparison, outcome, and study design (PICOS) structure was used to develop the search strategy.

Protocol development and focused question

The study protocol was designed before the start of the review according to the PRISMA statement.[12] The protocol aimed at answering the focused question: Does PRF improve the stability of dental implant?

Eligibility criteria

- Population (P): Partially edentulous, Extraction, and Extraction socket
- Intervention (I): PRF, Autologous platelet concentrate, and Leukocyte platelet rich
- Fibrin, Injectable PRF, and Advanced PRF
- Comparison (C): PRF and Without PRF
- Outcome (O): Implant stability, Radiofrequency analysis, Osstell device, and ISQ
- Study design (S): Split mouth, Clinical trial, Randomized, and controlled trial
- Randomized and clinical trial.

Inclusion criteria

The following criteria were included in the study:

- PRF Protocol: 2700–3000 relative centrifugal forces (RCF) for 10–12 min.
- Split mouth Randomized and Controlled trials (RCTs), Controlled and Clinical trials.
- Immediate and Delayed implant placement with PRF in socket.
- Studies in English.

Exclusion criteria

The following criteria were excluded from the study:

- Parallel RCTs
- Case Report, Case Series, Cohort Studies, and Case–control Studies
- Animal studies *in vivo* and *in vitro*
- Studies of PRF without implant placement
- Platelet Concentrates other than PRF
- Radiofrequency Analysis using any device other than Osstell
- CGF Protocol and Protocol other than 2700–3000 for 10–12 min

Types of interventions

Experimental interventions

Use of dental implants with PRF or use of dental implants without PRF.

Comparator interventions

Implant stability with use of PRF and without use of PRF.

Types of outcomes

The primary outcome was implant stability measured by radiofrequency analysis with Osstell device (ISQ values).

Information sources and search

Electronic search

The following databases were searched from January 2000 to March 2021.

- PUBMED.

Cochrane Central Register of Controlled Trials (Central) (The Cochrane Library)

- Google Scholar
- Scopus
- Embase
- Web of science.

For any registered ongoing or completed but unpublished trial, following websites will be searched-

1. ClinicalTrials.gov (http://clinicaltrial.gov)
2. World Health Organization (WHO) International Clinical Trials Registry Platform
3. Cochrane Oral Health's Trials Register.

Searching other resources

- Manual search was conducted from the present back to the year 2000 in the following journals which were

considered to be the most relevant to the question of the present review:
  - Journal of Clinical Periodontology
  - Journal of Periodontology
  - Journal of Periodontology and Implant Science
  - International Journal of Periodontics and Restorative dentistry
  - International Journal of Oral and Maxillofacial Implants
  - Clinical Oral implant research
  - British Journal of Oral and Maxillofacial implant.
- Hand search for abstracts of major national conferences relevant to the review subject was done to identify trials that may have not been completed or published in full but are in agreement with our inclusion criteria.
- References of the published randomized and controlled trials were searched for any additional studies which may not be identified by electronic searches.
- Various Professors and Departmental Head of our institution involved actively in peer reviewing were contacted to help us with any relevant research detail.

Search strategy

Keywords, MeSH terms, and free terms were used to perform the search while Boolean operator (OR and AND) were used to combine the searches. The search strategy was limited to human studies and the English language. The search applied was the following:

(partially edentulous) OR (extraction) OR (extraction socket) OR (partial edentulism) AND (PRF) OR (PRF) OR (L PRF) OR (leukocyte PRF) OR (Autologous platelet concentrate) OR (I PRF) OR (injectable PRF) OR (advanced platelet-rich fibrin) OR (A PRF) AND (Dental implant) OR (tooth implant) OR (implant prothesis) OR (single implant) OR (immediate implant) OR (delayed implant) AND (ISQ) OR (Osstell radiofrequency analysis) OR (RFA)OR (ISQ) OR (osseointegration) OR (primary stability) OR (primary implant stability) AND (humans).

Data collection and analysis

Screening methods

Two reviewers (ST and SR) performed all the searches independently and screened the titles and the list of studies identified by the searching process according to the inclusion criteria of the review to identify eligible and potentially eligible studies. Any disagreements on eligibility were resolved by discussion but if this was not possible, an experienced third adjudicator (HR) was consulted to achieve consensus. Studies failing to meet the inclusion criteria were recorded along with the reasons for exclusion. The inter reviewer reliability of the full text analysis was calculated using Cohn's Kappa correlation coefficient.

Data extraction and management

ST and AKM developed and extracted data independently keeping in mind the guidelines of PRISMA and recorded information for the results of included studies using a customized Excel spreadsheet. When data were incomplete or missing, the authors of the published study were contacted for clarification. Any disagreements were resolved through discussion and where agreement could not be reached, data were excluded until further clarification was available. The following data were extracted from each included study:

- Trial design, location/setting, number of centers, and study duration.
- Details of the participants including demographic characteristics, criteria for inclusion and exclusion, and relevant information of implant stability at baseline, numbers randomized to each study arm, and numbers analyzed in each group.
- Details of the type of experimental/comparator intervention.
- Details of the outcomes reported, including method of assessment.
- Sample size and source of funding, declarations/conflicts of interest.
- Outcome data: For implant stability, data were extracted at baseline, 1 week, 4 weeks, 8 weeks, and 12 weeks.
- Where studies reported mean scores for implant stability but did not report means of variance, the variance was estimated from the standard deviations reported in similar trials that used the same index at the same time point as described in Chapter 16 of Cochrane Handbook for systematic reviews of interventions using Revman software.[13]

Quality Assessment (Assessment of risk of bias in included studies)

Two review authors (AM and KP) assessed the risk of bias of all included studies, independently and in duplicate, using Cochrane's domain-based, two-part tool as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.[14] For an overall assessment of low, high, or unclear risk of bias for each included study, seven domains of risk of bias were evaluated.

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias like baseline imbalances in potentially important prognostic factors between intervention groups and differential diagnostic activity by outcome assessors.

Data analysis

A meta-analysis was carried out only where studies of similar comparisons reported the same outcomes at the same time interval. Mean differences (MDs) were combined where studies used the same scale and standardized MDs where studies used different scales for continuous outcomes. Due

to anticipated heterogeneity, we used random-effects models for four meta-analyses but fixed effect model was used for one meta-analysis that had baseline values. Heterogeneity was assessed statistically using a Chi-square test and it was quantified using the I^2 statistics given in Section 9.5.2 of the Cochrane Handbook for Systematic Reviews of Interventions.

Results

Search and publication characteristics

The searches resulted in 630 publications in total. After screening the titles and abstract according to the inclusion criteria for this review, independently and in duplicate, discarding publications in the process, the literature search identified 265 potential publications in PubMed/Medline, 202 in Cochrane, four in Embase, 89 in Scopus, and 22 in Web of Science. Another 48 records were identified through hand searching and Google Scholar. Following removal of duplicates, 612 publications remained. Following the title and abstract screening, 18 papers were identified as in need of full-text assessment. A total of 10 articles were excluded at this stage leaving a final selection of eight studies for qualitative data extraction and six studies for meta-analysis. The search flow and the article selection process are demonstrated in Figure 1 and the reasons of exclusion of the full text articles are shown in Table 1.

Quality assessment of included publications

Eight included studies were RCTs. All studies were of split mouth design which compared implant stability using platelet-rich fibrin versus implant stability without platelet-rich fibrin. Cochrane's domain-based, two part tool was used to assess risk of bias of each included study. Six studies did not give

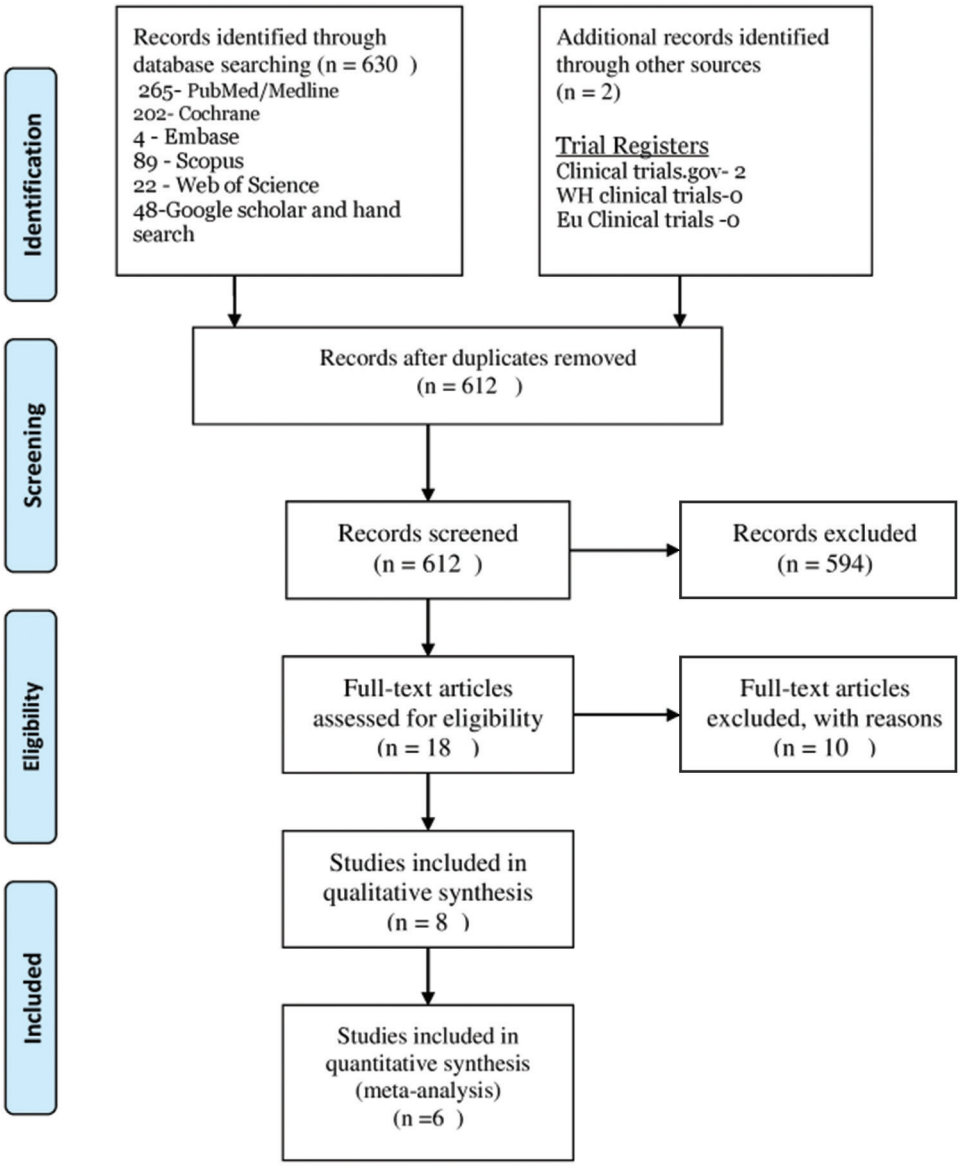

Figure 1: Flow chart depicting the search strategy and study selection process

information about performance bias while two studies assigned of low risk of bias as they have mentioned about the examiner collecting and analyzing the data were blinded to allocation. Four studies mentioned about randomization but no further details, so assigned unclear risk of bias. Three studies did not give any information regarding randomization, so high risk of bias. Only one study mentioned about randomization, so considered under low risk of bias. All included studies were deemed low risk of bias while considering attrition, reporting, and other bias category shown in Figures 2 and 3.

Description of included publications

There were eight studies (Ragab *et al*. 2013,[15] Oncu *et al*. 2015,[6] Hussein *et al*. 2017,[16] Tabrizi *et al*. 2018,[17] Torkazaban *et al*. 2018,[18] Diana *et al*. 2018,[19] Birant *et al*. 2019,[20] and Oncu *et al*. 2019)[21] that analyzed total of 153 patients. Immediate implant placement was carried in three of the studies, Ragab *et al*. 2013, Diana *et al*. 2018, and Oncu *et al*. 2019. The implants were placed at least 6 months post-extraction in other five studies. Total of 367 implants were placed in 153 patients. One hundred and eighty-three implants were placed in study group where PRF was given and 184 implants were placed in non-PRF group which served as control. The participants were of age group ranging from 20 to 66 years. A detailed summary of the characteristics of studies is mentioned in Table 2.

Characteristics of the intervention

In all eight studies, the PRF membrane was placed in the prepared implant bed and the implant was then torqued in place.

Table 1: Excluded studies and reason for exclusion

Toffler *et al*. (2010)	PRF in sinus not osteotomy
Tajima *et al*. (2013)	PRF in sinus not osteotomy
Angelo *et al*. (2015)	PRF in sinus grafting prior to implant placement
Boora *et al*. (2015)	PRF in peri-implant tissues not osteotomy
Hehn *et al*. (2016)	PRF in peri-implant tissues not osteotomy
Oncu *et al*. (2016)	Animal study
Shaker *et al* (2016)	Periotest device used
Khan *et al*. (2018)	PRF in peri-implant tissues not osteotomy
Temmerman *et al*. (2018)	PRF in peri-implant tissues not osteotomy

PRF: Platelet-rich fibrin

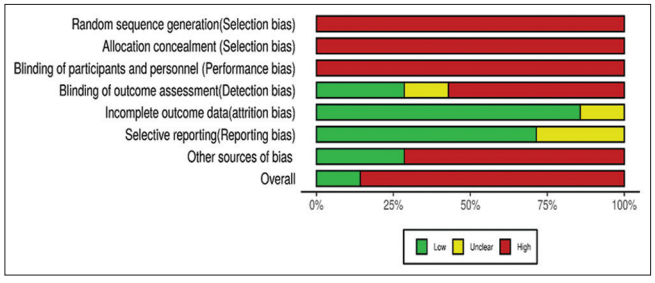

Figure 2: Risk of bias graph: Judgement about each risk of bias item presented as percentage across all included studies

In five studies, the PRF was produced using the Choukroun's PRF protocol and centrifuged at 2700 rpm for 12 min. In Hussein *et al*. 2017, PRF was produced using Choukroun's protocol and centrifuged at 3000 rpm for 12 min and in Ragab *et al*. 2013 at 3000 rpm for 10 min and in Tabrizi *et al*. 2018 at 2800 rpm for 12 min.

Characteristics of the outcomes

The stability of the implants was evaluated with resonance frequency analysis (RFA). The measurements were carried out with the Osstell device (Osstell) by connecting the transducer (SmartPeg) to the implant. Two measurements were made on the mesiodistal and buccolingual, and mean ISQs were calculated. RFA measurements were performed immediately after surgery and repeated after implant placement at different time periods in different studies ranging from 1 week to 6 months.

Data synthesis

Meta-analysis was carried out only where studies of similar comparisons reported the same outcomes at the same time interval. Due to anticipated heterogeneity, random-effects model was used for four meta-analyses but fixed effect model was used for one meta-analysis that had baseline value. Where studies reported mean scores for implant stability but did not report means of variance, the variance was estimated from the standard deviations reported in similar trials that used the same index at the same time point as described in Chapter 16 of Cochrane Handbook for systematic reviews of interventions using Revman software.[13]

When the standard error was not available directly and the standard deviation of the differences was not presented, a simple approach was used to impute the standard deviation, as is commonly done for other missing standard deviations using an imputed value, correlation coefficient individually for both experimental and control groups.

$$Corr_E = \frac{SD^2_{E\,baseline} + SD^2_{E\,final} - SD^{\,2}_{E\,change}}{2 \times SD_{E\,baseline} \times SD_{E\,final}}$$

To impute a standard deviation of the change from baseline for the experimental intervention, following formula was used:

$$SD_{E\,change} = \sqrt{\begin{matrix} SD^2_{E\,baseline} + SD^2_{E\,final} \\ -(2 \times Corr \times SD_{E\,baseline} \times SD_{E\,final}) \end{matrix}}$$

Three studies (Oncu *et al*. 2015, Hussein *et al*. 2017, Torkzaban *et al*. 2018) that measured the implant stability at baseline, 1 week, and 4 weeks, the value of difference in mean and standard deviation was directly put. Where only baseline and final standard deviations were known but

difference from baseline were not given, the missing standard deviation was imputed using correlation coefficient. In two studies, Ragab *et al*. 2013 and Tabrizi *et al*. 2018 values for difference in mean and standard deviation from baseline could not be estimated as their baseline values were not reported.

Results of individual studies and synthesis of results

Implant stability was reported in all the included studies by means of ISQ values by measurements of RFA by Osstell.

Baseline

At the time of implant insertion, baseline ISQ values were reported by five studies, Oncu *et al*. 2015,[6] Hussein *et al*. 2017,[16] Diana *et al*. 2018,[19] Birant 2019,[20] and Oncu *et al*. 2019.[21] A forest plot was constructed using a fixed-effect model. Degree of freedom (df) was 4. Tau^2 is 0.00 which describes the between study variance. The value of Chi-square is 1.53 which describes the statistical test for heterogeneity. The heterogeneity of the studies at baseline was deemed no heterogeneity as $I^2 = 0\%$.The confidence interval (CI) estimated at 95% CI for baseline value was found to be −3.55,0.79. As the CI in baseline contained zero, there was no statistically significant difference between two groups at the time of insertion. The *P*-value is 0.82 which indicates that it is not statistically significant. Pooled results for each study are shown in Figure 4.

1 week post-insertion

Data at 1-week post-implant insertion were provided by four studies (Oncu *et al*. 2015, Torkzaban *et al*. 2018, Birant 2019, and Oncu *et al*. 2019) and result showed a statistically significant difference in the ISQ values between the two groups in favor of intervention. A random effect model was used to construct a forest plot. I^2 was calculated to be 76 % (substantial heterogeneity) and df was 3. The p-value for heterogeneity was $P = 0.006$. Tau^2 is 7.44 which describes the between study variance. The CI estimated at 95% CI for 1-week post-insertion was found to be 1.22, 7.76. As the CI did not contain zero, there was strong evidence that the treatment was effective favoring the intervention (PRF). Pooled results for each study are shown in Figure 5.

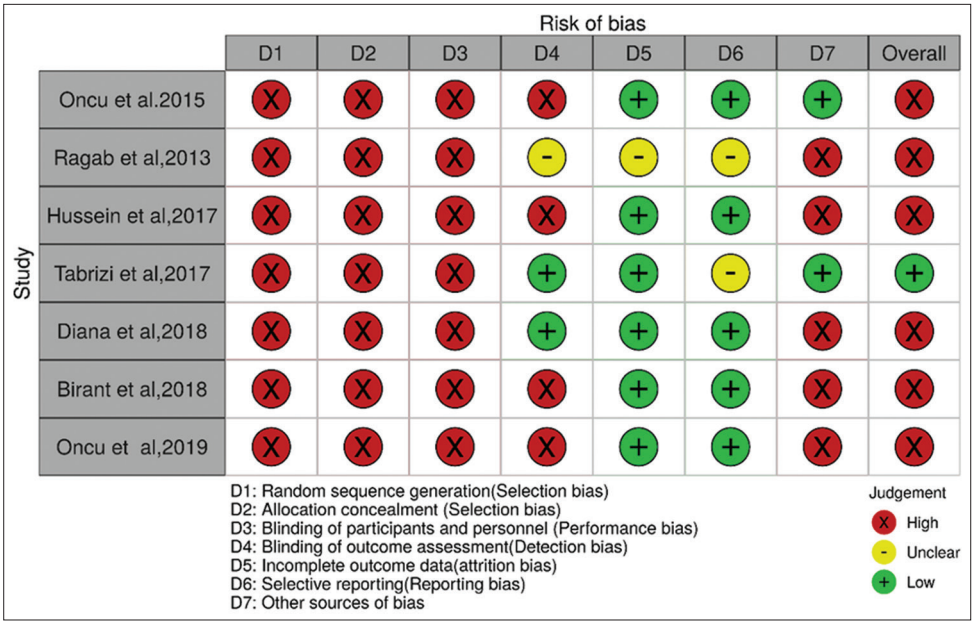

Figure 3: Risk of bias summary: Judgement about each risk of bias item for each included studies

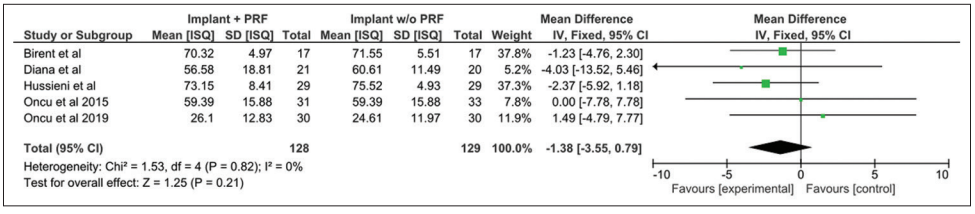

Figure 4: Forest plot of mean difference in Implant stability at baseline immediately post-insertion

Table 2: Study characteristics

Study	Study design and duration	Number of participants (Implants)	Participant age	Intervention	Outcome variable	PRF formulation	Results
Ragab *et al*., 2013	RCT,6 months (B,2,4,6 months)	10 patients, 20 implants	20–45 years	Test: Implant+PRF was used on one side Control: Implant w/o PRF.	ISQ Value	3000 rpm only one spin for 10 minutes	No significant difference between the mean of Osstell values for both test and control sides at baseline, 2, and 4 months while at 6 months, the control side showed statistically significant higher Osstell values
Oncu *et al*., 2015	RCT, 1 year (B,1 week, 1 month, 3 months)	26 patients	40.2±11.5 years	T: Implant+L-PRF C: Implant w/o L-PRF	ISQ Value	2700 rpm for 12 min with a table centrifuge (PC-02, Process Ltd	Statistically significant diff between stability of LPRF+and LPRF. (Osstell device)
Hussein *et al*., 2017	RCT, 3 month	19,58	28–66 years	T: Implant+PRF C: Implant w/o PRF	ISQ value	3000 rpm for 12 min	Primary stability ISQ were 73.15±8.41 for the study group and 75.52±4.93 for the control group. 4th week, ISQ were 68.1±7.52 for the study group and 68.52±8.84 for the control group
Tabrizi *et al*., 2018	RCT 6 weeks (2,4,6 weeks)	20,40	39.6±6.74 years	T: Implant+PRF C: Implant w/o PRF	ISQ Value	2,800 rpm/10 min	ISQ: SS higher in the PRF group at 2 (T: 60.6±3.4 vs. C: 58.2±3.6, *P*=0.04), 4 (T: 70.3±3.3 vs. C: 67.1±4.3, *P*=0.014) and 6 weeks (T: 78.5±3.3 vs. C: 76.1±2.9, *P*=0.027
Diana *et al*., 2018	RCT, 1 year (B, 3 months)	31,41	Mean age 28.5 years	Autologous PRF+peri-implant region: study group No augmentation: control group	ISQ Value	Choukroun's protocol at the time of surgery, and the PRF clot was compressed between two sterile, moist, gauze-covered glass slabs of standard size for 30 s	ISQ: Study group 56.58±18.81 to 71.32±7.82; control group 60.61±11.49 to 70.06±8.96 (*P*=0.01).
Torkzaban *et al*., 2018	RCT, 1 month (B,1 week, 1 month)	10 patients, 50 implants		Test: Implant+PRF was used on one side Control: Implant w/o PRF.	ISQ Value		At the end of the first week (T2), ISQ was 59.85±5.32 in the PRF group and 55.99±3.39 in the non-PRF group. Compared to baseline, the ISQ increased in the PRF group by 0.12±0.47 (*P*=1.000) and decreased in the non-PRF group by 2.42±0.36 (*P*<0.001). At 1 month postoperatively, ISQ significantly increased by 6.89±0.96 in the PRF group and by 4.82±0.92 in the non-PRF group compared to baseline (*P*<0.001).
Birant *et al*., 2019	RCT, 3 months (B,1,4,8,12 weeks)	17 patients, 34 implants	mean age of 48.3±10.4 years.	Test: Implant+PRF was used on one side Control: Implant w/o PRF.	ISQ Value	2,700 rpm for 12 min	Immediate post-surgical mean ISQ of PRF+implants was 70.32±4.97, and the mean ISQ was 71.55±5.5 in the control group. At the end of the third month, mean ISQ of PRF+implants was 77.38±5.18 and the mean ISQ was 74.29±5.65 for PRF-group

(Contd...)

Table 2: *(Continued)*

Study	Study design and duration	Number of participants (Implants)	Participant age	Intervention	Outcome variable	PRF formulation	Results
Oncu *et al*., 2019	RCT, 1 month (B, 1st week, 4th week)	20 patients, 64 implants	44.2 ± 12.5 years	Test: implants, PRF + group Control: Implants, (PRF-group)	ISQ Value	2,700 rpm for 12 min with a table centrifuge (PC-02, Process Ltd).	ISQs) of the PRF + implants was 69.3 ± 10.5 mean ISQs for the PRF-implants was 64.5 ± 12.2 at the end of the 1st week. The mean ISQs at 4 weeks postoperatively were 77.1 ± 7.1 for the PRF + group and 70.5 ± 7.7 for the PRF-group. (Osstell device)

RCT: randomised controlled trials

4-week post-insertion

Five studies (Oncu *et al*. 2015, Hussein *et al*.2017, Torkzaban *et al*. 2018, Birant 2019, Oncu *et al*. 2019) reported ISQ at 4-week post-implant-insertion and again the difference was deemed statistically significant favoring the intervention group. A forest plot was constructed using a random-effect model. df=4 and $P < 0.00001$. The pooled MDs was 3.65 with 95% CI of 2.21, 5.09. The results were in favor of the intervention and pooled results for each study are found in Figure 6.

8-week post-insertion

Two studies (Hussein *et al*. 2017, Birant 2019) reported ISQ at 2-month post-implant-insertion and the difference was deemed statistically insignificant ($P = 0.05$). A forest plot was constructed using a random-effect model. df=1 and $P = 0.05$. The I^2 was 0% and was interpreted as no heterogeneity. Tau^2 is 0.00 which describes the between study variance. The pooled MDs was 3.25 with 95% CI of 0.03, 6.47. The results were statistically insignificant ($P = 0.05$). The results were in favor of the intervention and pooled results for each study are found in Figure 7.

12-week post-insertion

Four studies (Hussein *et al*. 2017, Diana *et al*. 2018, Birant 2019, and Oncu *et al*. 2019,) reported ISQ at 3 months post-implant-insertion and the difference was deemed statistically significant favoring the intervention ($P = 0.02$).A forest plot was constructed using a random effect model with df=3 and P=0.02. The I^2 was 0% and was interpreted as no heterogeneity. Tau^2 is 0.00 which describes the between study variance. The pooled MDs was 2.79 with 95% CI of 0.48, 5.10. The results were statistically significant ($P = 0.02$) favoring the use of intervention (PRF) and pooled results for each study are found in Figure 8.

Discussion

Implant stability is essential for the long-term success of implant placement. It consists of two variants, mechanical (Primary) and biological (secondary) stability. Simunek *et al*. placed 90 alkali-treated surface implants interforaminally, whose stability was measured in different time intervals from 1 to 10 weeks, demonstrated that ISQ values were more prominently decreased in the 1st week post-insertion.[22] Rodrigo *et al*. presented implant failures of 19% for ISQ <60

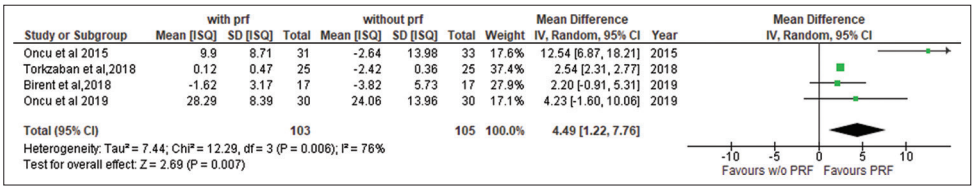

Figure 5: Forest plot of mean difference in implant stability at 1-week post-insertion

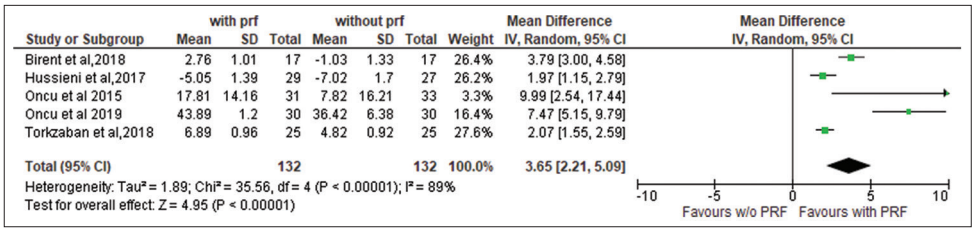

Figure 6: Forest plot of mean difference in Implant stability at 4-week post-insertion

and 100% survival for ISQ >60 when measurements were taken before loading.[23] Baltayan *et al*. demonstrated a correlation between growing ISQ values and increased sensitivity in detection of implant failure. They suggested that the stability of implant with ISQ <60 should be considered questionable while an implant with ISQ >70 should be very stable.[24]

Studies *in vitro* and *in vivo* have demonstrated a beneficial effect of PRF on osteoblastic activity. He *et al*. in their *in vitro* study of rat osteoblasts concluded that PRF enhanced osteoblastic proliferation and differentiation in a clearer and longer lasting way than PRP.[7] Temmerman *et al*. described a better quality and quantity of newly formed bone in the PRF-induced growth in comparison to unassisted bone healing in their split mouth RCT micro CT/CBCT quantitative analysis.[25] The present systematic review findings suggest that PRF does not have effect on primary stability of implants, but has a beneficial effect on the secondary stability. The five studies that presented baseline values immediately post-insertion showed no statistical significance between ISQ values of the test and control group. On the other hand, there was a statistically significant increase in secondary stability as this has been demonstrated by four studies in 1st week, five studies in 4 week, and four studies in 12-week post-implant insertion.

At the present time, numerous protocols have been suggested for production of PRF. There are also different centrifuge machines used with different properties and different results by means of the clot's content of cells, fibrin, and growth factors release potential. Recent studies have shown that the differences in centrifuge produce different vibration level and lower the vibration level, better the PRF clot produced.[26] Furthermore, the speed of centrifugation is another parameter with an effect to the quality of the clot with a demonstrated superiority of a low speed centrifugation concept with reduction of RCF.[27] Likewise, there has been recent evidence in relation to the different qualities of PRF clots with different types of tubes and different types of centrifugation (horizontal vs. fixed angle).[28,29] As a result, it is yet to be established with combination of the above mentioned parameters. It would produce highest quality product with the highest beneficial potential which would then need to be measured through high quality studies.

The present systematic review suggests that PRF does not have an effect on primary stability of the implants, but has a beneficial effect on secondary stability. Implant stability at 1-week and 4-week post-insertion provided by four studies, (Oncu *et al*. 2015, Torkzaban *et al*. 2018, Birant 2019, and Oncu *et al*. 2019) showed a statistically significant difference in ISQ values favoring PRF group. Four studies (Hussein *et al*. 2017, Diana *et al*. 2018, Birant 2019, and Oncu *et al*. 2019) reported ISQ values at 3-month post-implant-insertion and the difference was statistically significant favoring the PRF group. Although all the seven studies were split mouth RCTs, they were assessed as at high risk of bias overall, as they had at least one domain rated at high risk of bias. The reason that all studies were assessed as at high risk of bias was due to the problems with randomization method, allocation concealment, blinding of participants, and personnel. Six studies had no information regarding blinding of participants and personnel and in one study, participants were not blinded. Despite most studies included in the meta-analysis being assessed as at high risk of bias, we did not downgrade the assessments for Radio frequency analysis (RFA). This is because we believe that further research is very unlikely to change our confidence in the estimate of effect for this outcome. Although there was high heterogeneity for most of the meta-analysis, we did not downgrade this due to consistency of the direction of effect.

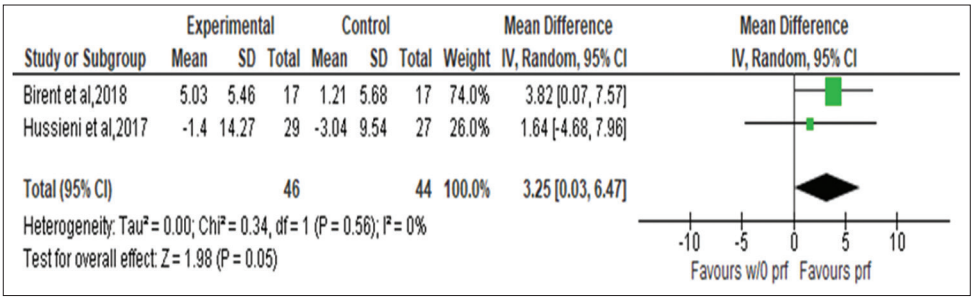

Figure 7: Forest plot of mean difference in implant stability at 8-week post-insertion

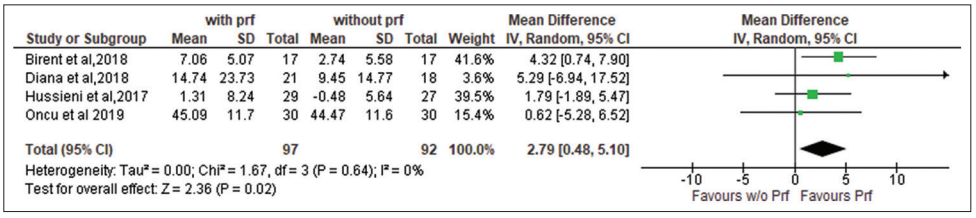

Figure 8: Forest plot of mean difference in implant stability at 12-week post-insertion

To prevent judgments about the eligibility criteria for studies to be included in this review, only the split mouth RCTs were selected. Clarification regarding the types of participants and type of intervention was obtained for inclusion of studies. Amendment for the assessment of the blinding domains in the "Risk of bias" tool to allow studies to obtain a judgment of "low" or "unclear" risk of bias in certain circumstances compared to the blanket judgment of high risk of bias that was stated in the published protocol was done. A hierarchy to guide data extraction and analysis was developed to facilitate data extraction and analysis. Each decision was appropriately justified and was made to improve the scientific quality and clinical applicability of the review. Estimation of the standard deviation was done for two studies that measured radiofrequency analysis at 8 weeks and four studies that measured radiofrequency analysis for 12 weeks using data from the same outcomes measured at the same time point in other similar studies so that we could include it in meta-analysis.

There is variation of the quality of included studies and risk of bias was deemed unclear or high. The moderate number of patients and implants of the included studies could lead to an overestimation of the treatment effect. Another important limitation is the limited number of studies included in this systematic review and the evident heterogeneity among these studies. The different implant types, lengths, and diameters used in the included trials, the different qualities of bone and the resultant insertion torque, different centrifugation protocols, and varieties of centrifugation tubes used bear the risk of compromised results of the overall treatment effect.

There were hardly any reviews of the effect of PRF on implant stability but recently we could find a systematic review by Lyris *et al.* 2021 accepted for publication in British Journal of Oral and Maxillofacial surgery.[30] Although the results of our meta-analysis are similar to this review, there is broader electronic database with more number of included studies and intervention type. In spite of limitations of this study, the results demonstrate a potential of PRF in shifting the implant stability curve to the left and as a result of that displays a possible implication for clinical practice.

Conclusion

The present systematic review revealed that there is a clinically and statistically significant difference between the stability of implants with and without PRF. Implant stability was enhanced by covering the implant surface with PRF. Thereby displays a possible implication for clinical practice by means of decreasing the time interval needed between implant placement and leading to shorter treatment periods which may improve the implant treatment acceptance.

It would be reasonable to suggest that long follow-up time clinical trials and histologic studies with a greater number of patients and implants placed are needed to reach more definitive conclusions. Interventional designs should be in keeping with the consolidated standards of reporting trials (CONSORT) statement (www.consort-statement.org). Information on various confounding factors should be reported to facilitate multivariable analysis of risk factors. Studies should have proper documentation and follow-up of dropouts, as described by the CONSORT statement.

Finally, a desirable next step would be the conduction of more number of clinical trials on comparing the loading times between a control group and PRF group with loading being performed on a pre-set ISQ value for different populations with proper control selection and adequate sample size. Implant types, lengths, and diameters as well as centrifugation protocols and tubes used for centrifugation should be standardized in these trials and long-term follow-up is needed to reach more definitive conclusions.

Authors' Declaration Statements

Ethics approval

NA.

Consent for publication

None.

Availability of data and material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

Competing interests

The authors do not report any conflicts of interest.

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Author contributions

Conceptualization: Subash Chandra Raj (SR) and Shaheda Tabassum (ST)

Formal Analysis: Hemamalini Rath (HR)

Investigations: Shaheda Tabassum and Asit Kumar Mishra (AKM)

Methodology: Hemamalini Rath, Annuroopa Mohapatra (AM), and Kaushik Patnaik (KP)

Project Administration: Subash Chandra Raj

Writing-Original draft: Subash Chandra Raj and Shaheda Tabassum

Writing-Review and Editing: Subash Chandra Raj, Shaheda Tabassum, Annuroopa Mohapatra, and Kaushik Patnaik.

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