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# EFFECT OF PLATELET RICH FIBRIN AS AN ADJUNCT TO BIOACTIVE GLASS COMPARED TO BIOACTIVE GLASS ALONE FOR THE TREATMENT OF INTRABONY DEFECTS IN CHRONIC PERIODONTITIS PATIENTS - A SYSTEMATIC REVIEW

Periodontology

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## ABSTRACT

**Background:** Platelets are the richest source for cytokine and growth factors which are two important components of regeneration and Platelet Rich Fibrin (PRF) has gained popularity in the past two decades. PRF and bioactive glass (BG) have shown effective results in the reduction of Probing pocket depth (PPD), Gain in clinical attachment level (CAL) and defect fill in intrabony defects.

**Materials and Methods:** Electronic searches were performed in PubMed, MEDLINE, Cochrane Library, Google Scholar and EbscoHost for the identification of relevant studies, till 30 September 2020 in English language. Additionally, hand search was also carried out in the relevant journals. The review protocol followed the PRISMA guidelines and was registered in PROSPERO (CRD42020211755). The risk of bias of the studies was independently evaluated using Cochrane Risk of Bias tool.

**Results:** Five RCTs were included, which investigated the effects of PRF as an adjunct to bioactive glass comparing with Bioactive glass alone in the treatment of intrabony defects. In all the included studies it was found that PRF as adjunct had better results in the outcomes measured when compared with Bioactive glass alone.

**Conclusion:** The current review has shown evidence suggesting that platelet rich fibrin can prove to be effective as a regenerative material, for the treatment of intrabony defects, in combination with bioactive glass.

## KEYWORDS

Platelet rich fibrin, Bioactive glass, Intrabony defects, Randomised controlled trial

## INTRODUCTION

Chronic periodontitis is an immunoinflammatory manifestation with loss of clinical attachment due to destruction of the attachment apparatus of the periodontium and adjacent supporting bone.[1,2] Periodontal diseases are characterized with destruction of connective tissue attachment with severe loss of periodontal tissues. The aim of the periodontal therapy is to eliminate the inflammatory processes present, to arrest the progression of periodontal disease, regeneration of the destructed periodontal tissues and maintenance of the oral health and desired function.[3,4]

Regeneration has been defined as reproduction or reconstitution of a lost or injured part to restore the architecture and function of the periodontium (American Academy of Periodontology 1992).[5] Regenerative approaches in contemporary periodontics have drastically increased patient's treatment options and enhanced future long-term health of most teeth that have periodontal destruction.[6]

Specific periodontal pathogens which include *Porphyromonas gingivalis (P.gingivalis), Prevotella intermedia (P. intermedia) and Treponema denticola (T. denticola), Tannerella forsythia (T. forsythensis,), Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum (F. nucleatum)* cause a host-mediated immune response which results in loss of the gingival tissues. Clinically, the disease results in the formation of soft tissue pockets or deepened crevices in between the gingiva and tooth root. If these sites are left untreated, destruction and loss of supporting bone will occur, which results in the formation of intrabony defects.[7,8,9]

Conventional open flap debridement (OFD) falls short of regenerating tissues destroyed by the disease, and current regenerative procedures offer a limited potential toward attaining a complete periodontal reconstruction.[10] Although to date the goal of predictable regeneration has not been attained, but there are evidences to suggest variety of treatment modalities that offer regenerative techniques which include the application of root conditioners, bone grafts, bone substitutes, guided tissue regeneration, growth factors, application of tissue engineering, stem cell therapy or the combination of two or more of the above listed approaches leading to significant amount of regeneration.[11,2]

Platelet-rich fibrin (PRF) described by Choukroun et al is a second-generation platelet concentrate that allows to retrieve fibrin membranes enriched with platelets and growth factors.

PRF comprises a fibrin network and leads to superior cell migration and proliferation.

Thus, it acts as a vehicle for carrying cells that are essential for tissue regeneration. It also serves as a resorbable membrane for guided tissue regeneration.[12]

One of the stand-alone factors in the regeneration and production of periodontal tissues are periodontal ligament cells. These are involved in synthesis of extracellular matrix as well as differentiation of cementoblasts and osteoblasts.[11,12]

Many growth factors that seem to play an important role in periodontal wound healing are platelet derived growth factor (PDGF), insulin-like growth factor (IGF) and transforming growth factor- β (TGF-β) which are released from PRF. Placing autologous platelets in periodontal defects elevates the local concentration of growth factors, which enhances the healing outcomes.[11,12]

PRF consists of a series of cytokines and structural glycoproteins embedded within the fibrin meshwork. These various components have well known synergestic effects on wound healing processes. PRF used in various surgical procedures such as intrabony periodontal defects, grade II furcation, sinus floor augmentation during implant placement, coronally displaced flap in multiple gingival recessions and in facial plastic surgery procedures have shown promising results.[10]

Bone replacement grafting materials remain among the most popular therapeutic modalities for the treatment of periodontal intrabony defects. A wide range of grafting materials, including autografts, allografts, xenografts, and synthetic materials, have been proposed and tried for the treatment of intrabony and furcation defects in periodontal conditions.[7] Alloplastic materials such as hydroxyapatite and tricalcium phosphate have been used in the treatment of intrabony defects.[13] One such synthetic bone graft that is bioactive glass, 45S5 Bioglass which has shown to bond to both bone and soft tissue. The term 'bioactive' has been defined (Hench & Wilson 1993)[14] as "a material that elicits a specific biological response at the interface of the material resulting in the formation of bond between the tissues and the material". This material differs from other bioactive ceramics in the rate of bonding to bone that can be controlled by varying the chemical composition.[15]

Bioglass is a silicate based alloplastic material, whose composition is 45% silica, 24.5% calcium oxide, 24.5% sodium oxide and 6% phosphorus pentoxide (by weight).

The unique and special feature of Bioglass, which makes it superior

from other bioceramic alloplastic materials, is the rapidity of a series of surface reactions which result in the formation of a hydroxycarbonate apatite layer.[16]

Bioglass once in contact with oral fluids, has an exchange of ions which results in formation of a physiochemical bond between the bioactive glass material, gingival tissue and bone.[11] This material has also been shown to be effective in maintaining the alveolar ridge following tooth extraction. Thus, the particulate composition of bioactive glass is especially promising for the treatment of intra bony defects arising from periodontal disease.[17]

In the present systematic review of clinical trials, bioactive glass is placed in the defect followed by placement of PRF over it as an interposition membrane. Such a protocol offers an improved space marking effect of the barrier, which is conducive to cell events leading to periodontal regeneration. With the resolution of inflammation there is shrinkage of gingival tissue due to increase in gingival recession. Placement of the PRF over the graft separates the interface between the gingival tissue and the root surface preventing epithelial migration. This helps to maintain the flap in a high and stable position, enhances neoangiogenesis and reduces the necrosis and shrinkage of the flap, thus providing maximal root coverage. These findings explain the biologic rationale for the use of a combination of BG and PRF.[1]

Hence the present systematic review aims to evaluate the efficacy of PRF when used as an adjunct to bioactive glass compared to bioactive glass alone for the treatment of intrabony defects in chronic periodontitis patient.

## MATERIAL AND METHODS

### 2.1) STUDY REGISTRATION AND PROTOCOL:

This systematic review was registered under the number CRD42020211755 in the PROSPERO database, created by the University of York, responsible for the registration and dissemination of systematic reviews and carried out according to the PRISMA guidelines.

### 2.2) FOCUSED QUESTION

Between Platelet rich fibrin with bioactive glass and bioactive glass alone which modality of treatment has better outcome in treating intrabony defects with chronic periodontitis patients in the age group of 20-50 years?

### 2.3) Eligibility Criteria

The PICO (patient, intervention, comparison, and outcome) strategy was followed in this systematic review which are key for designing all stages of an interventional systematic review.

### PICO ANALYSIS:

- (P) Types of participants: Adult human patients with age group of 20-50years diagnosed with chronic periodontitis who have completed a cycle of non-surgical periodontal therapy and present with residual pockets and intrabony defects (defects with a base apical to the interdental alveolar crest, surrounded by one, two or three bony walls or in combination with minimum 3 mm of intrabony component).
- (I) Types of interventions: A) Regenerative surgery with PRF as an adjunct to bioactive glass and bioactive glass alone.
- (C) Comparison between interventions: All possible comparisons between PRF with bioactive glass and bioactive glass alone in the treatment of intrabony defects.
- (O) Type of outcomes measures: Primary outcomes: CAL gain, PPD reduction, radiographic Bone Fill (RBF)
- (S) Types of studies: Only randomized controlled clinical trials (RCTs) were considered in the review.

Additionally,

**The following additional inclusion criteria were considered:**

RCTs, with or without a split-mouth design comparing the results of at least 2 of the investigated surgical techniques above in patients with periodontal intrabony defects≥ 3mm (2 or 3 walled defect radiographically)

- Studies with PPD ≥ 5mm and CAL ≥ 5mm following phase 1 therapy
- Studies with chronic periodontitis
- Only studies published in English were considered

**In this Systematic Review, the following points were considered as exclusion criteria:**

- RCTs comparing alterations in a same technique (i.e., PRF alone and Bioactive glass or PRP with Bioactive glass).
- RCTs with unclear/not specified type of treated intrabony defects.
- RCTs considering patients with localised aggressive periodontitis.
- RCTs evaluating data on tobacco consumption, pregnancy or medically compromised patients.
- Case reports, descriptive studies, review articles, editorial letters, conferences, book chapters, abstracts opinion articles, animal studies, insufficient information and *in vitro* studies will be excluded.

### 2.4) INFORMATION SOURCE AND LITERATURE SEARCH:

For the identification of randomization, clinical trials to be considered for inclusion in this systematic review, PubMed, MEDLINE, Cochrane Library, Google Scholar and EBSCOhost were employed as electronic databases, and a literature search was carried out with a personal computer on articles published up to and including September 2020.

Last electronic search was carried out on 30 September 2020. Following search electronically the terms alone and in combination were used in PubMed search builder:

PRF[All Fields] AND (bioactive[All Fields] AND ("glass"[MeSH Terms] OR "glass"[All Fields])) AND (intrabony[All Fields] AND ("abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "defects"[All Fields])) AND ("randomized controlled trial"[All Fields] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trial"[All Fields] OR "randomized controlled trial"[All Fields]) PRF[All Fields] AND (bioactive[All Fields] AND ("glass"[MeSH Terms] OR "glass"[All Fields])) AND (bioactive[All Fields] AND ("glass"[MeSH Terms] OR "glass"[All Fields]) AND alone[All Fields]) AND (intrabony[All Fields] AND ("abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "defects"[All Fields])) PRF[All Fields] AND ("Bioglass" [Supplementary Concept] OR "Bioglass"[All Fields] OR "perioglas" [All Fields]) AND (period[All Fields] AND alone[All Fields]) AND (intrabony[All Fields] AND ("abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "defects"[All Fields]))

Electronic search was carried out without any limits and language restriction to include all the possible clinical trials in the potentially relevant article search phase of the systematic review. Reference list of the reviews and of the identified randomized trials were also checked for possible additional studies. The article search was then narrowed down manually by the reviewer according to the inclusion criteria of the present systematic review to include all the RCTs in English language only and the articles involving treatment of intra bony defects.

Additionally, hand search was also carried out in all relevant journals up to and including June 2020.

JOURNALS INCLUDED FOR HAND SEARCH: Journal of Periodontology
Journal of Clinical Periodontology
Journal of Periodontal Research

### 2.5) STUDY SELECTION:

Study selection was conducted by independent reviewers in the following stages:

1. Initial screening of the potentially suitable titles and abstracts against the inclusion criteria to identify potentially relevant papers.
2. Before initial screening, all the items found through electronic and manual searches were grouped into a single list, excluding duplicates.
3. Independent screening of the titles and abstracts (when available) of all reports identified.
4. When studies met the inclusion criteria or when insufficient data from abstracts for evaluating inclusion criteria were gained, the full article was obtained.
5. Full text articles which met the inclusion criteria were considered eligible in the further screening.

### 2.6) DATA COLLECTION PROCESS AND DATA ITEMS:

All studies which met the inclusion criteria then were assessed for quality and data recording. A standardized specifically designed data extraction form was used to record data and a data chart was prepared from each included study, encompassing number of patients, demographics, definition and diagnosis of periodontitis, clinical methods (assessment and treatment), follow-up duration, clinical and radiographic outcomes and patient-reported outcomes. Two reviewers independently extracted data. When disagreement between the two reviewers was detected, consensus was achieved by discussion with the third reviewer/statistical advisor.

### 2.7) STUDY CHARACTERISTICS:

Only Randomised Controlled Trials, with or without a split-mouth design, was included in this SR. CAL gain had to be expressed as mean clinical attachment level increase in millimetres of the treated sites of each study arm at follow-up visit. PPD reduction had to be expressed as mean periodontal probing depth reduction in millimetres of the treated sites of each study arm at follow up visit. Radiographic BF (Bone Fill) had to be expressed as mean intrabony component decrease in millimetres of the treated intrabony defects of each study arm at follow-up visit. Pocket closure had to be reported as presence of PD≤ 4mm at experimental site at study follow-up. PROMs (Patient Reported Outcome Measures) and AE (Adverse Events) had to be described at least in a narrative form.

### 2.7) RISK OF BIAS IN INDIVIDUAL STUDIES:

Cochrane Risk of Bias tool was used for assessing the risk of bias. Majorly, seven domains (random sequence generation, allocation concealment, blinding of the outcome assessor, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other bias) were evaluated and included in a graph. The Risk of bias of the included studies were categorized according to given in figure 1:

(A) Low risk of bias if all domains were met.
(B) Unclear risk of bias if one or more domains were partly met.
(C) High risk of bias if one or more domains were not met.

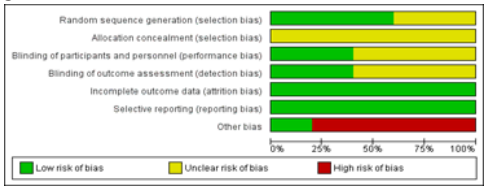


**Figure 1: The Risk of Bias Of The Included Studies Were Categorized As Follows:**

## RESULTS

### 3.1) STUDY SELECTION:

The search strategy provided a total of 1056 Studies. After screening the title and abstracts, 18 studies were found to be duplicates of which 11 studies were excluded (Table 1). The remaining 7 studies were potentially eligible and were read in full by the evaluators. At the end of the analyses, 5 articles published between 2016 to 2020 met the inclusion criteria and were included in the present systematic review. The flowchart of article screening and selection process is given in Figure 2.

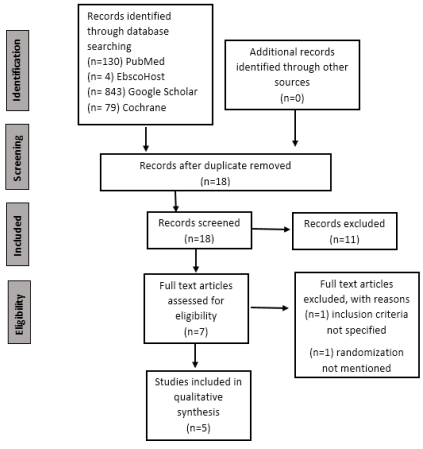


**Figure 2: Prisma Flow Diagram**

**Table 1: Table of excluded studies**

| AUTHORS | YEAR | TITLE | STUDY DESIGN | REASON FOR EXCLUSION |
|---|---|---|---|---|
| Rajula M et al | 2018 | Evaluation of Clinical Effectiveness of Bioactive - Glass and Platelet - Rich Fibrin in the Management of Intrabony Defects - A Comparative Study | A Comparative Study | Randomization not mentioned |
| Yajamanya S et al | 2017 | Bioactive glass versus autologous platelet-rich fibrin for treating periodontal intrabony defects: A comparative clinical study | A Comparative Clinical Study | Inclusion criteria not specified |
| Verma M et al | 2018 | Effective Management of Periodontal Intraosseous Defects using combination of Bioactive Glass + Platelet-rich Fibrin: A Clinical and Radiographic Evaluation | Case Report | Sample size less than 10 |
| Chhina et al | 2016 | Potential of Platelet Rich Fibrin in Regenerative Periodontal Therapy: Case Series | Case Series | Randomization not mentioned |
| Singh N et al | 2020 | A Study to Evaluate the Efficacy of Platelet Rich Fibrin with Nanocrystalline Beta-Tricalcium Phosphate in the Treatment of Periodontal Intrabony Defects | RCT | Different material used other than Bioactive Glass |
| Singh R et al | 2016 | Perioglas® And Prf As Graft Materials in The Treatment of Intrabony Defects in Chronic Generalized Periodontitis: A Clinical And Radiological Evaluation | Prospective RCT | Randomization not mentioned |
| Grover V et al | 2013 | Evaluation of the efficacy of a bioactive synthetic graft material in the treatment of intrabony periodontal defects | Comparitive study | Randomization not done |
| Satyanaraya na KV et al | 2012 | Clinical Evaluation of Intrabony Defects in Localized Aggressive Periodontitis Patients with and without Bioglass- An In-vivo Study | Prospective RCT | Inclusion criteria not met |
| Thorat et al | 2011 | Clinical effect of autologous platelet-rich fibrin in the treatment of intra-bony defects: a controlled clinical trial | Controlled clinical trial | Inclusion criteria not met |
| Subbaiah et al | 2011 | Efficacy of a bioactive alloplast, in the treatment of human periodontal osseous defects-a clinical study | Clinical Study | Different study design |
| Sharma A et al | 2011 | Treatment of 3-Wall Intrabony Defects in Patients With Chronic Periodontitis With Autologous Platelet-Rich Fibrin: A Randomized Controlled Clinical Trial | RCT | Difference in comparative group |

| | | | | |
|---|---|---|---|---|
| Zamet et al | 1997 | Particulate bioglass® as a grafting material in the treatment of periodontal intrabony defects | RCT | Difference in comparative group |
| Ong M et al | 1998 | Evaluation of a Bioactive Glass Alloplast in Treating Periodontal Intrabony Defects | RCT | No comparative group |

### 3.2) STUDY CHARACTERISTICS:

Details of the included studies are presented in table format in Table 2. The studies selected in this systematic review were published in the last 5 years which were all conducted in India. The studies included comparison between bioactive glass with PRF and bioactive alone in patients who were diagnosed with intrabony defects; the exact inclusion criteria was seen in all the studies, however only 1 study[26] varied in the inclusion criteria. All the studies reported the conduct of initial phase I therapy before the commencement of surgical procedure. The sample sizes of the all the included studies varied from 20 to 45 sites except for one study[1] which mentioned the sample size as 20 patients. Only 2 studies[1,2] considered a split mouth study design whereas the other three studies considered a parallel arm design. The included studies evaluated primary outcome measures as Probing pocket depth (PPD), Clinical Attachment Loss (CAL), both of these parameters were measured using UNC 15 probe and customized acrylic stents. Also, Radiographic Bone Fill (RBL) was assessed using radiographic techniques. However, there was heterogeneity in the techniques used, two studies assessed using Radiovisiograph[3,4] while the other two studies assessed using intra oral periapical[2,26]. Only Bodhare et al[1] evaluated using CBCT technique. The maximum follow-up ranged from 6 months to 9 months in the included trials.

**Table 2: Table of study characteristics**

| Author | Year | Country | Study Design | Age | Sample Size | Intervention And Comparison | Primary Outcomes | Measurement Of Parameters | Follow Up |
|---|---|---|---|---|---|---|---|---|---|
| Sravanan D et al | 2019 | India | RCT -Parallel group | 25-50 | 30 Sites | Group 1-PRF+Glass, Group 2- Bioactive glass alone | PPD, CAL And Bone Fill | UNC 15 Probe, Stents And Radiographs | Baseline And Post 6months |
| Bodhare G et al | 2019 | India | RCT- Split mouth | 35 | 20 Patients | Group 1-PRF+Bioactive glass , Group- Bioactive glass | CAL And Bone Fill | UNC 15 Probe, Stents And Radiographs | Baseline,3 And 6months |
| Agrawal I et al | 2017 | India | RCT- Parallel group | NA | 45 Sites | Group 1 - OFD+PRF, Group 2 - OFD + Novabone Putty , Group 3- OFD+PRF+Novabone Putty | Bone Fill | UNC 15 Probe, Stents And Radiographs | Baseline And 6months |
| Naqvi A et al | 2017 | India | RCT- Split mouth | 20-50 | 20 Sites | PRF+Bioactive active glass and Bioactive glass alone in intrabony defects | PPD, CAL And Bone Fill | UNC 15 Probe, Stents And Radiographs | Baseline,3,6 And 9months |
| Ashawan P et al | 2016 | India | RCT-Parallel group | 35 | 20 Sites | Group 1-PRF+Glass, Group - Bioactive glass alone | PPD, CAL And Bone Fill | UNC 15 Probe, Stents And Radiographs | Baseline, 3months And 6months |

### 3.3) RISK OF BIAS WITHIN AND ACROSS STUDIES:

Figure 3 below shows the methodological quality of the individual studies evaluated using the Cochrane Risk of Bias 2.0 tool. Three studies [1,2,26] showed low risk of bias with regard to selection bias. Only two studies [1,2] had blinded the outcome assessor, the participant and personnel. There were no concerns regarding attrition and reporting bias. Only 2 studies [1,2], presented with an overall low risk of bias amongst the included studies

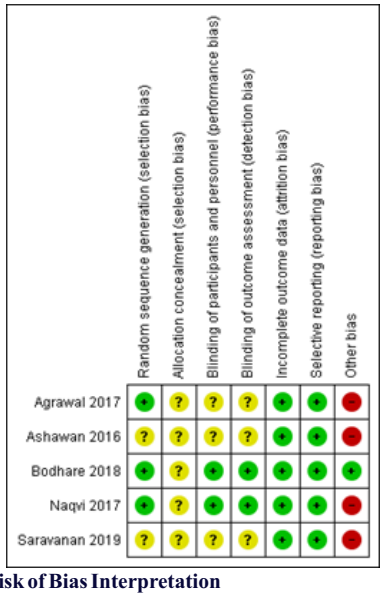


**Figure 3: Risk of Bias Interpretation**

### 3.4) RESULTS OF INDIVIDUAL STUDIES:

The general information of selected studies is summarized in Table 3. The included 5 studies were published between 2016 to 2020. All the studies were carried out in India and involved 155 sites in the age group of 20-50 years according to the intervention and comparison group of each included study. The follow-up interval of the studies ranged from baseline to 9 months, with a period minimum of up to 6 months. Out of 5 studies 2 studies were split mouth design while the other 3 were parallel arm design.

Two studies out of five also evaluated Gingival Recession between PRF group and Non PRF group and the results were found to be statistically significant in the PRF + Bioactive Glass (BG) group compared to PRF group alone. Out of the 5 studies 2 studies reported the data at baseline and after 6months, while other 2 studies reported the data at baseline, 3months and after 6months and 1 study reported a follow up period of baseline, 3 months, 6months and at 9months.

In the study by Bodhare et al [1] at 6 months, there was a statistically significant reduction in PPD in Group 1 when compared to Group 2. There was also statistically significant CAL gain at 3 months and 6 months in Group 1 when compared to Group 2. The difference in the measurement values of CEJ –BD at baseline and 6 months denotes the bone fill. At 6 months the mean CEJ-BD exhibited a reduction indicating a bone fill for Group 1 and Group 2 respectively. Bone fill was significantly higher for Group 1 when compared to Group 2.

Evaluating the study by Ashwanan et al [4] the mean pocket depth reduction, gain in clinical attachment level and gain in Bone fill showed no statistical significance when compared between test and control groups at baseline to 3 month and 6 month post-operatively.

In the study by Agarwal et al [26] there was statistically significant difference between bone fill and bone defect resolution in all groups from baseline to 6 months.

The study by Sravanan D et al [3] showed that the mean PPD was very significantly reduced in the test sites as compared to the control sites ($P < 0.001$). Similarly, mean CAL was also significantly reduced in the test sites as compared to the control sites ($P < 0.001$). A further radiographic evaluation revealed that the mean radiographic defect fill (RDL) was significantly higher in test sites.

The study by Naqvi et al [2] showed a significantly greater mean bone fill which was found in the test group (7.1 ±1.37 mm) as compared to the control group (5.7±1.64 mm), (p-value<0.043) the difference in PPD

between the test and the control group was not significant. A greater gain in CAL from baseline to 9 months was found in test group (4.10±1.73) when compared to the control group (3.15±1.06).

## DISCUSSION

### 4.1) SUMMARY OF EVIDENCE

Periodontal regeneration is a biological term defined histologically as reconstitution of the tooth's supporting tissues, including periodontal ligament, alveolar bone and cementum over a root surface deprived of the attachment apparatus.

Platelet-rich fibrin (PRF), developed by Choukroun et al 2001, is a second-generation platelet concentrate which is widely used to accelerate soft and hard tissue healing. It is advantageous over the more extensively used platelet-rich plasma (PRP). PRF is capable of increasing osteoblast attachment, proliferation and simultaneously up regulating collagen-related protein production. Effective bone regeneration is promoted by these actions in combination.

Bioactive glasses are alloplastic materials and act by osteoconduction. Bioglass particulate exhibits enhanced new bone formation which is many times faster as compared to hydroxyapatite.

The aim of periodontal therapy is to arrest and control the periodontal infection and finally to regenerate lost periodontal structures. The complete regeneration of the periodontium has been difficult to achieve because of differences in healing abilities among periodontal tissues. [10]

To improve the quality of this systematic review, we included only randomised controlled clinical trials for the systematic review analysis. Also, only studies involving PRF as an adjunct with bioactive glass and bioactive glass alone by the investigators were included in this systematic review.

The present systematic review analysed the 9 months efficacy of bioactive glass with PRF procedures in the management of intrabony defects in patients with chronic periodontitis as there is limited research to conclusively evaluate the efficacy of PRF as an adjunct to bioactive glass and bioactive glass alone in treatment of intrabony defects.

In all the included studies, the primary outcomes were assessed using custom made occlusal acrylic stents with grooves to standardize the UNC 15 probe angulation and position and bone fill was assessed using radiographs.

No clinical evidences of undesirable local and systemic responses were detected and it indicated that not only the two materials but also their combination, were well tolerated. Most of the studies reported a gain in CAL, and bone fill and reduction in PPD.

Two studies [1,4] mentioned the use of imaging techniques to measure radiographic bone fill out of which study by Bodhare et al [1] used CBCT scans and the study by Ashwanan et al [4] made the use of intraoral radiovisiograph.

All the studies had primary outcomes as Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL) and Radiographic Bone Fill, however 2 studies that is Bodhare et al [1] measured only CAL and bone fill as a primary outcome while Agarwal et al [26] measured only bone fill as primary outcome.

In the study by Bodhare et al [1] at 6 months, there was a statistically significant reduction in PPD for both the groups at 6 months when compared to baseline. Similarly, study by Sravanan D et al [3] showed that the mean PPD was very significantly reduced in the test sites as compared to the control sites ($P < 0.001$) meanwhile 2 studies Naqvi et al [2] and Ashwanan et al [4], the mean pocket depth reduction showed no statistical significance when compared between test and control groups.

There was statistically significant CAL gain when compared to baseline in all the studies in this Systematic review except the study by Ashwanan et al [4] where gain in clinical attachment level showed no statistical significance when compared between test and control groups at baseline to 3 month and 6 month post-operatively.

The study by Naqvi et al [2] showed statistically significantly greater bone fill (p-value<0.043) which was found in the test group as compared to the control group. Similarly, the study by Bodhare et al [1] and D Sarvanan et al [3] revealed a significantly higher mean radiographic bone fill in test sites treated with bioactive glass and PRF. However, Ashwanan et al [4] and Agrawal et al [26] showed no statistically significant result between test and control groups.

Results of meta-analysis reports by Singh MP et al [27] with respect to the treatment of intrabony defects, support the following: When compared to OFD procedures alone, using bone grafts in combination with OFD increase bone level, reduce bone loss, increase clinical attachment level, and reduce PPDs. Taking into account the results obtained, it can be said that bone grafting is one of the most promising forms of regenerative therapy.

The risk of bias was high for three studies [3,4,26] and low for two studies [1,2] in all the domains. To minimize the risk of bias, it is expected that future research must be conducted with high methodological rigor aimed at better methods of allocation concealment and the blinding proposed used in the trials.

**Table 3: Results of Included Studies**

| STUDY | | PPD | CAL | RBL |
|---|---|---|---|---|
| | | p- value | | |
| Bodhare et al | 3 months | -- | -- | **--** |
| | 6 months | 0.8268 | 0.0282 | **0.0077** |
| | 9 months | -- | -- | -- |
| Ashwanan et al | 3 months | 0.180 | 0.640 | 0.156 |
| | 6 months | 0.394 | 0.863 | 0.185 |
| | 9 months | -- | -- | -- |
| Agarwal et al | 3 months | -- | -- | -- |
| | 6 months | 0.260 | 0.450 | **0.001** |
| | 9 months | -- | -- | -- |
| Sravanan et al | 3 months | -- | -- | -- |
| | 6 months | **<0.001** | **<0.001** | **<0.001** |
| | 9 months | -- | -- | -- |
| Naqvi et al | 3 months | 0.169 | 0.371 | 0.466 |
| | 6 months | 0.9512 | 0.148 | **0.049** |
| | 9 months | 0.117 | 0.155 | **0.043** |

## LIMITATIONS

**Certain limitations to the present systematic review such as:**

1. Measurement of clinical parameters based upon the sites was not standardized.
2. Radiographic evaluation differed in each study which is subjective of re-evaluation
3. Varied Study designs protocol were used in the studies which could lead to increase in risk of bias
4. Larger sample size is required to provide statistically significant result
5. Longer follow up duration would give us a better and a clear evaluation of the data recorded.

## CONCLUSION

Based on the present systematic review it can be concluded that the evidence for beneficial additive effect of Platelet rich fibrin in regenerative treatment of intra bony defects has been increasing in recent years. Platelet rich fibrin can prove to be effective as a regenerative material, for treatment of intra bony defects, in combination with bioactive glass. Further long term, multi-centre clinical trials are essential to authenticate these treatment strategies in evidence based practice.

## DECLARATIONS

**Author contribution statement:**

All authors listed have significantly contributed to the development and the writing of this article.

**Funding statement:**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Competing interest statement:**

The authors declare no conflict of interest.

## REFERENCES

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