Additive effect of platelet rich fibrin in treatment of Intrabony defects- a systematic review and meta-analysis

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ABSTRACT

Background: Over years various treatment modalities have been used in the management of periodontal intra bony defects effectively. Application of Autologous platelet concentrates has been widely applied to treat periodontal intra bony defects either solely or in combination with various other regenerative procedures. Aim: To systematically evaluate the additive effect of Platelet rich fibrin (PRF) in treatment of intra bony defects when used along with other regenerative procedures in terms of clinical and radiological outcomes. Material and methods: Randomized clinical trials evaluating the additive effect of Platelet rich fibrin (PRF) in treatment of intra bony defects were identified through screening in electronic databases and hand search in relevant journals. Reporting and methods were evaluated through an analysis of risk of bias and quality scores. Meta-analysis was also carried out for the variable of interest. Results: Four clinical trials were identified accomplishing inclusion criteria after full text reading and focused on evaluating additive effect of Platelet rich fibrin (PRF) when used with open flap debridement. Conclusion: Platelet rich fibrin (PRF) can prove to be effective as a sole regenerative material, for treatment of intra bony defects, in combination to open flap debridement.

KEY WORDS: Platelet rich fibrin, Intra bony defects, Chronic periodontitis

INTRODUCTION

Regeneration has been defined as the reproduction or reconstitution of a lost or injured part to restore the architecture and function of the periodontium. (American Academy of Periodontology 1992). The goal of periodontal therapy has always been the regeneration of lost attachment apparatus. The objective of the periodontal reconstructive therapy is to regenerate all the tissues of the periodontium, including a functional periodontal ligament, alveolar bone and cementum. Currently, there is a variety of treatment modalities available for periodontal regenerative therapy, which includes bone grafts and substitutes, guided tissue regeneration, the use of growth factors, applications of tissue engineering, or combination of two or more of the above listed approaches.

The contribution of blood derived platelets to the bone healing process is thought to be based on the GFs present in it. The following GFs are reported to be present in platelet aggregates: platelet derived growth factor (PDGF), transforming growth factor-beta (TGF B), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), insulin like growth factor 1 (IGF1), and basic fibroblast growth factor (bFGF), as well as three blood proteins known to act as cell adhesion molecules for osteo-conduction (fibrin, fibronectin and vitronectin).

In recent years, there has been a growing interest in the use of platelet concentrates for the treatment of many intraoral clinical conditions, including periodontal defects. However, there has been no agreement about the advantages derived from the adjunct of platelet concentrates to periodontal surgical procedures and various regenerative materials in some reviews.

The first systematic review by Plachokova et al in 2008 that evaluated the effect of platelet rich plasma on clinical applications in dentistry reported beneficial effects of PRP in treatment of periodontal defects. Another systematic review by Kotsovillis et al evaluated the effect of a PRP adjunct in treatment of intra osseous defects underlined the limits and the heterogeneity of available data and cautiously concluded that the specific selection of bioactive agents and procedures combined with PRP may be important. A recent systematic review by Delfabro et al also evaluated the effect of platelet rich plasma in various regenerative procedures of periodontal defects and gingival recession and concluded that PRP may be advantageously used as an adjunct to grafting procedures in treatment for intrabony defects.

Autologous Platelet concentrates includes the Platelet rich plasma, Platelet rich fibrin, as, which in recent times being dramatically used as an adjunct in various regenerative procedures for treating intraosseous defects. The adjunctive use of platelet concentrates is recent and it’s efficiency remains controversial. Several techniques for platelet concentrates are available, however their applications have been confusing because each method leads to a different product with different biology and potential uses. Platelet concentrates are
classified in to four categories, depending on their leucocyte and fibrin content: P-PRP(Pure), L-PRP(Leucocyte), P-PRF (Pure) and L-PRF (Leucocyte).

Platelet rich fibrin (PRF) is considered as a second generation platelet, as its technique of preparation is simpler when compared to PRP. In addition, the GFs in PRF shows a sustained release for a period of 21 days with a peak rise at 7 days thereby inducing proliferation, differentiation and migration of cells responsible for periodontal regeneration.

To our knowledge, till date, there has been no evidence based systematic review evaluating the additive effect of Platelet rich fibrin (PRF) in regenerative treatment of periodontal intrabony defects. Hence, the aim of this systematic review is to systematically evaluate the additive effect of Platelet rich fibrin (PRF) in treatment of intra bony defects when used in combination with other regenerative procedure in terms of clinical and radiological outcomes.

MATERIAL AND METHODS

STRUCTURED QUESTION:
1. What is the effect of Platelet rich fibrin (PRF) in treatment of intra bony defects when used in combination with other regenerative procedures?

PICO ANALYSIS:
Patients: Patients with periodontal intra bony defects
Intervention: Treated with application of PRF in combination with other regenerative procedures
Comparison: Compared to those treated with regenerative procedures alone.

LITERATURE SEARCH:
For the identification of randomization clinical trials to be considered for inclusion in this systematic review, PUBMED, MEDLINE and COCHRANE CENTRAL were employed as electronic databases, and a literature search was carried out with a personal computer online in electronic form prior to its publication in material form (according to the so-called ‘E-pub ahead of print’) were considered eligible for inclusion in this systematic review. Last electronic search was carried out on 30 June 2012. Following search terms alone and in combination were used by means of PUBMED search builder:

“platelet rich plasma”, “autologous platelet concentrate”, “platelet rich fibrin”, “intra bony defects”, “infra bony defects”, “two-walled defects”, “three-walled defects” etc.

No Limits and language restriction were applied during the electronic search to include all the possible clinical trials in the potential relevant article search phase of the systematic review. No time restriction was applied. 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 2012.

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

INCLUSION CRITERIA:
The inclusion criteria for the articles to be included in this present systematic review were as follows:
1. RCT, either of a parallel group or of a split-mouth design.
2. Presence of at least one experimental group, in which PRF was clinically applied as an adjunct to other therapeutic bioactive agents / procedures for the therapy of periodontal intra osseous defects.
3. Presence of an appropriate non-PRF control group, in which the same therapeutic bioactive agents/procedures as those employed in at least one experimental group were clinically applied for the therapy of periodontal intra osseous defects, without the adjunctive effect of PRF.
4. All patients included in the RCT should present with intra bony defects.
5. All patients included in the RCT should have no systemic diseases that could potentially influence the outcome of periodontal therapy.
6. Publication in the dental literature in English language.
7. Report of clinical attachment level and pocket depth or defect depth at baseline and at the end of follow-up period as outcome variables.

EXCLUSION CRITERIA:
1. Mixed RCT design, including both parallel group and split design.
2. Articles having follow-up period of less than 9 months.
3. Periodontal intra bony defects extending into furcation areas of teeth.
4. Periodontal intra bony defects extending apically with endodontic involvements.

TYPES OF OUTCOME MEASURES
Gain in clinical attachment level is considered as the primary outcome variable and Pocket depth reduction and Radiological bone fill as secondary outcome variable.

SEARCH RESULTS:
An electronic search was conducted in database of PUBMED to identify the relevant RCTs. (Table 1) Altogether 51 studies were found and screened for inclusion. 44 of the studies were excluded after examining the title and the abstract due to non-relevance of the topic to the need. Full texts of 7 studies were retrieved for detailed evaluation. 3 studies were excluded after detailed evaluation for which the reason of exclusion is stated in Table 2. Therefore 4 studies were included in the review( Table 3). The systematic search flow chart has been included in Figure 1. The general information of the se-
Table 1: Search Methodology

Search Builder

((Platelet[MeSH Major Topic]) OR (platelet rich fibrin) OR (autologous platelet concentrate) OR (platelet rich concentrate) OR (PRF)) AND ((Periodontitis[MeSH Major Topic]) OR (Chronic Periodontitis[MeSH Major Topic]) OR (Aggressive Periodontitis[MeSH Major Topic]) OR (Periodontal disease[MeSH Major Topic]) OR (intra-bony defects) OR (infrabony defects) OR (angular defects) OR (vertical interproximal defects) OR (endo-osseous defects) OR (two walled defects) OR (three walled defects) OR (infrabony defects))

Table 2: Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Author and Year</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lekovic et al 2011</td>
<td>Control and experimental group both uses PRF</td>
</tr>
<tr>
<td>2</td>
<td>Chang et al 2011</td>
<td>Not a clinical trial</td>
</tr>
<tr>
<td>3</td>
<td>Christagau et al 2006</td>
<td>Use of Platelet Rich Plasma</td>
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</tbody>
</table>

Table 3: General information of selected articles

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Author</th>
<th>Study Test</th>
<th>Control Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pradeep et al 2012</td>
<td>RCT-PRF</td>
<td>OFD Significant decrease in PD when PRF vs. OFD and PRF/HA VS OFD P&lt;0.001</td>
</tr>
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<td>2</td>
<td>Pradeep et al 2012</td>
<td>RCT-Parallel</td>
<td>B-6.40 ± 1.33 9-3.37 ± 0.56 PRF+HA B-6.63 ± 1.10 9-2.97 ± 0.93 Significant decrease in PD when PRF vs. OFD and PRF/HA VS OFD P&lt;0.001</td>
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<td>3</td>
<td>Thorat et al 2011</td>
<td>RCT-Parallel</td>
<td>B-7.88 ± 2.19 9-3.19 ± 1.05 Significant PD reduction both between and within group P&lt;0.001</td>
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<td>4</td>
<td>Sharma A et al 2011</td>
<td>RCT-Parallel</td>
<td>B-8.56 ± 1.67 9-4.02 ± 2.11 Significant PD reduction both between and within group P&lt;0.001</td>
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Table 4: general interpretation of pocket depth reduction of selected articles

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Table 5: General interpretation of gain in clinical attachment of selected articles

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<tr>
<th>Sl. No.</th>
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<th>Study Test</th>
<th>Control Interpretation</th>
</tr>
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<tr>
<td>1</td>
<td>Pradeep et al 2012</td>
<td>RCT-PRF</td>
<td>OFD Significant increase in CAL gain both within and between the groups P&lt;0.001</td>
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<td>Pradeep et al 2012</td>
<td>RCT-Parallel</td>
<td>B-6.40 ± 1.33 9-3.37 ± 0.56 PRF+HA B-6.63 ± 1.10 9-2.97 ± 0.93 Significant increase in CAL gain both within and between the groups P&lt;0.001</td>
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</table>

Figure 1: Search Flow Chart
Table 6: General interpretation of radiological bone fill of selected articles

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Author and year</th>
<th>Study design</th>
<th>Test group</th>
<th>Control group</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pradeep et al 2012</td>
<td>RCT Parallel</td>
<td>PRF- B- 5.80 ± 0.81</td>
<td>Significant bone fill when PRF Vs. OFD</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>2.</td>
<td>Pradeep et al 2012</td>
<td>RCT Parallel</td>
<td>PRF+HA- 9- 4.87 ± 1.04</td>
<td>PRF + HA Vs OFD</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>3.</td>
<td>Thorat et al 2011</td>
<td>RCT Parallel</td>
<td>B-5.06 ± 0.82</td>
<td>Significant bone fill in test group as compared to control</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Sharma A et al 2011</td>
<td>RCT Parallel</td>
<td>PRF+HA- 9- 4.87 ± 0.92</td>
<td>Significant bone fill both within and between the group.</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 2: Forest plot depicting reduction in pocket depth for experimental group over control group.

Figure 3: Funnel plot depicting reduction in pocket depth for experimental group over control group.

Figure 4: Forest plot depicting gain in clinical attachment level for experimental group over control group.

Figure 5: Funnel plot depicting gain in clinical attachment level for experimental group over control group.

QUALITY ASSESSMENT OF INCLUDED STUDIES:
Quality assessment for the included RCTs were performed in accordance to Cochrane Reviewer’s Handbook (Higgins and Green 2009). The included RCTs were evaluated through four methodological RCT phases: (i) sequence generation / method of randomization (ii) Allocation concealment (iii) blinding of personnel and outcome assessors and (iv) completeness of outcome data. (Table 7) Four other criteria were also evaluated for estimating the risk of bias. These includes: (i)Sample size determination, (ii) Baseline comparisons, (iii) Inclusion and Exclusion criteria and (iv) Presence/absence of any error in methodology. (Table 8)
The meta-analysis performed taking gain in clinical attachment level as outcome variable reported with one study\(^{35}\) standing out of funnel plot indicating a varied result.

DISCUSSION:

Meta-analysis: The results of meta-analysis performed taking reduction in pocket depth were consistent with this finding where one study\(^{29}\) lies beyond the funnel plot depicting the study showing a varied reduction in pocket depth. This variation of pocket depth reduction in this particular study\(^{29}\) may be due to lack of baseline comparison and inclusion of defect with varied characteristics. The meta-analysis performed taking gain in clinical attachment level as outcome variable reported with one study\(^{35}\) standing out of funnel plot indicating a varied result. However, a long term follow up would eliminate this heterogeneity and provide a much reliable result.

CONCLUSION:

Based on the results obtained from the present systematic review it can be concluded that the 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 sole regenerative material, for treatment of intra bony defects, in combination with open flap debridement. Further long term, multi centre clinical trials are essential to authenticate these treatment strategies in evidence based practice.

RESULTS:

Interpretation of results:

Four studies\(^{29,30,34,35}\) were included in this systematic review which evaluates the effect of Platelet Rich Fibrin when used along with open flap debridement (OFD). Out of these 4 studies, 2 studies\(^{29,34}\) showed a significant pocket depth reduction and clinical attachment gain with use of PRF in test group, when compared to control group, where only open flap debridement procedure was employed. When compared within the groups, PRF used as an adjunct group showed a statistically significant Pocket depth reduction and CAL gain, at the end of the follow up, in all the 4 studies\(^{29,30,34,35}\). All of the studies were designed with a 9 month follow up duration.

Radiologically, the bone fill was found to be statistically significant in all of the 4 studies\(^{29,30,34,35}\), suggesting that the use of PRF as an adjunct with OFD, showed a much higher significant bone fill, than what could have been achieved by OFD alone.

Quality of studies looked up on:

All of the articles included in this systematic review are of high quality based up on a score of “low” for risk of bias. Moreover, all studies included are randomized clinical trials with high level of evidence of score “2”. Hence, the interpretations obtained from these studies are proposed to be reliable.

Meta-analysis:

The results of meta-analysis performed taking reduction in pocket depth were consistent with this finding where one study\(^{29}\) lies beyond the funnel plot depicting the study showing a varied reduction in pocket depth.

REFERENCES


28. Piemontese M, Aspriello SD, Rubini C, Ferrante L, Procaccini M. Treatment of periodontal intrabony defects with demineralized freeze-dried bone allograft in combina-


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