Effectiveness of Adjuncts with Demineralized Freeze Dried Bone Allograft in Treatment of Intrabony Defects – A systematic review

GB Parthasarathy¹, ND Jayakumar², M Sankari², SS Varghese², G Karthikayan², S Panda²

Abstract

Objective: To systematically evaluate the effect of adjuncts with demineralized freeze dried bone in the treatment of intrabony defects in terms of clinical and radiological outcomes.

Methods: A search was conducted for randomized controlled trials in cases of chronic periodontitis to evaluate the effect of adjuncts with demineralized freeze dried bone in the treatment of intrabony defects. The electronic databases like PUBMED and the Cochrane Central Register of Controlled Trials were used as data sources. Gain in clinical attachment level was considered as the primary outcome variable while Pocket depth reduction and Radiological bone fill were considered to be the secondary outcome variables.

Results: Of all the articles screened, seven controlled human clinical trials met the eligibility criteria and provided clinical and radiological outcome data on the effectiveness of adjuncts with Demineralized Freeze Dried Bone Allograft (DFDBA) in the treatment of intrabony defects. Amongst the above mentioned seven trials, three controlled clinical trial showed significant results while four controlled clinical trials did not show significant results. From this systematic review, it can be concluded that the treatment with Autologous Platelet Concentrate (PRP) in combined with DFDBA showed significant results in probing pocket depth reduction and clinical attachment level gain. Cyclosporine with DFDBA showed significant radiological bone fill and Enamel Matrix Derivative (EMD) in combination with DFDBA with 12 months follow-up showed significant soft tissue and hard tissue healing. However, long term studies are needed to clarify the effectiveness of adjuncts with DFDBA in the treatment of intrabony defect.

Conclusion: PRP in combination with DFDBA showed significant results in probing pocket depth reduction and clinical attachment level gain. Cyclosporine with DFDBA showed significant radiological bone fill and EMD in combination to DFDBA with 12 months follow-up showed significant soft tissue and hard tissue healing. However, long term studies are needed to clarify the effectiveness of adjuncts with DFDBA in the treatment of intrabony defect.

Key words: Demineralized freeze dried bone allograft; Chronic periodontitis; Intrabony defect; Guided tissue regeneration; Antimicrobials; Immunosuppressive agents; Autologous platelet concentrate and Enamel matrix derivative

Effetividade da utilização de enxertos ósseos desmineralizados liofilizados no tratamento de defeitos intraósseos – uma revisão sistemática

Resumo

Objetivo: Avaliar de forma sistemática o efeito da utilização de enxertos ósseos desmineralizados liofilizados, com adjuvante, no tratamento de defeitos intraósseos, com desfechos clínicos e radiográficos.

Métodos: Foi realizada uma busca por ensaios controlados e randomizados em casos de periodontite crônica para avaliar os efeitos da utilização de enxertos ósseos desmineralizados liofilizados como adjuvantes no tratamento de defeitos ósseos. Para tal, foram utilizadas as bases de dados PUBMED e COCHRANE. O ganho nos níveis de inserção clínica foi considerado como a variável primária no desfecho, enquanto a redução da profundidade de sondagem e a qualidade óssea ao exame radiográfico foram definidas como variáveis secundárias.

Resultados: De todos os artigos avaliados, sete ensaios clínicos controlados alcançaram os critérios de elegibilidade, apresentando dados clínicos e radiológicos acerca da efetividade dos enxertos ósseos desmineralizados liofilizados, utilizados como adjuvantes no tratamento de defeitos intraósseos. Dentre os sete estudos selecionados, três ensaios clínicos mostraram resultados significativos, enquanto quatro ensaios não mostraram dados significativos. A partir desta revisão sistemática, é possível concluir que o tratamento com plasma rico em plaquetas, associado com enxerto de osso desmineralizado liofilizado apresenta resultados favoráveis, com a redução da profundidade de sondagem, além de ganho nos níveis de inserção clínica. Por outro lado, a combinação de ciclosporina A, com enxerto ósseo desmineralizado liofilizado, resultou em melhora significativa da qualidade óssea ao exame radiográfico. A avaliação da combinação de derivados da matriz do esmalte, com enxerto ósseo desmineralizado liofilizado, revelou melhora do reparo de tecidos moles e duros, de acordo com avaliação ao longo de 12 meses.

Conclusão: Apesar dos efeitos promissores da combinação de enxertos ósseos desmineralizados liofilizados com plasma rico em plaquetas, ciclosporina A ou derivados da matriz do esmalte, estudos adicionais em longo prazo ainda são necessários para confirmar a efetividade da utilização de enxertos ósseos desmineralizados liofilizados para o tratamento de defeitos intraósseos.

Palavras-chave: Enxertos ósseos desmineralizados liofilizados; Periodontite crônica; Defeitos intraósseos; Regeneração tecidual guiada; Antibióticos; Agentes imunossupressores; Plasma rico em plaquetas; Derivados da matriz óssea

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Received: October 10, 2014
Accepted: October 21, 2015

Conflict of Interests: The authors state that there are no financial and personal conflicts of interest that could have inappropriately influenced their work.

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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 periodontal reconstructive therapy is to regenerate all the tissues of the periodontium, including a functional periodontal ligament, alveolar bone and cementum. Currently, there are various treatment modalities available for periodontal regenerative therapy, inclusive of bone graft, guided tissue regeneration, growth factors, or combination of two or more of the above listed approaches.

Allografts can be obtained from a tissue bank in the form of freeze dried bone allograft (DFDBA) or demineralized freeze dried bone allograft (DFDBA). The use of DFDBA in periodontal defects has become popular since studies have reported defect fill of greater than 50% in majority of the treated sites. Histologically, when placed in infrabony defects, DFDBA demonstrated significantly more new cementum, new connective tissue, and bone formation in infrabony defects grafted with DFDBA than in non-grafted sites. Allografts, in general, have osteoinductive potential which induces bone formation due to the influence of bone induction proteins (BMPs). The primary action of BMPs is to differentiate the mesenchymal precursor cells.

In Platelet rich protein (PRP), platelet-derived growth factor (PDGF) has the primary effect of a mitogen, initiating cell division. It was shown that osteoblasts proliferated in response to PDGF alone or with the addition of a progression factor, to induce mitosis. Similar results were also found with isolated periodontal ligament (PDL) cells. Transforming growth factor-beta (TGF-β), a multifunctional growth factor that is chemotactic for bone cells, increases the differentiation property of osteoblasts, osteoblast precursors and extracellular matrix formation, such as type I collagen. Further, it stimulated the proliferation of gingival fibroblastic cells, formation of blood vessels, remodeling of extracellular matrix and formation of granulation tissue during the healing of periodontal tissue. PDGF and TGF-β are abundant in the alpha granules of platelets.

Guided tissue regeneration (GTR) is based on the exclusion of gingival connective cells from the wound and prevention of the apical downgrowth of gingival epithelial cells inside the osseous defects which, because of this periodontal defect, can be colonized only by cells derived from the surrounding periodontal ligament. Polylactic acid, polyglycolic acid (PLA/PGA) membrane is synthethic bioabsorbale barrier membrane made from a copolymer of glycolide and lactide broken down by hydrolytic degradation.

Tetracycline is thus added to graft materials to combine these desirable properties with those of the graft material. The immunosuppressant, cyclosporine-A (CsA) has been used to prevent the organ transplant rejection through its suppression action on specific T-cell populations. Augmenting the results of a morphometric finding, a study on rats suggests that an increased quantity of bone formation is induced by DFDBA with Cyclosporine A (CsA)-administration. Taking a clue from the above observations, it appears logical that if CsA is incorporated into DFDBA, it may ward off any possible side-effect of CsA.

The assumption of combining graft material with EMD is based on the fact that two distinct wound healing processes, osteoinduction and /or osteoconduction, and promotion of periodontal regeneration, respectively, may exert a synergistic effect. The graft helps to overcome the risk of a flap collapse following application of EMD, especially in deep intrabony defects, enhancing wound stability and providing space for the regeneration process. At the same time, the DFDBA graft also allows EMD to enhance periodontal regeneration. Use of DFDBA serves the purpose of scaffold with certain differentiation factors like bone morphogenic protein (BMP). However, there is a lack of signaling molecules which accentuate the process of healing by inducing cell proliferation. Hence, the use of adjuncts like PRP or EMD can have additive effects. Further, the use of GTR, antimicrobials and immunosuppressive drugs has also shown significant effects in both soft tissue and hard tissue healing. Hence, the aim of the present systematic review is to evaluate the effect of use of these adjuncts with DFDBA in treatment of intrabony defects, in terms of clinical and radiological outcomes.

Structured Questions:

1. What is the effect of Autologous Platelet Concentrates (APCs) along with DFDBA in the treatment of intrabony defects when used alone or in combination? PICO ANALYSIS:
   - Patients: Patients with periodontal intrabony defects.
   - Intervention: Treated with application of APCs and DFDBA.
   - Comparison: Compared to those treated with DFDBA alone.
   - Outcome: To be assessed in terms of Pocket depth reduction, Gain in attachment level and Defect fill.

2. What is the additive effect of enamel matrix derivative along with DFDBA in the treatment of intrabony defects? PICO ANALYSIS:
   - Patients: Patients with periodontal intrabony defects.
   - Intervention: Treated with addition of enamel matrix derivative with DFDBA.
   - Comparison: Compared with those treated with DFDBA alone.
   - Outcome: To be assessed in terms of Pocket depth reduction, Gain in attachment level and Defect fill.
3. What is the additive effect of Antimicrobial drugs along with DFDBA in the treatment of intrabony defects?

PICO ANALYSIS:

- **Patients:** Patients with periodontal intrabony defects.
- **Intervention:** Treated with addition of antimicrobial drugs along with DFDBA.
- **Comparison:** Compared with those treated with DFDBA alone.
- **Outcome:** To be assessed in terms of Pocket depth reduction, Gain in attachment level and Defect fill.

4. What is the additive effect of immunosuppressive drugs along with DFDBA in the treatment of intrabony defects?

PICO ANALYSIS:

- **Patients:** Patients with periodontal intrabony defects.
- **Intervention:** Treated with addition of immunosuppressive drugs along with DFDBA.
- **Comparison:** Compared with those treated with DFDBA alone.
- **Outcome:** To be assessed in terms of Pocket depth reduction, Gain in attachment level and Defect fill.

5. What is the additive effect of guided tissue regeneration (GTR) along with DFDBA in treatment of intrabony defects?

PICO ANALYSIS:

- **Patients:** Patients with periodontal intrabony defects.
- **Intervention:** Treated with addition of GTR along with DFDBA.
- **Comparison:** Compared with those treated with DFDBA alone.
- **Outcome:** To be assessed in terms of Pocket depth reduction, Gain in attachment level and Defect fill.

**Methods**

**Search Strategy**

For the identification of randomized 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 on articles published up to and including July 2013. Articles available online in the electronic form prior to its publication in material form (according to the so-called ‘E-pub ahead of print’) were also considered eligible for inclusion in this systematic review. Last electronic search was carried out on 30 July 2013. Following search terms alone and in combination were used by means of PUBMED search builder: “demineralized freeze dried bone allograft”, “DFDBA”, allograft, allogenic graft material, allogenic graft material, “infra bony defects”, “intrabony defects”, “two-walled defects”, “three-walled defects”, osseous defects, angular defects, vertical defects, apico-coronal defects, walled defects, adjuncts, adjuvants, emdogain, EMD, platelet rich fibrin, PRF, platelet rich plasma, PRP, autologous platelet concentrate, guided tissue regeneration, GTR, barrier membrane, resorbable membrane, non-resorbable membrane, growth factor, signaling molecule, platelet derived growth factor, PDGF, bone morphogenic protein, BMP, root conditioning, root biomodification, immunosuppressive drugs, tetracycline, citric acid, EDTA, probing depth, clinical attachment level, radiological defect depth, bone fill.

The authors did not apply any limits and language restriction during the electronic search in order to include all the possible clinical trials in the potential relevant article search phase of the systematic review. Time restriction was also not 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 intrabony defects. Additionally hand search was also carried out in all relevant journals up to and including July 2013.

**Journals Included for Hand Search**

- Journal of Periodontology.
- Journal of Clinical Periodontology.

**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 DFDBA in combination to adjuncts was used for the therapy of periodontal intra osseous defects.
3. Presence of an appropriate control group, in which DFDBA alone was used for the therapy of periodontal intra osseous defects, without the adjuncts.
4. All patients included in the RCT should present with intrabony 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 at baseline and at the end of follow-up period as the primary outcome variable and pocket depth or defect depth at baseline and at the end of follow-up period as secondary outcome variable.

**Exclusion Criteria**

1. Mixed RCT design, including both parallel group and split design.
2. Articles having follow-up period of less than 6 months.
3. Periodontal intrabony defects extending apically with endodontic involvements.

**Types of Outcome Measures**

Gain in clinical attachment level was considered as the primary outcome variable. Pocket depth reduction
and Radiological bone fill were considered as secondary outcome variables.

Search Results

An electronic search was conducted in database of PUBMED to identify the relevant RCTs. Altogether, 57 studies were found and screened for inclusion. Finally, 41 studies were excluded after examining the title and the abstract due to non-relevance of the topic of study. Full manuscripts of 16 studies were retrieved for detailed evaluation and 10 studies were excluded after detailed evaluation. In addition, one article was included in hand search. Therefore, 7 studies were included in the review (Table 1). The general information of the selected articles and interpretation of outcome measures are also included in the Tables 2, 3 and 4.

Quality Assessment of Included Studies

Quality assessment for the included RCTs was 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 5). 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 (Tables 6 and 7).

Results

Interpretation of results

Out of the seven articles included, three articles showed a positive effect, when adjuncts were used with DFDBA for management of intrabony defects. PRP used in combination to DFDBA showed significant soft tissue healing while cyclosporine, in combination with DFDBA showed significant hard tissue healing. In another study, EMD was used in combination with DFDBA with 12 months follow up and it showed significant healing of both soft tissue and hard tissue healing.

Table 1. General information of selected articles

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Author and Year</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Test Group</th>
<th>Control Group</th>
<th>Study Duration</th>
<th>Limitation</th>
<th>Future Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Aspriello et al. 2011 [10]</td>
<td>RCT - parallel</td>
<td>56 sites</td>
<td>DFDBA+EMD</td>
<td>DFDBA alone</td>
<td>12 months</td>
<td>–</td>
<td>Further studies are needed to clarify if the combination of bone graft and EDM in treatment of infrabony defect</td>
</tr>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>RCT - split mouth</td>
<td>30 sites (15 patients)</td>
<td>DFDBA+ cyclosporine A</td>
<td>DFDBA alone</td>
<td>6 months (24 weeks)</td>
<td>Short duration and small sample size. Standardization of radiograph is not explained</td>
<td>Long term follow up required with larger sample size</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>RCT - parallel</td>
<td>41 Sites (32 patients)</td>
<td>DFDBA+EMD</td>
<td>DFDBA alone</td>
<td>6 months</td>
<td>Short duration and Small sample size</td>
<td>Long term follow up with larger sample size required</td>
</tr>
<tr>
<td>5</td>
<td>Piemontese et al. 2008 [13]</td>
<td>RCT - parallel</td>
<td>60 sites (60 patients)</td>
<td>DFDBA+PRP</td>
<td>DFDBA + Saline</td>
<td>12 months</td>
<td>Use of PRP failed to provide additional value in terms of hard tissue fill</td>
<td>Long term, multi centre clinical trial could be undertaken</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>RCT - split mouth</td>
<td>28 sites (14 patients)</td>
<td>DFDBA+TCN</td>
<td>DFDBA alone</td>
<td>12 months</td>
<td>A distinct limitation to this study was the variation in types of defects treated</td>
<td>Long term follow up with larger sample size required</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [56]</td>
<td>RCT - split mouth</td>
<td>30 sites (15 patients)</td>
<td>DFDBA+ePTFE</td>
<td>DFDBA alone</td>
<td>6 months</td>
<td>Short duration and Small sample size. Method of randomization not mentioned.</td>
<td>Further studies are needed to clarify the correlations between radiographic and clinical method for assessing treatment effects</td>
</tr>
</tbody>
</table>
### Table 2. General information of variable of interest and interpretation pocket depth reduction

<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>
<th>Methodology Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Agarwal et al. 2012 [1]</td>
<td>RCT - parallel</td>
<td>B - 6.25±0.67</td>
<td>3 - 3.38±0.18</td>
<td>Reduction in PD of 2.00±0.19mm compared to 2.75±0.37mm for test</td>
<td>UNC 15 periodontal probe used for measurement</td>
</tr>
<tr>
<td>2</td>
<td>Aspriello et al. 2011 [10]</td>
<td>RCT - parallel</td>
<td>DFDFA + EMD B - 9.0 (2.126)</td>
<td>DFDFA B - 8.5 (1.6625)</td>
<td>Significant decrease in PD P&lt;0.05</td>
<td>No specific periodontal probe used for measurement</td>
</tr>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>RCT - split mouth</td>
<td>DFDFA + CoA B - 7.60±0.43</td>
<td>DFDFA B - 7.47±0.51</td>
<td>No significant probing depth between groups</td>
<td>Goldman fox/Williams colour coded periodontal probe used for measurement</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>RCT - parallel</td>
<td>DFDFA + EMD B - 7.24±1.71</td>
<td>DFDFA B - 6.53±1.61</td>
<td>No significant PD reduction test group 2.54±1.42 and control group 2.45±0.35</td>
<td>UNC 15 periodontal probe used for measurement</td>
</tr>
<tr>
<td>5</td>
<td>Piemontese et al. 2008 [13]</td>
<td>RCT - parallel</td>
<td>DFDFA + PRP B - 8.4±1.9</td>
<td>DFDFA + saline B - 8.0±1.5</td>
<td>Significant PD reduction both between and within groups P&lt;0.05</td>
<td>UNC 15 periodontal probe used for measurement</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>RCT - parallel</td>
<td>DFDFA + TCN B - 7.53±1.51</td>
<td>DFDFA B - 6.73±1.39</td>
<td>No Significant PD reduction between groups DFDFA+TCN - 3.93±1.87</td>
<td>Michigan periodontal probe used for measurement</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [58]</td>
<td>RCT - split mouth</td>
<td>B - 7.4±1.6</td>
<td>B - 7.1±2.1</td>
<td>No statistically significant PD reduction between the group</td>
<td>Loma linda 20 calibrated periodontal probe used for measurement</td>
</tr>
</tbody>
</table>

### Table 3. General information of variable of interest and interpretation gain in clinical attachment level

<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>
<th>Methodology Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Agarwal et al. 2012 [3]</td>
<td>RCT - parallel</td>
<td>B - 7.13±0.61</td>
<td>3 - 5.38±0.56</td>
<td>No Significant CAL gain of 2.75±0.37</td>
<td>UNC 15 periodontal probe used for measurement</td>
</tr>
<tr>
<td>2</td>
<td>Aspriello et al. 2011 [10]</td>
<td>RCT - parallel</td>
<td>B - 8.5 (1.75)</td>
<td>B - 8.0 (1.5)</td>
<td>Significant CAL gain both within and between the groups P&lt;0.001</td>
<td>Periodontal probe used for measurements not mention</td>
</tr>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>RCT - split mouth</td>
<td>B - 6.67±0.55</td>
<td>B - 7.13±0.39</td>
<td>No significant CAL gain in between the groups</td>
<td>Goldman fox/Williams colour coded periodontal probe used for measurement. Customized acrylic stents used for standardization</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>RCT - parallel</td>
<td>B - 7.74±2.53</td>
<td>B - 7.00±1.86</td>
<td>Significant CAL gain compared to baseline. P&lt;0.01 no statistically significant difference in CAL gain was found between the two groups</td>
<td>UNC 15 periodontal probe used for measurement</td>
</tr>
<tr>
<td>5</td>
<td>Piemontese et al. 2008</td>
<td>RCT - parallel</td>
<td>B - 8.8±1.6</td>
<td>B - 8.5±2.4</td>
<td>Significant CAL gain in between the groups. p&lt;0.05</td>
<td>UNC 15 periodontal probe used for measurement. Use of stent not mentioned</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>RCT - parallel</td>
<td>B - 7.87±1.25</td>
<td>B - 7.33±2.02</td>
<td>No significant CAL gain in between the groups. But significant CAL gain within the group p&lt;0.001</td>
<td>Michigan periodontal probe used for measurement</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [58]</td>
<td>RCT - split mouth</td>
<td>B - 6.7±1.2</td>
<td>B - 6.6±2.2</td>
<td>No Statistical significant CAL gain in between the groups</td>
<td>Loma linda 20 calibrated periodontal probe used for measurement</td>
</tr>
</tbody>
</table>
Table 4. General information of variable of interest and interpretation radiological bone fill

<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>
<th>Methodology Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Agarwal et al. 2012 [3]</td>
<td>RCT - parallel</td>
<td>B - 4.00±0.42 3 - 3.75±0.53 6 - 2.88±0.40</td>
<td>B - 3.50±0.33 3 - 3.25±0.37 6 - 2.88±0.33</td>
<td>No Significant bone fill</td>
<td>Long cone paralleling technique with bite blocks used for taking radiographic IOPA and scanned for assessment</td>
</tr>
<tr>
<td>2</td>
<td>Aspriello et al. 2011 [10]</td>
<td>RCT - parallel</td>
<td>B - 9.0 (2.5) 12 - 6.0 (2.0)</td>
<td>B - 9.0(2.625) 12 - 5.5(3.0)</td>
<td>Significant bone fill (P&lt;0.05)</td>
<td>Long cone paralleling technique with bite blocks used for taking radiographic IOPA and scanned for assessment</td>
</tr>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>RCT - split mouth</td>
<td>B - 10.67±0.45 12 weeks - 8.53±0.43 24 weeks - 6.87±0.31</td>
<td>B - 10.27±0.56 12 weeks - 8.13±0.43 24 weeks - 7.20±0.39</td>
<td>Significant bone fill (P&lt;0.01)</td>
<td>Long cone paralleling technique with bite blocks used for taking radiographic IOPA and scanned for assessment</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>RCT - parallel</td>
<td>B - 4.50±1.82 6 - 2.35±1.60</td>
<td>B - 4.83±1.61 6 - 2.55±1.38</td>
<td>No Significant bone fill both within and between the group P=0.01</td>
<td>Standardized radiographic technique used for taking IOPA with reference point</td>
</tr>
<tr>
<td>5</td>
<td>Piemontese et al. 2008 [13]</td>
<td>RCT - parallel</td>
<td>B - 9.2±1.4 12 - 5.9±1.6</td>
<td>B - 9.0±1.7 12 - 6.4±1.9</td>
<td>Significant bone fill within both groups P&lt;0.001 No significant difference between the group</td>
<td>Long cone paralleling technique with bite blocks used for taking radiographic IOPA and scanned for assessment</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>RCT - parallel</td>
<td>B - 7.60±1.80 12 - 5.33±1.72</td>
<td>B - 7.72±2.06 12 - 5.53±1.73</td>
<td>No significant difference between the group</td>
<td>Vertical bitewing IOPA taken using conventional film holder. The radiograph was standardized by stabilizing the patients head with cephalometric head positioner</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [58]</td>
<td>RCT - split mouth</td>
<td>B - 7.4±2.4 6 - 5.3±2.2</td>
<td>B - 7.0±2.4 6 - 5.1±2.3</td>
<td>Significant bone fill within both groups P&lt;0.001 No significant difference between the group P=0.27</td>
<td>Standardized radiographs taken and analyzed using Computer assisted densitometric image analysis(CARDIA)</td>
</tr>
</tbody>
</table>

Table 5. Level of evidence of selected articles

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Author and Year</th>
<th>Study Design</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>RCT - split mouth</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>RCT - parallel</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>RCT - parallel</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [58]</td>
<td>RCT - split mouth</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6. Risk of bias – major criteria

<table>
<thead>
<tr>
<th>No.</th>
<th>Author and Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Assessor Blinding</th>
<th>Dropouts</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Agarwal et al. 2012 [3]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>2</td>
<td>Aspriello et al. 2011 [10]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>5</td>
<td>Piemontese et al. 2008 [13]</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [58]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Table 7. Risk of bias – minor criteria

<table>
<thead>
<tr>
<th>No.</th>
<th>Author and Year</th>
<th>Sample size calculation</th>
<th>Baseline comparison</th>
<th>Inclusion/Exclusion criteria</th>
<th>Error in Methodology</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Agarwal et al. 2012 [3]</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>Aspriello et al. 2011 [10]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>3</td>
<td>Dhawan et al. 2010 [6]</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Hoidal et al. 2008 [12]</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>5</td>
<td>Piemontese et al. 2008 [13]</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>Masters et al. 1996 [52]</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>7</td>
<td>Guillemin et al. 1993 [58]</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Quality of studies looked up on

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

Discussion

The present review attempted to systematically evaluate any available randomized-controlled trial and/or comparative clinical study on the effectiveness of adjuncts with demineralized freeze dried bony allograft in the treatment of intrabony defects. Quality assessment of the selected studies was performed according to the revised recommendation of the CONSORT statement and the selected criteria. Two studies [3,58] were included in this review to assess the effectiveness of use of GTR barrier membrane with DFDBA in treatment of periodontal infrabony defects. One of the studies [3] used PLA/PGA barrier membrane and showed significant differences in probing depth reduction and clinical attachment level gain when compared to the groups from baseline to six months, but no significant difference was found between the test and control group. Another study [58] used ePTFE barrier membrane and showed no significant difference in pocket depth reduction and clinical attachment level gain both in the test and control group. Both the studies did not show any significant radiological bone fill at the end of 6 months between the groups. Thus, it can be concluded that the resorbable or non resorbable barrier membrane alone with DFDBA did not have any significant or major effect when compared the use of DFDBA alone. Hence the use of GTR barrier membrane with DFDBA might not serve as good adjunct; however, it is impractical to conclude from the results of two studies. Hence, further studies with larger sample size and longer follow up are required.

Two studies [10,12] were included to assess the effectiveness of EMD when used along with DFDBA and were compared to use of DFDBA alone. One study by Aspriello et al with parallel design of randomized controlled clinical trial with 12 month follow-up was included for evaluating the effectiveness on EMD with DFDBA. This study showed significant pocket depth reduction, clinical attachment gain and radiological bone fill at the end of 12 months, in the test group compared to DFDBA alone. Another study by Hoidal et al with a parallel design of randomized controlled clinical trial with 6 month follow-up was also included. No adjunctive effects of EMD with DFDBA were noticed in this study. Hence, it may concluded that EMD along with DFDBA showed positive results in both soft tissue and hard tissue healing. Significant results were seen only in the long term follow up study while the 6 months follow up study failed to show significant results.

A study by Piemontese M et al. [13] evaluated the effect of PRP on DFDBA with a follow up period of 12 months. The study showed significant pocket depth reduction and clinical attachment gain at the end of 12 months in the test group compared to DFDBA alone. Hence, use of PRP showed a overall positive effect on soft tissue healing. However, the use of PRP failed to provide additional value in terms of hard tissue fill.

A study by Dhawan S et al. [6] (split mouth design of randomized controlled clinical trial with 24 weeks follow up) was included for the evaluation of use of immunosuppressive drugs (cyclosporine A). The study showed no significant difference in reduction of probing depth and clinical attachment level gain when compared between the groups. However, the study showed significant radiological bone fill between the groups with DFDBA loaded with CsA compared to DFDBA alone.

Conclusion

Based on the results obtained from the present systematic review, it can be concluded that the effectiveness of adjuncts with DFDBA in surgical treatment of intrabony defects has been increasing in the recent years. This systematic review revealed that the soft tissue gain after treatment with PRP in combination with DFDBA showed a significant result in both probing pocket depth reduction and clinical attachment level gain. On the other hand, with regard to hard tissue response, cyclosporine A in combination with DFDBA showed significant radiological bone fill. More long term, multi centric clinical trials are needed to clarify if
the combination of DFDBA and adjuncts for treatment of periodontal intrabony defects would be useful compared to the use of DFDBA alone.

References


