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Review

Growth factors and beta-tricalcium phosphate in the treatment of periodontal intraosseous defects: A systematic review and *meta*-analysis of randomised controlled trials

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ABSTRACT

Objective: To evaluate the effectiveness at different points in time, of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) coated onto a beta-tricalcium phosphate (β-TCP) carrier compared to β-TCP alone, or to recombinant human growth/differentiation factor-5 (rhGDF-5) adsorbed onto a β-TCP scaffold in intraosseous periodontal defects.
Design: A digital search for randomised controlled trials (RCTs) was conducted on MEDLINE/PubMed. The quality of reporting and the risk of bias of the included RCTs were assessed using the CONSORT guidelines and the Cochrane risk of bias tool. The difference between the means of the outcomes at baseline and at follow-up for each group was tested using the Student's *t*-test for paired samples. The difference between the means of the outcome changes at follow-up between groups was analysed using the Student's *t*-test for two independent samples. Prior to each analysis a test of homogeneity of variances (Ansari-Bradley) was performed.
Results: From 11 articles assessed for eligibility, 5 RCTs were included in this review. The risk of bias was considered to be low in 2 articles, medium in 1 study and high in 2 studies.
Conclusions: In the treatment of periodontal intraosseous defects the application of rhPDGF-BB/β-TCP improved all outcomes when compared to β-TCP at 6 months follow-up. Either rhPDGF-BB/β-TCP or rhGDF-5/β-TCP seemed to provide similar results in terms of probing pocket depth (PPD) reduction and clinical attachment level (CAL) gain. The application of rhGDF-5/β-TCP resulted in a more pronounced reduction in gingival recession (GR) depth at 6 months follow-up compared to rhPDGF-BB/β-TCP.

Contents

Abbreviations: rhPDGF-BB, recombinant human platelet-derived growth factor-BB; rhGDF-5, recombinant human growth/differentiation factor-5; β-TCP, beta-tricalcium phosphate; RCT(s), randomised controlled trial(s); GF(s), growth factor(s); PPD, probing pocket depth; CAL, clinical attachment level gain; GR, gingival recession; LBG, linear bone growth; %BF, per cent bone fill.

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1. Introduction

Various treatment modalities such as guided tissue regeneration, root surface conditioning, and the use of enamel matrix derivative or platelet rich plasma, have been proposed and implemented in order to promote and/or sustain periodontal regeneration, and are discussed in several high-quality reviews and clinical papers (Needleman, Tucker, Giedrys-Leeper, & Worthington, 2005; Mariotti, 2003; Esposito, Grusovin, Papanikolaou, Coulthard, & Worthington, 2009; Stramazzotti et al., 2015; Aspriello, Ferrante, Rubini, & Piemontese, 2011; Piemontese, Aspriello, Rubini, Ferrante, & Procaccini, 2008).

Different types of growth factors (GFs), biologically active polypeptidic molecules such as platelet-derived growth factor (PDGF), vascular endothelial growth factor, fibroblast growth factor, insulin-like growth factor, transforming growth factor-β and bone morphogenetic proteins, have been linked to periodontal tissue physiology. Amongst these, PDGF has been studied intensively as a result of its regenerative qualities on the periodontal attachment apparatus (*de novo* formation of periodontal ligament, cementum and bone) determined histologically (Lynch et al., 1989; Lynch et al., 1991). *In vitro* studies have demonstrated that PDGF may regulate the osseous metabolic activity of the periodontal defect, and the maintenance of the extracellular matrix in the human periodontal ligament by increasing the release of pyridinoline cross-linked carboxyterminal telopeptide of type I collagen and vascular endothelial growth factor (Sarment et al., 2006; Cooke et al., 2006), and by inducing the proliferation of the periodontal ligament cells in a time- and dose-dependent manner and promoting the synthesis of type I collagen in an inverse dose-dependent manner (Ojima, Mizuno, Kuboki, & Komori, 2003).

Current therapy for periodontal defects usually focuses on the use of alloplastic materials such as beta-tricalcium phosphate (β-TCP). β-TCP represents a synthetic and biocompatible material with a Ca: P ratio similar to that of bone mineral. Intrabony periodontal defects treated with open flap debridement (OFD) and the consecutive implantation of β-TCP resulted in improvements of clinical outcomes such as PPD reduction and CAL gain, (Chawla, Lamba, Faraz, & Tandon, 2011; Stavropoulos et al., 2010) but the histologic evaluation has demonstrated that β-TCP may not be capable to form new connective tissue, cementum and bone. (Stavropoulos et al., 2010). However, the osteoconductive nature of β-TCP (Lu & Zreiqat, 2010) makes it a good scaffold for GFs, and recent histologic findings suggest that the combination of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) or recombinant human growth/differentiation factor-5 (rhGDF-5) and β-TCP can support regeneration in intraosseous periodontal defects (Ridgway, Mellonig, & Cochran, 2008; Stavropoulos et al., 2011).

The current literature of randomised controlled trials (RCTs) on the use of GFs in combination with β-TCP exclusively in human intraosseous periodontal defects has not been addressed systematically. Therefore, the objectives of this paper were to review the current evidence on the aforementioned topic, with respect to clinical and radiographic criteria and adverse events. Where possible, a *meta*-analysis on pre-specified outcomes at different points in time was performed, in order to determine if the use of GFs combined with an osteoconductive scaffold such as β-TCP provides significant improvements when compared to controls, and if the implantation of two different GFs, each combined with β-TCP, lead to similar or different results, in terms of periodontal regeneration.

2. Materials and methods

2.1. Research question (PICO)

The focused question was: "In patients with chronic periodontitis presenting intraosseous defects, will the application of GFs combined with β-TCP improve the clinical and radiographic outcomes at different points in time, when compared to other regenerative procedures?"

2.2. Search strategies

The search strategy protocol was developed following a structured pattern in order to identify relevant published RCTs that addressed the focused question. The electronic search was conducted on MEDLINE/PubMed, and was limited to articles published in English from January 1, 1980 to December 31, 2014. Different keywords were connected with the Boolean operator AND as follows: "beta-tricalcium phosphate AND growth factor, beta-tricalcium phosphate AND platelet-derived growth factor, platelet-derived growth factor AND periodontal regeneration, platelet-derived growth factor AND periodontal defect, beta-tricalcium phosphate AND growth differentiation factor, growth differentiation factor AND periodontal regeneration, growth differentiation factor AND periodontal defect, beta-tricalcium phosphate AND insulin-like growth factor, insulin-like growth factor AND periodontal regeneration, insulin-like growth factor AND periodontal defect, beta-tricalcium phosphate AND fibroblast growth factor, fibroblast growth factor AND periodontal regeneration, fibroblast growth factor AND periodontal defect, beta-tricalcium phosphate AND bone morphogenetic protein, bone