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REVIEW ARTICLE

Effectiveness of Agents Like Platelet-rich Plasma, Oxidized Regenerated Cellulose and Microfibrillar Collagen in Hard-tissue Healing: Validation of Their Comparative Effectiveness

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ABSTRACT

Autologous platelet-rich plasma (PRP) can be a valid agent that is effective in inducing and accelerating bone healing for the treatment of periodontal defects and also to accelerate alveolar bone regeneration. Early healing appeared to be impaired by the presence of microfibrillar collagen (MFC) and impeded by the presence of oxidized regenerated cellulose (ORC). In contrast, alkylene oxide copolymer (AOC) did not inhibit bone healing and suggest that AOC may be a better bone hemostatic material for procedures where bony fusion is critical and immediate hemostasis required.

Keywords: Platelet-rich plasma, Microfibrillar collagen, Oxidized regenerated cellulose, Alkylene oxide copolymer, Tissue healing.

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INTRODUCTION

Bone formation and repair require many biological and cellular processes, which are achieved by a variety of cell types that promote cellular proliferation, differentiation and tissue organization. Among these agents are mesenchymal stem cells (MSCs)—stimulated by growth factors to become osteogenic cells that will carry out regeneration—and the intrinsic osteoconductive and osteoinductive abilities of bone that incite osseous formation and bony cell migration.[1] Based on these mechanisms, there is great interest in tissue engineering to obtain structures that enable the support and control of cell growth.[2]

Growth factors have been used to promote bone repair and have shown suitable results in experimental models.[3] These biological agents are responsible for regulating certain cell actions and have been described as effective externally applied enhancers of bone healing processes, cell differentiation, cell proliferation and angiogenesis stimulation.[4]

Many strategies have been developed to accelerate bone repair, including treatment with exogenous growth factors, the use of tentative bone grafts, scaffolds and the development of new methods and alternatives for administering inducing agents and osteogenic drugs enable to promote bone regeneration.[5] These agents aim to improve wound healing by accelerating bone growth focusing on each stage of the repair process: inflammation, vascularization, remodeling, osteoinduction or osteoconductivity.[6]

Some of the materials investigated and used to accelerate the growth of new bone tissue are autologous platelet-rich plasma (PRP), oxidized regenerated cellulose (ORC) and microfibrillar collagen (MFC). Their therapeutic strategies are based on acceleration of healing by concentrations of growth factors, which are universal initiators of nearly all healing events.[7]

Resorbable bone hemostasis materials are often selected because of their perceived lack of interference with bone healing. Previous studies of bone healing in the presence of hemostatic agents have produced conflicting results with conclusions often based on histological observations rather than quantitative measurements of bone growth.[8]

This paper compares the effects on bone healing of PRP, ORC and MFC. The products of ORC and MFC were selected because they are often used in surgery for bone hemostasis, and presumably it is assumed that ORC and

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MFC do not significantly interfere with bone healing because they are resorbable. The objective of this study is to provide quantitative data on early bone healing following application of bone substitutes for procedures where bony fusion is critical and early healing is desired:

- *Autologous platelet-rich plasma:* The therapeutic strategy is based on acceleration of healing by concentrations of growth factors, which are universal initiators of nearly all healing events.[7] The growth factors present in PRP are well known, including TGF-b1 and TGF-b2, vascular endothelial growth factor (VEGF), three isomers of PDGF and endothelial growth factor (EGF). These growth factors are considered to have the ability to accelerate chemotaxis, mitogenesis, angiogenesis and synthesis of collagen matrix and favor tissue repair when applied on bone wounds.[9]

  Recent studies have reported the low efficacy of PRP to accelerate bone healing.[10] However, Sammartino et al (2005) showed that the use of PRP is certainly a valid method that is effective in inducing and accelerating bone regeneration for the treatment of periodontal defects after impacted mandibular third molar surgery.[11] Gurbuzer et al (2010) concluded that autologous PRP may not lead to increased bone healing in soft tissue after impacted third molar surgery.[12]

  There is a divergence of opinion on the activity of PRP. Such discrepancies are probably related to the lack of suitable standardization and definition of the different PRP preparations; the protocols and biological techniques used in the elaboration and administration of PRP differ widely.[13] Variations in some key properties of PRP, including platelet concentrations, type of clot activator, leukocyte count and the time that the fibrin scaffold is put in to place around the tissue after clotting has started, can influence the different biological effects markedly.[14]
- *Oxidized regenerated cellulose and microfibrillar collagen:* Oxidized regenerated cellulose depends upon multiple mechanisms of action for hemostasis and bone healing, including physical and mechanical actions in tamponade and surface interaction with proteins, platelets. Oxidized regenerated cellulose may also promote hemostasis chemically due to its low pH, which generates a brownish artificial clot containing acid hematin. Oxidized regenerated cellulose inhibited early bone healing as compared to control but less so than MFC ($p < 0.01$).[15] This finding is consistent with a number of previous animal studies.[16] Oxidized regenerated cellulose caused an intense inflammatory response and impaired osseous regeneration with residual material still present in the defect after 120 days. Conversely, Finn et al found no residual ORC 2 months after application in a canine iliac crest defect model and did not observe any adverse effect on bone regeneration on microscopic examination.[17] In a more recent study, Dias et al employed histomorphological techniques to compare the effect of laboratory grade oxidized cellulose with a type-1 bovine collagen sponge on bone healing in a 4 mm diameter bone defect sheep model.[18] Although little difference was reported between the two groups, and bone healing was assessed as complete after 6 to 8 weeks, no control group was included in the study.[18]

MICROFIBRILLAR COLLAGEN

The hemostatic properties of MFC rely on the promotion of platelet aggregation as well as physically blocking bleeding vessels. The advantages are fast induction of hemostasis, low tissue reaction and rapid resorption.[8] A major disadvantage is difficulty in manipulating the agent when attempting to apply it to the area of bleeding. Microfibrillar collagen is actively degraded *in vivo* and is reported to be removed from the site of application in 45 to 90 days.[19] A surprising finding was the almost complete absence of bone healing 17 days following application of MFC,[15] an effect similar to that observed with the use of non-resorbable bone wax.[20] The histological images for MFC treated defects show a clearly defined defect margin indicating that minimal healing has occurred over the 17 postsurgical days. These findings are consistent with histological evaluation of rabbit cranial defects filled with MFC that were shown to be significantly larger than untreated control defect at 4 and 7 weeks postsurgery.[21]

In contrast, other authors have performed osteotomies of the greater trochanter in a canine model and found no evidence that MFC interfered with bone healing at 3 months.[22,23] In a study that employed a 5 mm rat tibial defect, residual MFC material was found in the defect at 90 days and the MFC did not impede bone healing, since the bone defects had healed at 60 days.[22] On qualitative microscopical examination after 2 months, residual MFC was observed in the defect, but no adverse effects on bone regeneration was noted. Although effective in achieving immediate and effective hemostasis, the adverse effects of MFC on osteogenesis would suggest that this agent would impair healing in the clinical setting, and this finding is in agreement with the recommendation that MFC should be removed from the site of application as it interferes with bone healing.[8]

Microfibrillar collagen and alkylene oxide copolymer (AOP) achieved immediate and effective bone hemostasis.[15] Oxidized regenerated cellulose achieved hemostasis 1 to 2 minutes after application. Effective hemostasis was maintained following application of all three hemostatic materials studied. Alkylene oxide copolymer did not inhibit bone healing when compared to untreated

(control) defects and thus may be a good clinical agent in cases where bony fusion is critical and where immediate hemostasis is required. The results confirm the use of AOP that does results in faster bone healing compared to either ORC or MFC, presumably because AOP is cleared from the bone defect much earlier, facilitating bone regeneration and resultant healing.

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