Original Article

Bone resorption analysis of platelet-derived growth factor type BB application on collagen for bone grafts secured by titanium mesh over a pig jaw defect model

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ABSTRACT

Purpose: The aim of this investigation was to evaluate whether the addition of the platelet derived growth factor type BB (PDGF-BB) to a collagen matrix applied on a titanium mesh would favor healing and resorption onto the grafted bone. A histologic and radiographic study of two different groups (test and control) was performed. **Designs:** A surgical procedure was performed on 8 pigs to obtain 16 bilateral mandibular alveolar defects. All the defects were then reconstructed with a mixture of autogenous bovine bone using titanium mesh positioning. Two groups, with a total of 16 defects were created: The first to study collagen sponge and PDGF-BB and the second to control collagen only. The collagen matrix was positioned directly over the mesh and soft tissue was closed without tensions onto both groups without attempting to obtain primary closure. Possible exposure of the titanium mesh as well as the height and volume of the new bone was recorded. **Results:** New bone formation averaged about 6.68 mm in the test group studied; the control group had less regenerated bone at 4.62 mm. **Conclusion:** PDGF-BB addition to the collagen matrix induced a strong increase in hard and soft tissue healing and favored bone formation, reducing bone resorption even if the mesh was exposed.

Key words: Bone tissue, collagen, growth factors, platelet-derived growth factor type BB

INTRODUCTION

Loss of teeth and alveolar bone can adversely affect the patient's speech as well as their ability to masticate. Surgical resection and traumatic injuries can deprive patients of adequate hard and soft tissue support for dentures and make the placement of dental implants much more difficult. Dental implants are effective in replacing missing teeth only when the underlying osseous foundation is adequate in size, volume, and quality. Unfortunately, many patients lack sufficient bone height and/or width to provide the needed support, and as a result, denture support and dental restorations are compromised. The lack of teeth and alveolar bone often leads to further resorption which can progress to severe bony deficits of the maxilla and mandible. Several bone-grafting techniques have been developed to correct bony deficiencies with varying degrees of success. Some of the more common technique

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includes autogenous bone harvested from the patient's iliac crest, tibia, mandible, or maxillary tuberosity. When autogenous bone grafting techniques are considered the gold standard, they do carry limitations including surgical complications, cost, and patient morbidity associated with harvesting bone.[1-9]

Multiple surgical approaches using graft materials from a variety of sources have been recommended to facilitate subsequent dental implants placement. Of note among these methodologies are the following: On-lay bone grafts, ridge splitting, sub-periosteal membrane-guided regeneration, alveolar osteotomies/sandwich grafts, inter-positional grafts, mandibular inferior border grafting, maxillary sinus floor grafting, grafting overexposed threads, distraction osteogenesis, and the use of growth factors. These adjunctive surgical procedures are performed to allow/facilitate implant placement and get superior clinical results.[4,7,10-16]

To replace missing bone prior to dental implant placement patients require grafting. As a result of this, often there is insufficient soft tissue to cover the bone graft completely. Adjacent tissues can be used to achieve tension-free closure but the process disrupts the normal soft tissue architecture, resulting in a decrease or obliteration of the vestibule. Consequently, when the bone graft heals, soft tissue grafting may also be required to reposition and re-establish the correct vestibular architecture.[9,11,17]

Free connective tissue grafts or split thickness skin grafts are commonly used to increase vestibular depth. Being effective in recreating depth and size, autogenous soft tissue transplants can result in donor site morbidity such as prolonged pain, swelling, infection, numbness, and bleeding. Healing of the donor site can take from 6 to 8 weeks, making surgical options less desirable.[18,19]

Insufficient keratinized gingiva adjacent to dental implants is another frequently occurring clinical indication for soft tissue grafting. Treatment options include free connective tissue grafts, xenogeneic grafts, or allogeneic materials, each having its own set of advantages and disadvantages. A common problem with many of these grafting techniques is contracture at the extended surgical area and mucosal-surface scarring. An ideal autogenous-substituting graft would heal rapidly with little contracture or granulation tissue formation, promote homeostasis, resist infection, and cause the patient less pain by eliminating the need of a second surgical site.[20-25]

The purpose of this investigation is to compare collagen matrix application with and without platelet-derived growth factor type BB (PDGF-BB) to control bone healing and resorption over an intra-oral bone created defect in pigs. The excellent stimulatory effects of PDGF-BB as a chemo-attractant and mitogen, along with its ability to promote angiogenesis, indicate it as a key mediator in tissue repair, which improves soft tissue healing over a bone graft.

This study also wanted to determine whether the addition of the PDGF to the collagen would improve hard and soft tissue healing over particulated bone grafts by inducing less bone resorption even when the titanium mesh is exposed.

Materials and Methods

Note: This study has been approved by the Loma Linda University Ethical Committee.

Eight, 26-week-old micro-pigs underwent a surgical procedure to create bilateral mandibular defects, for a total of 16 defects. The created defects reflected the Class V or VI of Cawood and Howell's classification, having vertical and horizontal components of resorption.[25] Extraction of right and left mandibular posterior teeth with simultaneous osteotomy followed by a healing time of 4 weeks was performed. Each defects was about 30 mm × 20 mm, carried out on the pigs' posterior mandible, and PA digital radiographs of each defect were obtained.

Test group: Collagen + PDGF: BB – 8 sites. Control group: Collagen only – 8 sites. Each pig had its mouth divided into two halves; each half had a test and the control group assigned to it. Three months after the first surgery, the pigs were scheduled for the second reconstructive surgery. Guided bone regeneration technique, using titanium mesh, was carried out on the tridimensially reconstruction of the created defects. A collagen matrix was applied to cover the bone graft and mesh, then the soft tissue was closed. Radiograph investigation of the reconstructed bone was performed to control the position of the mesh [Figure 1].

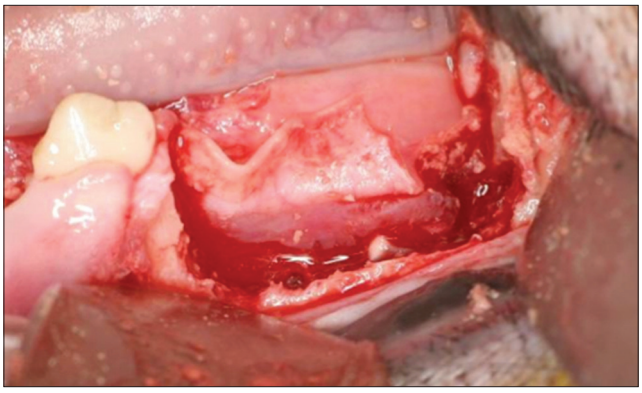

Figure 1: Mandibular defects created for the next implantation of the bone graft

The collagen used for the study was Mucograft®, a sponge matrix developed by Geistlich Pharma, Wolhusen, Switzerland in 2006 as a bio-resorbable matrix and was US Food and Drug Administration (FDA) approved for soft tissue regeneration in oral surgery. This product was made from porcine type I and III collagen and consisted of two functional layers: A smooth collagen layer is a compact structure and a porous layer. Depending on the treated surgical site, the material biodegraded within 3-10 weeks. Research has shown that the biodegradation of the product occurs with very little, if any, inflammatory cellular response.[4,24,26]

During the reconstructive surgery, a horizontal supra-crestal muco peri-osteal flap was elevated in the mandibular mucosa, extending to the periosteum overlying the defect. The incision was carried out on the alveolar ridge of the defect. Following visualization of the defect, a surgical stent was used to remove bone and a standardized 20 mm × 30 mm defect was created. Approximately 5 cc of bone was removed and then combined with 5 cc of deproteinized bovine bone particles. A titanium mesh model of the defect was created and then secured in place to prevent mobility of the graft during the healing process. The surgical site was then closed.

For both groups, collagen was placed over the titanium mesh. The mucosa was sutured without stretching the tissue and incomplete closure with exposure of some of the collagen matrix was performed. The collagen matrix in the test group was saturated with 2.5 ml of (0.3 mg/ml) of PDGF-BB (GEM 21S® Osteohealth Company Shirley, NY, USA) (0.75 mg) [Figures 2-5].

The recombinant human Platelet Derived Growth Factor type BB (rhPDGF-BB) provided the biological input for tissue repair by increasing angiogenesis and the proliferation of osteoblasts. This specific cytokine stimulated chemotaxis proliferation, a new gene expression in monocytes-macrophages and fibroblasts. It also increased tissue repair process, favored soft tissue and bony wound healing and when delivered exogenously, stimulated collagen production, improved wound strength, and initiated callous formation.[21,26]

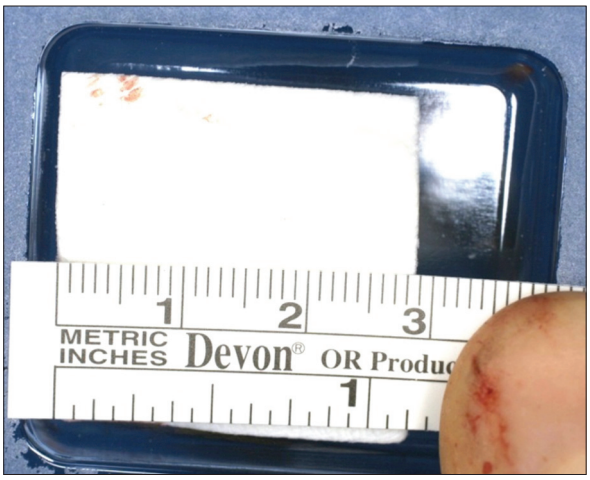

Figure 2: Collagen measure related to the defect size

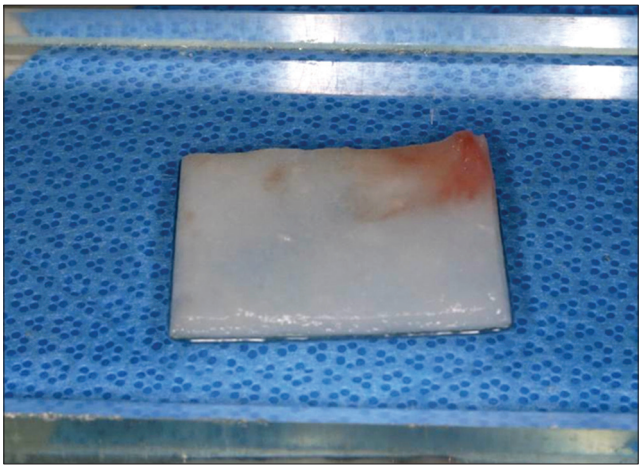

Figure 3: Collagen soaked with platelet derived growth factor type BB application

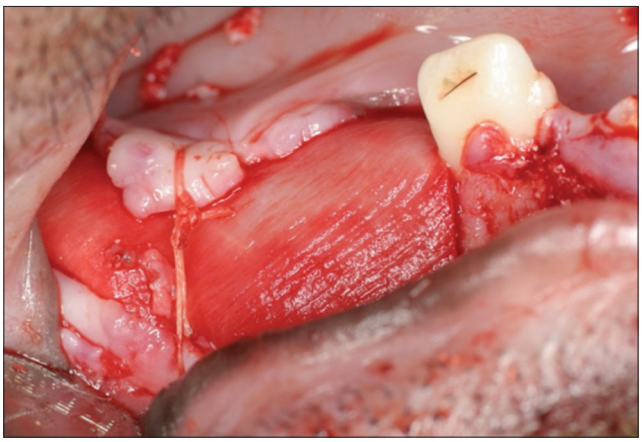

Figure 4: Collagen placed over the positioned mesh

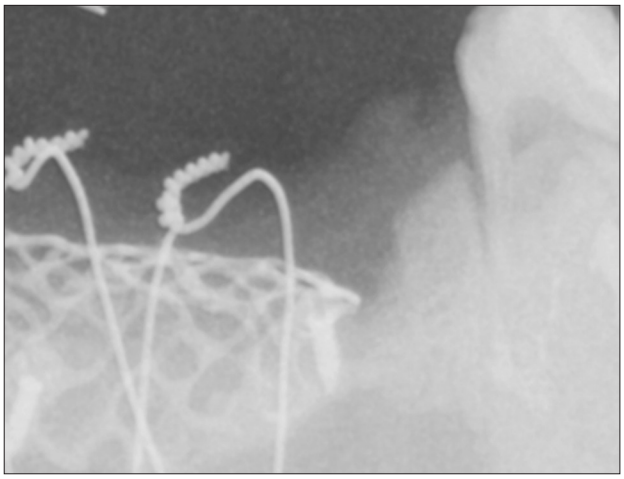

Figure 5: Rx image of the bone graft secured by the mesh

Moreover, rhPDGF-BB can easily be transmitted into a collagen carrier.

Following 3 months of healing, the pigs were humanely euthanized and radiographs of the grafted sites were taken. Histologic sections of bone and soft tissue were prepared and analyzed. The specimens were fixed in neutral buffered 10% formalin, dehydrated and infiltrated in resin, and then embedded and polymerized in resin blocks. The blocks were cut and ground using the Exakt-cutting-grinding system to a thickness of 50 μm and stained with Mayer's hematoxylin and eosin or Masson's Trichrome stain. Histological evaluation included searching for any residual matrix as well as any evidence of inflammation. The quantity of the grafted bone was also evaluated. Qualitative and quantitative histological evaluations of soft-tissue ingrowth and bone regeneration were performed on non-decalcified grounded sections. For statistical analysis, the Mann–Whitney–Wilcoxon test, the Kruskal–Wallis, and the paired *t*-test were applied. *P* values were adjusted using the Dunnett–Hsu adjustment [Figures 6-14].

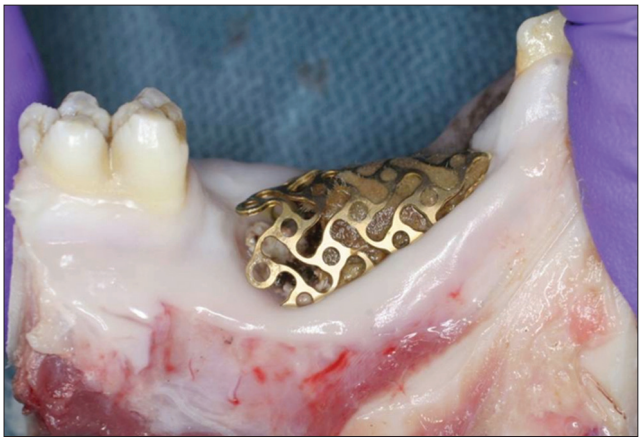

Figure 6: Clinical exposure of the mesh at the time of the pig's euthanasia

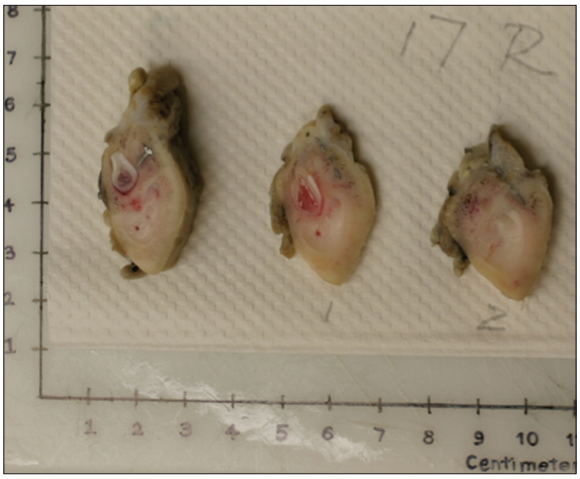

Figure 8: Sample of pigs mandible section ready for histology

Results

The amount of bone formation and incidence of graft exposures were evaluated [Table 1]. The areas of regenerated tissue were randomly selected per section [Figure 15].

The height of new bone was measured in separate sections. The height was reported as an average by measuring the distance from the non-grafted bone to the crest of the regenerated ridge. For the test group, the average of new bone formation was 6.68 mm whereas the Control group had an average less at 4.62 mm. Exposure of the titanium mesh occurred postoperatively for the majority of the pigs. In this animal study the exposure rate was test group – 50% and control group – 100%.

Discussion

In recent years, research to investigate bone resorption of autogenous/homologous/xenogeneic block grafts used

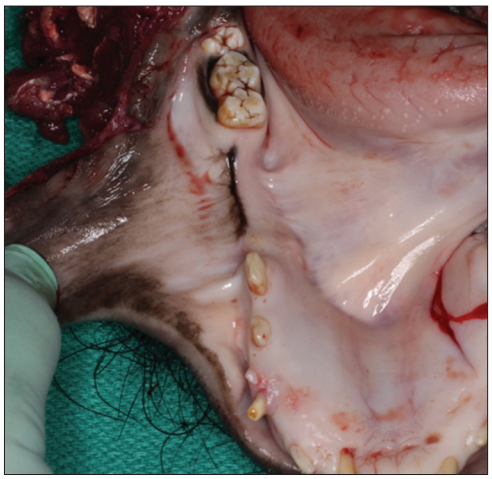

Figure 7: NO exposure of the mesh at the time of the pig's euthanasia

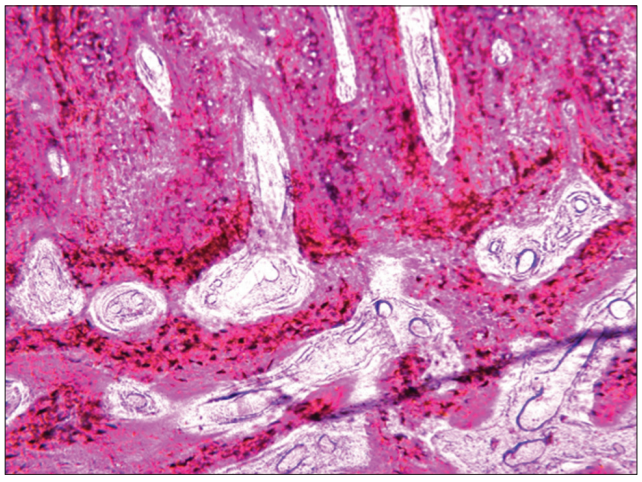

Figure 9: Mayer's hematoxylin and eosin investigation of the test group section. Anterior section

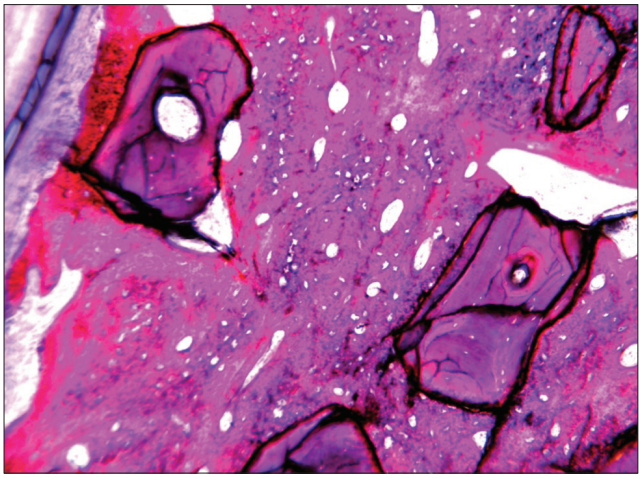

Figure 10: Mayer's hematoxylin and eosin investigation of the test group section. Posterior section

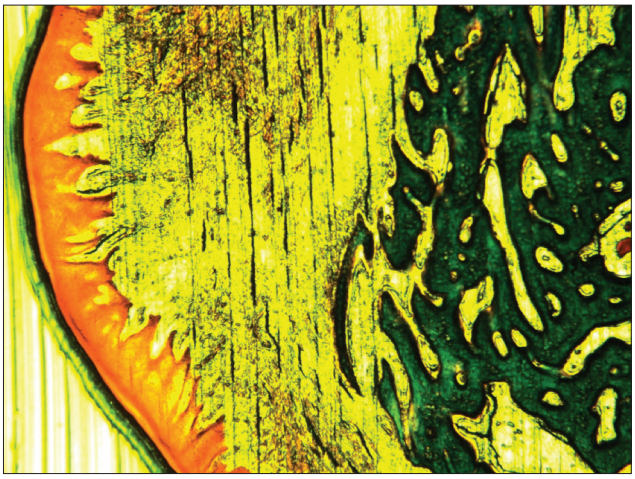

Figure 11: Masson's Trichrome stain investigation of the test group section

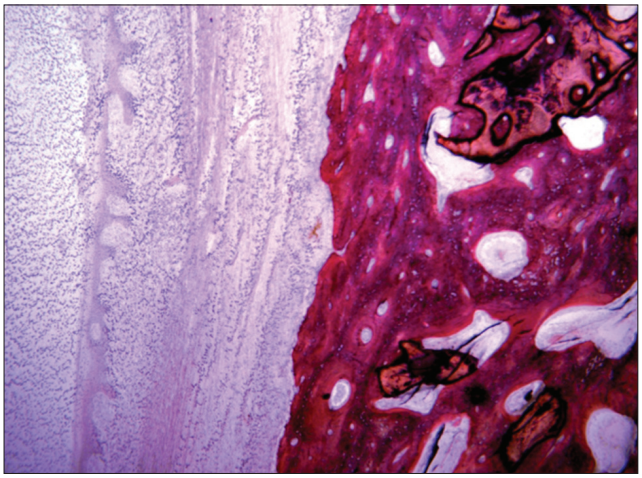

Figure 12: Mayer's hematoxylin and eosin investigation of the control group section. Anterior section

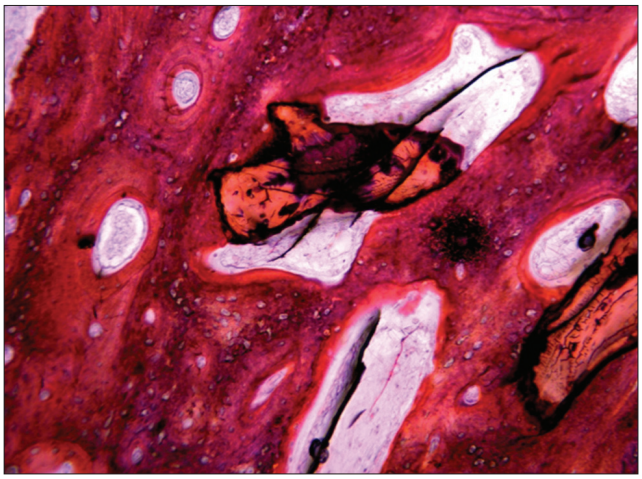

Figure 13: Mayer's hematoxylin and eosin investigation of the control group section. Posterior section

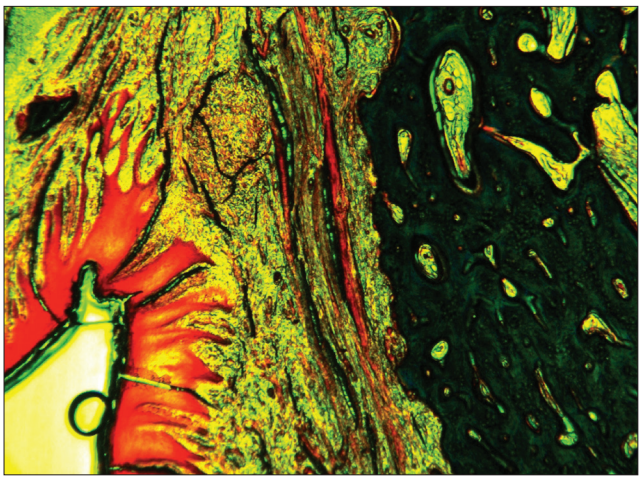

Figure 14: Masson's Trichrome stain investigation of the control group section

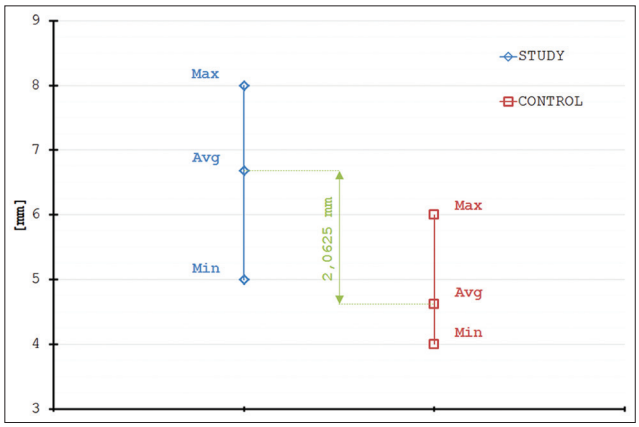

Figure 15: Two groups bone resorption values compared

for oral and maxillofacial surgery has been performed. Some investigations reported how in the 1st year after reconstructive surgery, the bone graft resorption is significant and may progress in the following years.[27] Other studies clearly demonstrated that simple appositioning of a cortico-cancellous bone graft over the mandibular buccal cortex for augmentation of the

Table 1: Bone resorption and mesh exposure in the test and control groups

Group	Specimen	Bone graft healing (mm)	Mesh exposure
Study	1T	7	N
	2T	5.5	Y
	3T	7.5	N
	4T	5	Y
	5T	7.5	Y
	6T	7.5	Y
	7T	8	N
	8T	5.5	N
Control	1C	5	Y
	2C	5	Y
	3C	4	Y
	4C	4	Y
	5C	5	Y
	6C	4	Y
	7C	5	Y
	8C	5	Y

T: Test, C: Control, N: NO exposure of the mesh, Y: Exposure of the mesh

alveolar ridge is a non-predictable method to increase ridge volume. The maintenance of the autogenous bone grafts may be influenced by several parameters such as embryological origin, architecture, orientation, and the nature and dimension of the graft.

However, some alveolar defects, particularly in reference to Cawood and Howell classes V and VI,[25] require bone grafting prior to dental implants placement. These clinical situations offer insufficient soft tissue to completely cover the bone graft without aggressively stretching the adjacent tissue. This adverse condition may determine significant bone resorption due to exposure of the grafted materials over a very short period therefore the previous regenerative surgery will fail.[21,24,28]

The advantages of using autograft bone, the treatment of choice or "gold standard" for skeletal reconstruction, are small due to limited tissue resources and donor morbidity. Pre-clinical studies have shown that growth factors induce normal autogenous bone in clinically relevant defects in the craniofacial skeleton, thereby favoring hard and soft tissue healing. The newly formed bone assumes characteristics of the adjacent resident bone and allows placement, osseointegration, and functional loading of dental implant.[27,29,30-33]

The results of this study, along with other recent investigations into the application of growth factors in bone regeneration techniques clearly underlined how the cytokine implanted on the carrier can accelerate the healing process.[34,35] Moreover, collagen carriers may improve soft tissue volume over the graft by inducing less incidence of bone graft exposure.[35,36]

Many biomaterials have been used as a biological barrier in the past to cover the grafts, allowing growth of host epithelial cells beneath the bone. Kim *et al*. reported that a double layer collagen membrane positioned over the bone graft[37] is helpful for the integration of the onlay block bone graft. An animal study performed by Thoma, *et al*. evaluated the effectiveness of a synthetic, biodegradable membrane made of polyethylene glycol. In that study, the placing of the biodegradable membrane successfully prevented collapse of the covering soft tissues protecting the graft.[38]

The collagen material used in this study (Mucograft®) is a bio-resorbable, bilayer matrix collagen used instead of soft tissue. Recent clinical studies have demonstrated how this collagen matrix® can be applied to increase both keratinized and non-keratinized mucosa with rapid degradation and healing process.[36,32,38] This study results showed that the addition of a PDGF to collagen® improved soft tissue healing, and therefore reduced mesh exposure and protected the grafted bone.

PDGF is a naturally occurring cytokine that has been shown to be an excellent activator for mesenchymal origin cells.[33-41]

The use of rhPDGF-BB in combination with an osteo-conductive scaffold has been recently published in diverse papers connected to growth factors applied onto a carrier for periodontal regeneration.[40,42-44]

The scientific base for this study is that PDGF stimulates angiogenesis, promotes cell migration in the bone defect from the surrounding tissue margins, and regulates cell proliferation.[44-46] The matrix, in addition to its role as a growth factor delivery vehicle, provides structural support for directing/recalling cells and helps the formation of new healing tissue.

The PDGF firstly acts by attracting neutrophils and macrophages and aiding in angiogenesis, chemotaxis, and mitogenesis. PDGF also regulates, Vascular endothelial growth factor (VEGF) further enhancing angiogenesis. Other growth factors like bone morphogenic proteins (BMPs) also play a role in chemotaxis and cell proliferation. However, those growth factors are primarily morphogenic.[38,40,46]

PDGF and BMPs regulate the controls for healing and regeneration of the bone tissue by repairing the tissue in case of bone fracture. From our study results, collagen combined with rhPDGF and maintains the volume of grafted bone and reduces bone resorption in case of mesh exposure. This may be due to improved soft tissue healing. Alternatively, it may be related to some osteo-induction activity of the growth factor. Literature, so far has different viewpoints regarding osteo-inductive properties of rhPDGF. It seems to induce proliferation more than morphogenesis.[40,47,48]

This study on pigs offers certain challenges about the post-operative compliance. Although the animals were maintained on a soft diet, they continued to chew on their metal cadges throughout the day. Exposure of the mesh was significantly higher in these animal specimens, which were clinically probable due to the above-mentioned factor. The exposure rates are as follows: Test group – 50%; control group – 100%. The rhPDGF test group showed significantly thicker soft tissue covering the bone graft. The clinical implications of the results are that there is no need for soft tissue grafting to cover the grafted site. Moreover, collagen membrane position allows tension-free closure over the bone graft. The addition of PDGF to the collagen® accelerates the soft tissue healing and promotes bone graft healing. The PDGF-BB added to the collagen ensures that the volume graft is maintained even if the mesh is exposed because it greatly enhances soft and hard tissue healing.

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