Alveolar Ridge Augmentation Using Recombinant Human Bone Morphogenic Protein (rhBMP-2): A Literature Review and Histologic Case Report

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Abstract

Background: Alveolar ridge deficiency is a common occurrence after tooth extraction creating a challenge to clinicians attempting to obtain predictable results for future implant placement. The use of bone grafts and growth and differentiating factors such as recombinant human bone morphogenic proteins (rhBMP-2) are well documented in alveolar ridge augmentation. The current clinical, radiographic and histologic case report presents the use of rhBMP-2 in alveolar ridge and sinus lift augmentation.

Methods: A 76-year-old male patient, in good general health, nonsmoker, presented with partial edentulous maxilla and retained maxillary canines. Maxillary anterior alveolar ridge and bilateral sinus augmentations were completed using rhBMP-2 solution uniformly dispensed over an absorbable collagen sponges (ACS) mixed with a xenograft bone material. A Titanium Mesh was used to aid in space maintenance for lateral ridge augmentation. CBCT and histologic core biopsies were performed to evaluate the new bone formation.

Results: After 7 months of healing, the CBCT revealed an increase in bone height from 7.27 + 1.69 mm to 13.43 + 2.43 mm for the maxillary sinuses. With regard to the maxillary anterior region, there was an increase in ridge width with horizontal bone gain from 5.76 + 2.10 mm to 9.68 + 0.39 mm. The histologic report indicated new vital bone induction by rhBMP-2 showing presence of woven and lamellar bone. Four dental implants were placed and successfully restored.

Conclusions: The use of rhBMP-2 in maxillary sinus and lateral ridge augmentation procedures shows positive clinical results as confirmed by radiographic and histologic analysis.

KEY WORDS: Bone morphogenic protein, growth factors, guided bone regeneration, maxillary sinus, bone grafts, dental implant

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INTRODUCTION

Dental implants are a universal treatment option for patients. However, clinicians are often faced with limited bone presence, especially when teeth were lost for a long period of time. Alveolar bone deficiency is a natural consequence of tooth extraction resulting in resorption of the edentulous ridge.[1] An average of 40% to 60% of the original alveolar bone height and width is lost after tooth extraction, with the greatest loss occurring within the first two years.[2] Many classifications exist to describe the morphology and quantify the severity of alveolar ridge resorption.[3-6] Wang et al. quantified the alveolar ridge deficiency and expanded on Siebert's classification by recommending treatment options based on the severity of the deficiency and defined it as small ($\leq$ 3mm), medium (4-6mm), and large ($\geq$ 7mm).[6] In addition, the span of the edentulous ridge also plays an important role in treatment planning ridge reconstruction and consequently the enhancement of ideal implant placement. Thus, alveolar ridge and maxillary sinus augmentation procedures have been attempted with successful results with the goal of placing dental implants in a proper esthetic and functional position.[7] Many techniques and materials have been used with bone grafts, guided bone regeneration and growth factors being the most relevant.[8,9]

LITERATURE REVIEW

Bone Grafts and Guided Bone regeneration

Bone grafts have long been used for treatment and correction of alveolar ridge deficiencies. The rationale behind using bone grafts is that they possess osteogenic (autograft), osteoinductive (autograft/allograft), or osteoconductive (xenograft/alloplast) properties.[10]

In periodontal regeneration, Melcher in 1976 reported barrier mediated selective cell repopulation that gave rise to the concept of epithelial exclusion to restore lost periodontal tissue and obtain new attachment.[11] This same concept is applied to regenerate lost alveolar bone known as Guided bone regeneration (GBR). GBR is used to regenerate bone in preparation for implant site development as in ridge and sinus augmentation or around exposed threads of dental implants.

Growth and Differentiating Factors

In addition to bone graft, growth and differentiating factors that can aid in periodontal regeneration and bone induction. Growth and differentiation factors play an important role in regulating wound-healing events such as chemotaxis, cell adhesion, proliferation, and differentiation.[12] These factors include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factors (TGF-α and -β), acidic and basic fibroblast growth factors (a- and b-FGF), epidermal growth factor (EGF), insulin-like growth factors (IGF-I and -II), cementum-derived growth factor (CGF), parathyroid hormone-related protein (PTHrP), and bone morphogenetic proteins (BMPs).[13]

The most investigated growth factors for osteoinductive activity include PDGF, PTH, and BMPs.[14-21] BMPs are differentiating factors belonging to the transforming growth factor-β [TGF-β] superfamily. They play a major role in bone formation and maintenance through differentiation, cell migration, proliferation and apoptosis. The most profound characteristic effect observed for BMPs are their ability to differentiate mesenchymal progenitor cells into chondroblasts and osteoblasts.[22] There are over 20 BMPs present with BMP-2 (Osteogenic Protein-2 [OP-2]), BMP-3 (Osteogenin), and BMP-7 (Osteogenic Protein-1 [OP-1]), BMP-12 (also known as Growth Differentiation Factor-7 [GDF-7]) and BMP-14 (also known as Growth Differentiation Factor-5 [GDF-5]) being the most prevalent ones in regenerative therapy.[23] In early 2007, INFUSE® bone graft (Medtronic Sofamor Danek, Memphis, TN) was approved by the United States Food and Drug Administration (FDA) as an alternative to bone grafts for sinus and localized alveolar ridge augmentations.[24] BMP-2 and -3 have shown good potential to correct intrabony and furcation bone loss. However, BMP-2 has been associated with ankylosis histologically.[25,26] Therefore, they are generally reserved for use around implants or for guided-bone regeneration. Although these growth and differentiating factors have been used with good clinical results, rhBMP-2 remains to be the most prevalent one in alveolar ridge augmentation.

Clinical Studies using rhBMP-2

Various randomized clinical trials (RCT) and case reports have been published discussing the quality and quantity of bone regenerated using rhBMP-2 in maxillary sinus augmentation.[27-30] The first multicenter RCT was designed to evaluate the safety and efficacy rhBMP-2 in maxillary sinus augmentation. The mean increase in alveolar ridge height ranged from 9.5 mm to 10.2 mm.[27] These results were comparable to the newly induced bone using autogenous or combination of autogenous/allogenous bone.[29] Later studies showed that extensive sinus membrane elevation is required with rhBMP-2 due to considerable graft shrinkage and low initial graft density. To overcome these drawbacks, Tarnow et al. in case series proposed that graft shrinkage might be prevented by the addition of xenograft and/or allograft within the Acellular Collagen Sponge (ACS).[30]

With regard to lateral ridge augmentation, Howell et al conducted the first safety and technical feasibility human study for use of rhBMP-2. The 16-week study, demonstrated no increase in alveolar ridge width or height with rhBMP-2 alone.[31] Thereafter, Cochran et al. followed up the functional stability of dental implants placed in the augmented sites in the previous study for three years. The amount of new bone growth that was induced in these sites was minimal to even less than baseline.[32] These studies failed to describe adequate conclusions due to the small sample size, lack of a control group and negligible bone growth. While comparing these findings with those of horizontal ridge augmentation obtained with conventional particulate bone substitutes and membranes, it is important to mention that a superior result of gain in ridge width of 3.6 mm could be recorded for conventional bone substitutes.[8] However, preclinical investigations in dogs have revealed that the compromised results with rhBMP-2/ACS alone were due to the failure of the ACS to adequately maintain support in supraalveolar wound space.[33] A prospective RCT addressed the insufficient mechanical properties of ACS and proposed a combination of an osteoinductive protein (rhBMP-2) with an osteoconductive material to overcome some of the difficulties encountered.[34] The study compared the quantity of bone that was induced using rhBMP-2 plus xenograft (test) versus xenograft alone (control) and showed no statistical difference in the amount of bone augmentation observed between the two groups. However, the study demonstrated the beneficial effects of higher bone maturation

Figure 1: Pre-op facial view of anterior maxillary region.

Figure 3: rhBMP-2/ACS mixed with xenograft bone material.

and increased graft to bone contact when combining rhBMP-2 with a xenogenic bone material.[34] The histomorphometric analysis for this study revealed a higher percentage of newly formed bone at the rhBMP-2 test sites 37% versus 30% of newly formed bone at the control sites. In addition, the fraction of mineralized bone identified as lamellar bone amounted to 76% (test) compared to 56% (control) indicating that rhBMP-2 accelerated the mineralization and maturation process. Further, the mean vertical defect fill (91%) at the control defects with xenograft alone corresponded well with the previous clinical studies (mean vertical defect fill 86%).

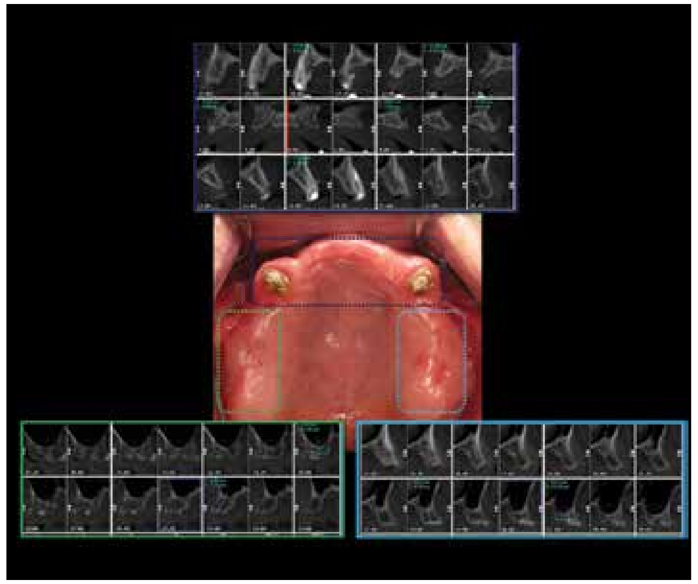

Figure 2: Pre-op occlusal clinical view and cone beam computed tomography scan of the maxilla.

Although not significant, the mean vertical defect fill at the rhBMP-2 treated sites was slightly better (96%) than control sites. The authors underscored the necessity to maintain space by adding xenogenic bone material to the osteoinductive rhBMP-2 for enhanced results.[34] Implant survival rates in test sites over three to five years were 100% which is in agreement with other systematic review that reported high survival of implants (median 100%) placed in regenerated bone.[8]

On the histologic level, previous studies reported definite bone induction using rhBMP-2 in maxillary sinus and alveolar ridge augmentation procedures.[27,29,31,35] Qualitative analysis of bone formation showed presence of moderate to large amounts of trabecular bone in the newly induced region with variations of woven bone (small to moderate) and/or, remodeling of woven bone to lamellar bone and/or presence of moderate to large amounts of lamellar bone alone. At the cellular level, small

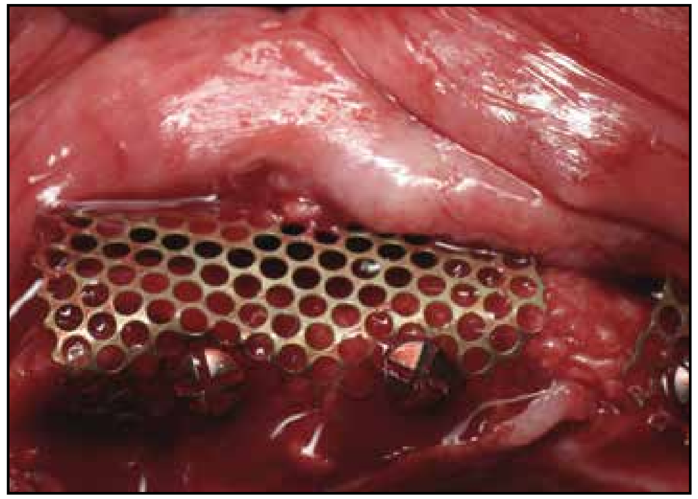

Figure 4: Occlusal view of Titanium Mesh secured with screws.

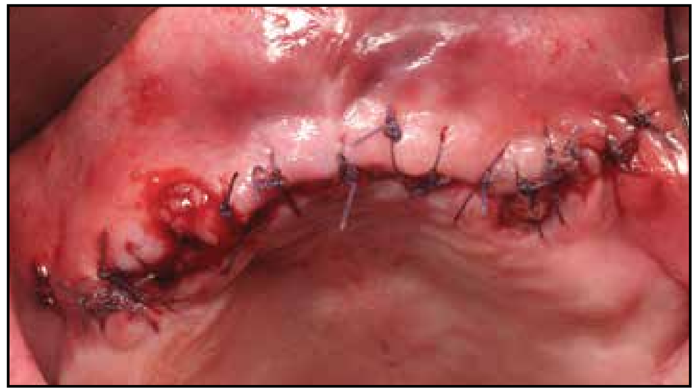

Figure 6: Post-op view of primary closure.

to moderate amounts of osteoblasts were present along with intermittent, smaller amounts of osteoclasts. Further, there was no evidence of remaining residual collagen sponge material in any of the rhBMP-2/ACS treated specimens with very few inflammatory cell infiltration.[27,29,31,35]

CASE REPORT

The current case report evaluates the use of 1.5 mg/ml rhBMP-2 with an absorbable collagen sponge (ACS) mixed with a bone replacement graft for lateral ridge augmentation and bilateral sinus lift augmentation procedures. A specific technique for space maintenance to achieve anterior ridge augmentation is described. The clinical, radiographic and histologic results are presented.

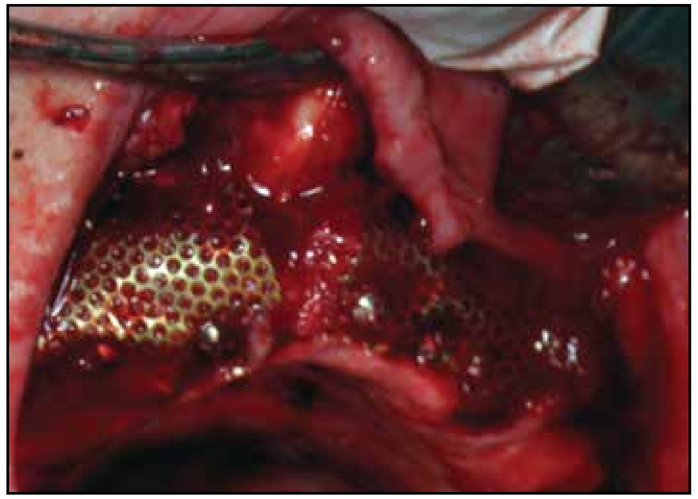

Figure 5: Placement of rhBMP-2/ACS and Xenograft bone material.

Figure 7: rhBMP-2/ACS mixed with xenograft bone material.

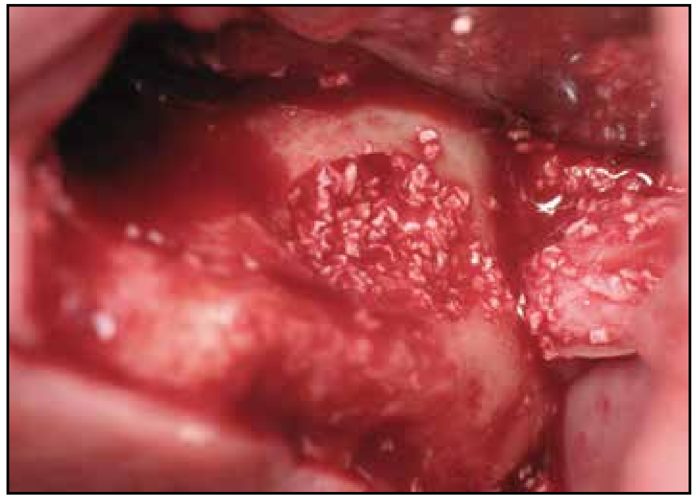

Figure 8: Facial view of rhBMP-2ACS and xenograft placed in the maxillary sinus.

Figure 9: Facial view of alveolar ridge healing at 7 months.

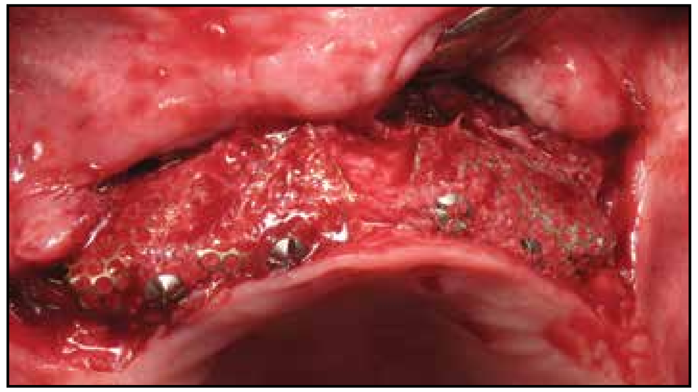

Figure 10: Re-entry facial view showing bone formation within the titanium mesh.

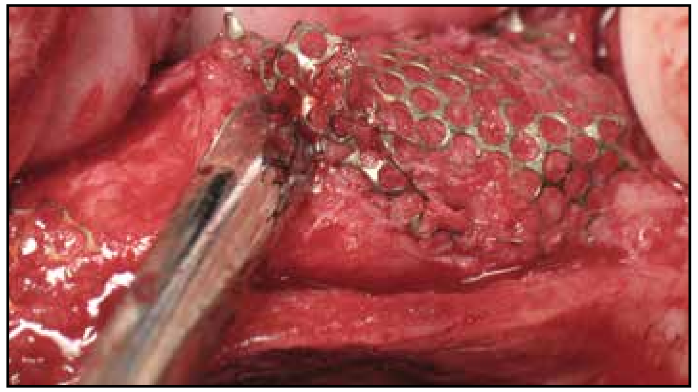

Figure 11: Clinical view showing bone formation within the Titanium Mesh.

Initial Presentation

A healthy 76-year-old male patient presented with partial edentulous maxilla and retained periodontally involved left and right maxillary canines (Figure 1). The clinical and radiographic examination revealed a class III ridge deficiency[3] for anterior maxilla with bilateral maxillary sinus pneumatization (Figure 2). The treatment plan included anterior lateral ridge augmentation with bilateral maxillary sinus augmentation for dental implant supported maxillary fixed prosthesis. An experienced periodontist (MR) performed the surgical procedure in its entirety.

Surgical Procedure (Anterior Ridge and Bilateral Maxillary Sinus Augmentations)

The patient received Amoxicillin 500 mg (Teva Pharmaceuticals, Sellersville, PA, USA) starting 24 hours before the procedure and for seven days after. Presurgically the patient rinsed with a 0.12% chlorhexidine (Hi-Tech Pharmacal Co., Inc. Amityville, NY, USA) solution for a minute

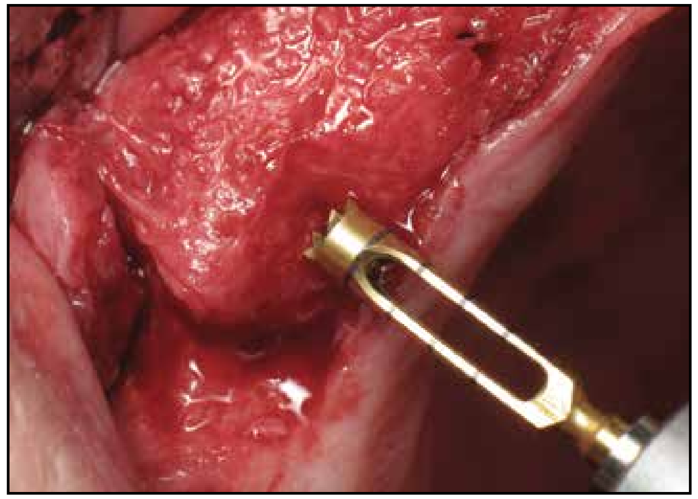

Figure 12: Core biopsy obtained using a 2.0 mm trephine drill.

Figure 13: A 2x6 mm core biopsy obtained for histologic analysis.

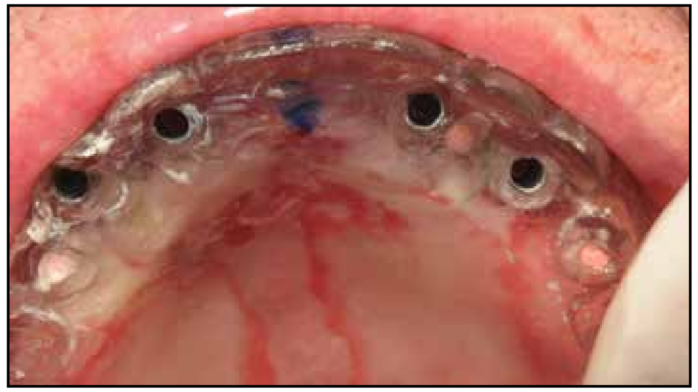

Figure 14: Surgical guide for implant placement.

Figure 15: Four dental implants placed.

and local anesthesia administered using 2% lidocaine with 1:100,000 epinephrine (Empi, Inc., St. Paul, MN). Periotomes were used to severe periodontal ligaments to facilitate extractions of #6, 11 with minimal trauma. The sockets were thoroughly debrided and facial bone loss was present affecting the coronal 1/2 of the sockets. A midcrestal incision was made with mucoperiosteal flap elevation to expose the ridge crest and facial cortex in the maxillary anterior region. The recipient bed was prepared by decorticating the ridge using a round bur to expose the cancellous bone. Using aseptic technique, 8.0 mg of lyophilized rhBMP-2 (INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN, USA) was reconstituted with 1.8 ml sterile water, gently rotated and withdrawn with sterile 5cc syringe. A sterile two (1 x 2 inches) ACS were prepared and the 2.0 ml aliquot of the 1.5 mg/ml rhBMP-2 solution was withdrawn and uniformly dispensed over them and allowed to soak for 20 minutes (binding period of the growth factor to the col-

Kinaia et al

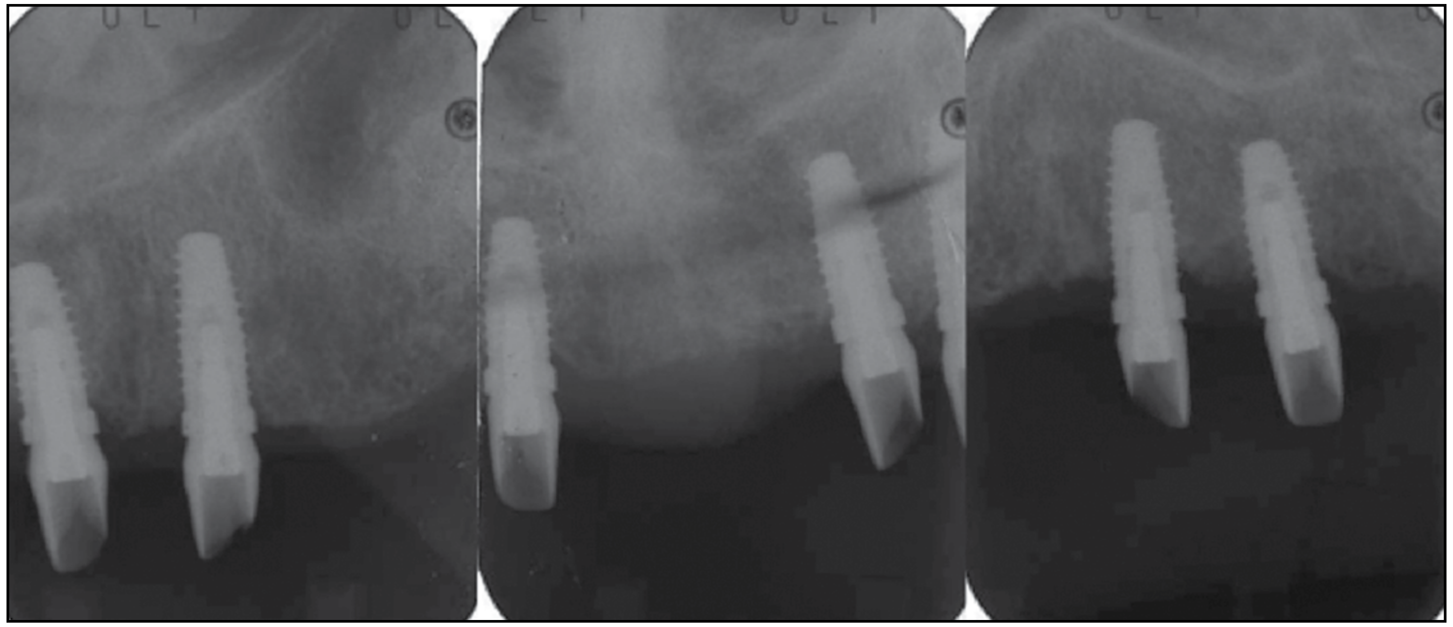

Figure 16: Radiographs of abutments connected to implants.

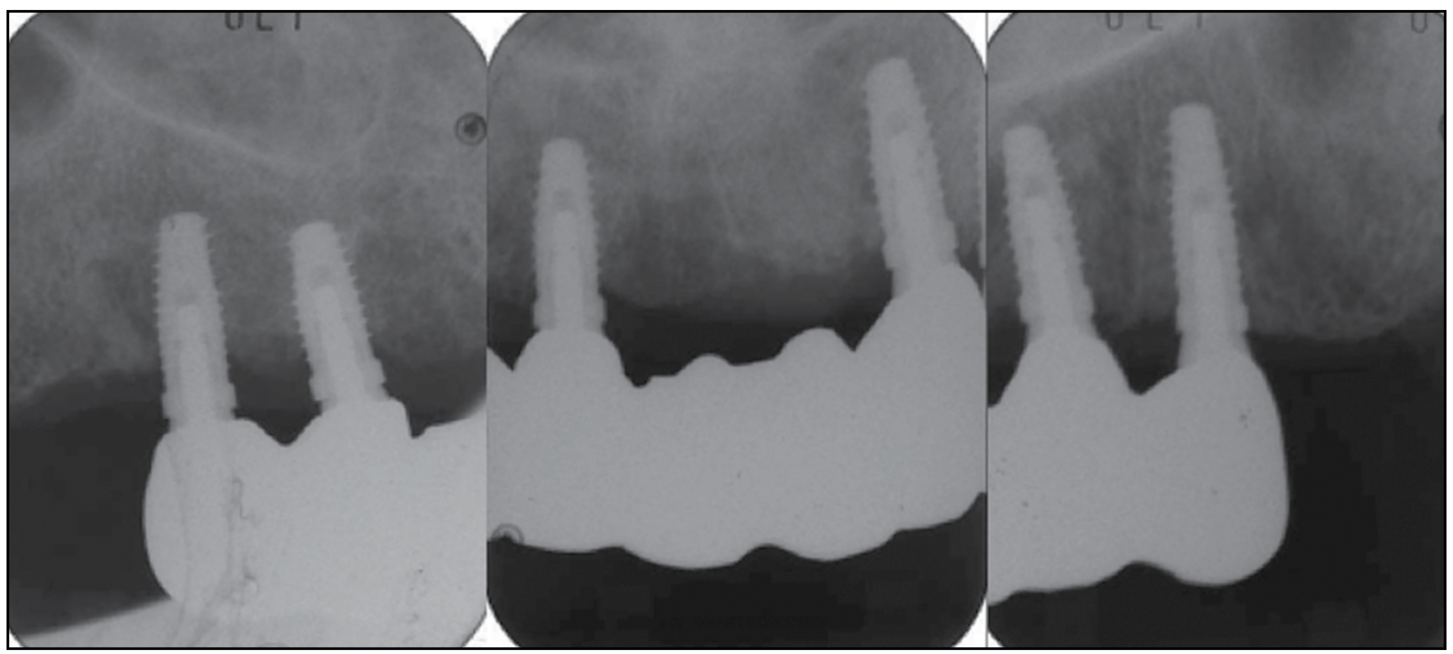

Figure 17: Radiographs of final maxillary fixed partial denture.

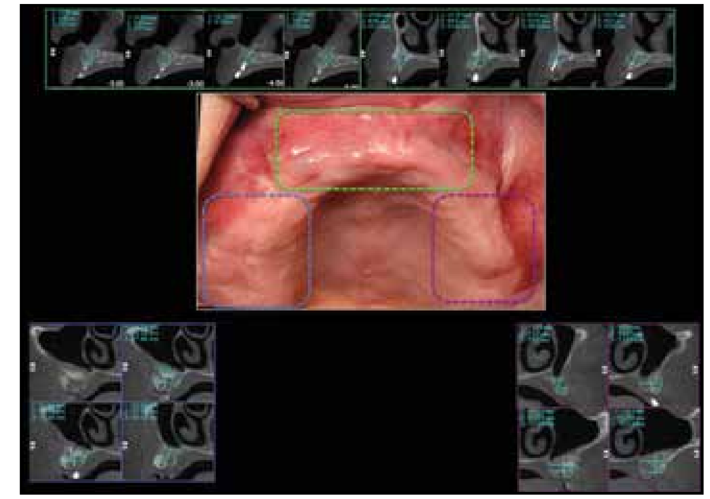

Figure 18: Post-op occlusal clinical view and cone beam computed tomography scan of the maxilla.

lagen barrier). The ACS were cut into 3 x 3 mm pieces and mixed with small quantity of xenograft bone material (BioOss, Geistlich Biomaterials, Inc., Wolhusen, Switzerland) (Figure 3).

For the purpose of space maintenance, Titanium Mesh device (TiMesh® Medtronic Goleta, CA, USA) was used, contoured and stabilized with bone screws to increase the horizontal width of the alveolar ridge (Figure 4). The combination preparation of rhBMP-2/ACS and xenograft was placed in the defect area and the sockets and gently compressed to fill the space up to the TiMesh surface (Figure 5). Primary closure was achieved by coronally advancing the flap and secured using 4-O vicryl (Polyglactin 910, Ethicon Inc., Johnson & Johnson Company, Somerville, NJ, USA) interrupted sutures (Figure 6). The patient was monitored periodically and the grafted sites were allowed to heal for 6 months.

The maxillary sinus augmentation was performed within 2 months after anterior ridge augmentation. Presurgical protocol was similar to ridge augmentation. An incision was made along the ridge crest with mucoperiosteal flap elevation to expose the maxillary posterior regions. Lateral window was outlined and schneiderian membrane elevated using special sinus curettes. Similarly to the anterior ridge augmentation, 1.5 mg/ml rhBMP-2/ACS were prepared, mixed with xenograft (Figure 7), and placed into the sinuses bilaterally (Figure 8). Primary closure was obtained using 4-0 interrupted vicryl sutures and the areas were allowed to heal for 7 months.

Re-Entry and Implant Placement

Re-entry was performed after 7 months of healing (Figure 9). Under local anesthesia, an incision was made with a mucoperiosteal flap elevation exposing the crest of the ridge and the facial cortex in the maxillary anterior region (Figure 10). The Ti Mesh was exposed and the screws removed. Interestingly, the Ti Mesh was intimately intertwined with the augmented bone and efforts were made to remove it as the bone grew into the indentations of the Ti Mesh (Figure 11).

Four 6 mm length core sample biopsies were obtained using 2.0 mm trephine drills from sites #6, 7, 10, 11 and labeled and sent to the lab for histological analysis (Figures 12, 13). Using the surgical guide, osteotomies were continued according to the implant company protocol and four implants (Osseotite®, Biomet *3i* Inc., Palm Beach Gardens, FL, USA) sizes 4/3 x 10 mm for #6; 4/3 x 11.5 mm for #7; 4/3 x 10 mm for #10; and 4/3 x11.5 mm for #11 were placed with excellent primary stability (40 NcM) (Figures 14, 15). Primary closure was obtained and the implants were allowed to heal for 6 months before loading. The implants were allowed a period of 6 months for adequate

Table 1: Difference in the Amount of Bone Regenerated Before and After Maxillary Sinus Augmentation				
	CBCT Pre		CBCT Post	
Tooth No.	Height	Width	Height	Width
#3	5.03	11.40	13.2	13.50
#4	8.54	8.70	10.15	7.62
#13	8.60	7.21	14.59	11.29
#14	6.91	11.44	15.79	14.34
Mean ± SD (in mm)	7.27 ± 1.69	9.69 ± 2.09	13.43 ± 2.43	11.69 ± 3.00

Table 2: Difference in the Amount of Bone Regenerated Before and After Lateral Ridge Augmentation in the Maxillary Anterior Region				
	CBCT Pre		CBCT Post	
Tooth No.	Height	Width	Height	Width
#6	13.74	9.53	15.32	9.83
#7	11.95	4.33	13.23	9.07
#8	11.82	4.46	17.52	9.40
#9	10.41	4.58	10.13	9.97
#10	12.94	4.67	14.85	10.13
#11	13.65	6.98	13.74	9.66
Mean ± SD (in mm)	12.42 ± 1.28	5.76 ± 2.10	14.13 ± 2.47	9.68 ± 0.39

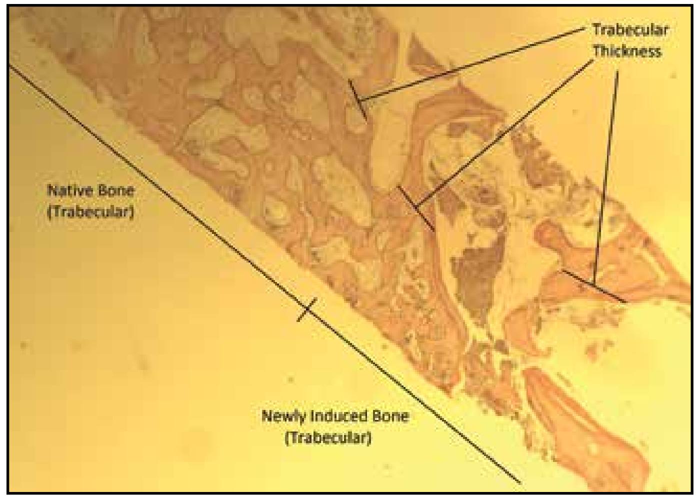

Figure 19: Site #11 (20X magnification) showing trabecular bone presence.

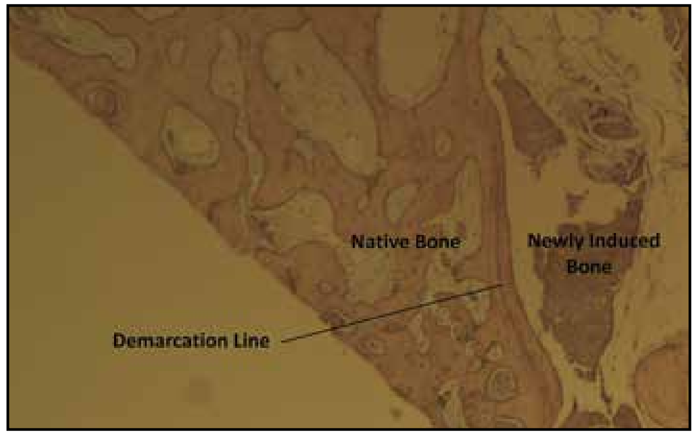

Figure 21: Site #11 (40X magnification) showing demarcation line separating newly induced bone from native bone.

osseointegration. Upon second stage surgery, the abutments were secured and verified using periapical radiographs and later restored with maxillary fixed partial denture (Figures 16, 17).

RESULTS

Radiographic (CBCT) Analysis

Cone beam computed tomography scans were taken at initial presentation (Figure 2) and 6

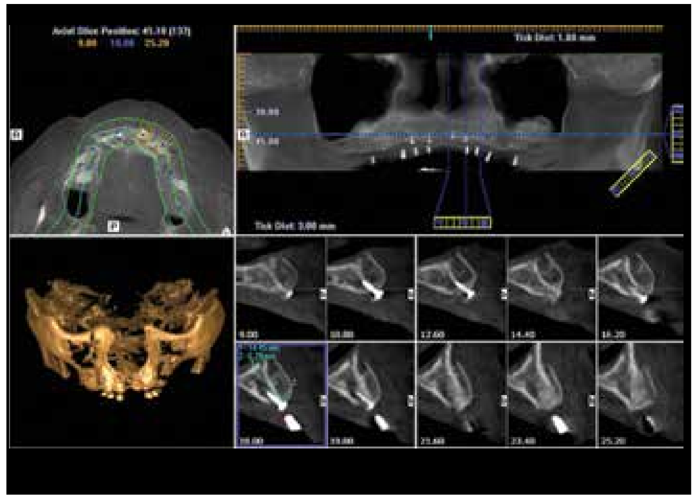

Figure 20: Post Surgical CBCT showing demarcation line for tooth site #11.

months after ridge augmentation (Figure 18). A radiographic comparison of the pre- and post-augmentation procedures, revealed adequate bone formation and gain in horizontal and vertical ridge width. For the maxillary sinuses, there was an increase in bone height from 7.27 ± 1.69 mm to 13.43 ± 2.43 mm. A similar finding for ridge width occurred with increase in horizontal bone gain from 9.69 ± 2.09 mm to 11.69 ± 3.00 mm (Table 1). With regard to the maxillary anterior region, there was an increase in bone height from 12.42 ± 1.28 mm to 14.13 ± 2.47 mm. There was a significant increase in ridge width with horizontal bone gain from 5.76 ± 2.10 mm to 9.68 ± 0.39 mm (Table 2).

Histological Analysis

A histological examination of the bone core biopsy specimens was conducted indicating new vital bone induction by rhBMP-2 (Figure 19). The post-surgical CBCT scan shows the demarcation line present (Figure 20). The line correlates with the histologic slides separating the native bone from

Kinaia et al

the newly induced bone (Figure 21). The qualitative analysis of bone formation showed presence of moderate to large amounts of trabecular bone in the newly induced region containing different variations in the amounts of woven and lamellar bone.

DISCUSSION

Alveolar ridge and maxillary sinus augmentation procedures are well documented as successful procedures with predictable results.[7,8] Many techniques and materials are used today with bone grafts being the predominant material utilized. The osteoinductive characteristics of the materials used plays a significant role in bone regeneration and hence growth factors are more often used today in addition or as an alternative to bone grafts.[8,9] To date, the role of growth factors such as bone morphogenic proteins remains to be experimental with more animal than human studies to support its clinical relevancy. Therefore, the aim of the current review and case report was to evaluate the quantity and quality of new bone regenerated using rhBMP-2 for alveolar ridge and maxillary sinus augmentation procedures.

The review of the literature reported a favorable gain in alveolar bone height with the use of rhBMP-2 in maxillary sinus lift procedures.[14] Since there is tendency for graft shrinkage with use of rhBMP-2/ACS alone, studies reported beneficial results with incorporation of a mineralized bone replacement graft into the infuse bone graft.[30] They reported a mean height increase of 14.7 ± 2.76 mm in sinus lift procedures using rhBMP-2 with a bone substitute material (xenograft or allograft).[30] In the current case report, a xenograft material was added to the rhBMP-2 to compensate for the possible shrinkage of the material. The results of the bilateral sinus lift are comparable to other studies with increase in bone height from 7.27 ± 1.69 mm to 13.43 ± 2.43 mm and increase in horizontal bone gain from 9.69 ± 2.09 mm to 11.69 ± 3.00 mm.

Contrary to the bone height gain with sinus lift augmentation, the literature reported a loss in alveolar bone height (although slight) using rhBMP-2 alone (-0.08 ± 2.5 mm) in lateral ridge augmentation procedures.[32] With regard to bone width using rhBMP-2, only two studies reported the amount of horizontal bone augmentation. The bone gain was minimal ranging from 0.23 mm to 0.4 mm.[31,32] Jung et al. showed that the beneficial effects of combining rhBMP-2 with a xenogenic bone material are a higher degree of bone maturation and an increased graft to bone contact where the bone substitute acted as a scaffold for space maintenance.[34] In the current case report, an increase in bone height from 12.42 ± 1.28 mm to 14.13 ± 2.47 mm was obtained with a significant increase in ridge width from 5.76 ± 2.10 to 9.68 ± 0.39 mm. These results were superior to those discussed above. It is the authors' opinion that this increase is attributed to the added use of TiMesh and xenograft for space maintenance. Such significant gain in alveolar ridge augmentation has recently been reported in human studies.[35,36]

CONCLUSION

Although the advent of osteoinductive growth factors such as rhBMP-2 along with traditional bone graft materials has opened new horizons in the field of guided bone regeneration therapy, the clinical documentation of use of rhBMP-2 based on the current literature review is sparse. There is a distinct lack of total number of investigations as well as randomized controlled trials that compare and contrast the use of rhBMP-2 in augmentation of localized ridge deficiencies. Nonetheless, the use of rhBMP-2 mixed with bone graft substitute in maxillary sinus and lateral ridge augmentation procedures along with titanium mesh for space maintenance shows positive initial clinical results. Further research may prove growth factors to be an additional armamentarium in bone augmentation.

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Disclosure
The authors report no conflicts of interest with anything mentioned in this article.

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