Gingival swelling and erythematous with DBM incorporated with rhBMP-2 after large postoperative cystic defect: a case report

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This paper presents the postoperative complications, gingival swelling, and erythematous of a patient at one week after bone graft using 4.5 cc of DBM incorporated with rhBMP-2 (Bio BMP2, Cellumed, Seoul, Korea) on a maxillary large cystic defect and bone remodeling result after six months. The postoperative complication and the effect of DBM incorporated with rhBMP-2 on a large cystic defect in this patient are discussed. (JOURNAL OF DENTAL IMPLANT RESEARCH 2020;39(1):11-16)

Key Words: Bone substitute, Bone morphogenetic protein, Demineralized bone matrix

INTRODUCTION

In the treatment of cystic lesions in the jaw, small cysts are usually spontaneously healed by the physiological mechanism of bone regeneration after enucleation. However, bone graft could be considered as a complementary method because significant bone defects after enucleation of large cysts for reducing pathologic fracture, or could not be healed spontaneously. In the case of using synthetic or xenogenic bone substitutes on the defects, the substitutes should be replaced with new bone formation by osteoblasts¹⁾, but there are some cases in which delayed remodeling due to exposure and infection of the grafted bone substitutes²⁾. Osteoinductive bone substitutes, high potency of bone formation capacity, such as autogenous bone graft or bone substitutes using recombinant human bone morphogenetic protein-2 (rhBMP-2) are helpful for rapid healing and reducing a risk of pathologic fracture. In addition, blood vessels can be formed and bone fusion with the surrounding bone can be promoted while minimizing the risk of infection and

dropout. However, autologous bone graft has the disadvantages such as long surgical time to acquire graft, donor morbidity or graft resorption³⁾. In order to overcome these disadvantages, allograft, synthetic bone, xenograft or application of rhBMP-2 could be considered as alternatives.

rhBMP-2 which uses an absorbable collagen sponge (ACS) as carrier has been approved by the FDA for use at a concentration of 1.5 mg/mL⁴⁾. However, the fact that the release rate of BMP from the collagen sponge is quite fast implies the clinical limitation of ACS as an rhBMP-2 carrier⁴⁾. On the other hand, the studies in vitro and in vivo about the kinetic aspects of demineralized bone matrix (DBM) as BMP carriers showed that sufficient kinetic release could be achieved, resulting in an effective combination of both functions as a carrier and a growth factor⁵⁾. Meanwhile, there are other clinical studies suggesting that using DBM alone or in combination with other types of bone substitutes has low levels of efficiency⁶⁾. To overcome this disadvantage of DBM, the products has been developed that DBM incorporated with rhBMP-2

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(DBM/rhBMP-2). However, the clinical evaluation of this product has not been studied. The aim of this case is to analyze the early and long term results of applying DBM/rhBMP-2 (Bio BMP2, Cellumed, Seoul, Korea) to a large sized cystic defect in the maxilla and to discuss focused on the effects of rhBMP-2 incorporated in DBM.

CASE REPORT

The study was approved by the Armed Forces Capital Hospital Institutional Review Board (IRB No. AFCH-19-IRB-024). A 22-year-old male who complained swelling on left cheek and mouth opening restriction was visited the armed forces capital hospital. On the radiographs, there was observed a large cystic lesion with diameter of about 10 cm on left maxilla.(Fig. 1A and B) The laboratory examination on the day of the visit revealed an in-

fectious condition as C-reactive protein (CRP) of 4.5 (mg/dL, reference<1.0 mg/dL), White Blood cell of 11.96 (10^3 /uL, reference<10 10^3 /uL), neutrophil of 77.7 (% , reference<75%) and monocyte of 1.12 (10^3 /uL, reference <0.48 10^3 /uL). Incision and drainage insertion were performed and the symptoms and CRP were improved after 3 days (CRP of 3.45 mg/dL) and 7 days (CRP of 0.14 mg/dL).

After improved the infectious symptoms, root canal treatment of involved teeth and marsupialization with incisional biopsy was performed using foley tube which was changed per three days.(Fig. 2A-C) The yellowish-brown fluid was discharged continuously and histologic results were showed chronic inflammation with fibrosis and bland looking stratified squamous epithelium, indicated dentigerous cyst rather than benign tumor or ameloblastoma.

Fig. 1. Pre-operative infected condition of the patient. (A) Cystic lesion on anterior to left posterior of maxilla on panoramic view. (B) Cystic lesion with pathologic fracture of thinned and expanded maxillary anterior wall on computer tomography. (C) Incision and drainage were operated with drain insertion.

Fig. 2. Marsupialization and root canal treatment. (A, B) The size of cyst was decreased compared with previous panoramic view at 14 weeks for marsupialization. (C) Marsupialization with foley tube which was changed per three days. (D) Foley tube was removed at 14 weeks for marsupialization.

At 14 weeks after marsupialization, the draining foley tube was removed because size of the cyst was not further decreased and the patency of maxillary sinus ostium

was secured on CT.(Fig. 2D) At two weeks after the tube removal, the enucleation of the cyst was operated under general anesthesia. After surgical field preparation, muco-

Fig. 3. Operation. (A) Operation of cyst enucleation. (A-I) Before operation. (A-II) Scalloped incision and elevation of mucoperiosteal flap. (A-III) Window opening on maxillary anterior wall with apicoectomy. (A-IV) Enucleated cyst. (A-V) Perforation of maxillary sinus schneiderian membrane. (A-VI to VIII) Repairing of perforated membrane with suture, Greenplast Q (Fibrin glue) and surgicel. (A-IX) 1 cc of Xgen (DBM) and 4.5 cc of Bio BMP2 (DBM/rhBMP-2) packed into the cystic defect. (A-X to XII) Greenplast Q (Fibrin glue), titanium mesh and ossguide covered on the grafts. (B) Schematic diagram of the grafts on cystic defect. (C) Post-operative intraoral image. (D) Post-operative panoramic view. (E) Post-operative computer tomography.

periosteal flap was elevated with scalloped incision from right maxillary canine to left maxillary tuberosity.(Fig. 3A-I and -II) Sinus anterior wall was opened by micro-saw and the cyst was carefully enucleated with apicoectomy from right maxillary incisor to left second premolar.(Fig. 3A-III to -V) There was observed partial missing of posterior wall of cystic cavity with perforation of sinus schneiderian membrane. The membrane around perforation was dissected and adapted both side for bridge form with 6-0 Vicryl (Johnson & Johnson International, New Jersey, USA).(Fig. 3A-VI) The remaining defects were covered Surgicel (Johnson & Johnson, New Brunswick, NJ) and Greenplast Q (GC pharma., Kyonggi-Do, Korea).(Fig. 3A-VII and -VIII) There was verified that the perforation was sealed and covered 1 cc of Xgen (Hansbiomed, Seoul, Korea) and packed with 4.5 cc of Bio-BMP 2 (Cellumed, Seoul, Korea). Before covering titanium mesh (Depth 0.085 mm, Hole size ϕ 0.4 mm, Neo

Biotech, Seoul, Korea), the grafts were applied the fibrin glue for reducing leakage of rhBMP-2.(Fig. 3A-IX and -X) Titanium mesh was adapted on bony window of maxillary anterior and fixed with mini-screws (Bone screw system, Osung MND, Kyonggi-Do, Korea).(Fig. 3A-XI) The entire mesh was covered with ossgide (SK Bioland, Cheonan, Korea).(Fig. 3A-XII) The gingival perforation, previous marsupialization site, was sealing with pedicled buccal fat pad for preventing fistula.(Fig. 3B) Then, interrupted suture was done on the incision line.(Fig. 3C-E)

At 1 week postoperatively, the patient complained sharp pain on Left buccal area and intraoral swelling with improved facial swelling.(Fig. 4A and B) At 2 days and 1 week after operation, computed tomography showed well-stabilization on the membrane perforation area but fluidic aspect on buccal side of the grafts and mesial side of buccinators.(Fig. 4C) Intra-oral swelling was increased and aspiration was performed with 50 cc syringe.(Fig.

Fig. 4. Post-operation. (A) Left cheek swelling at 7 days after operation. (B) Mild gingival swelling at 7 days after operation. (C) Fluidic aspect (arrow) on computer tomography at 9 days after operation. (D) Gingival swelling and erythematous at 9 days after operation. (E) No specific finding by aspiration on fluidic aspect and gingival swelling. (F) Gingival swelling and erythematous improved at 10 days after operation. (G) Gingival swelling and erythematous disappeared at 13 days after operation. (H) Fluidic aspect disappeared at 13 days after operation. (I) Radiopacity was slightly increased around surrounding bone on computer tomography at 3 months after operation. (J) Radiopacity was increased overall cystic defect on computer tomography at 6 months after operation.

4D) Through the aspiration, there was observed bloody exudate discharge without pus.(Fig. 4E) without further treatment, intraoral swelling and the fluidic aspect on buccal side of the grafts were improved at 4 days after aspiration.(Fig. 4G and 4H) There was mild increased radiopacity without rapid remodeling sign on CT at 3 months after operation.(Fig. 4I) At 6 months after operation, CT showed increasing radiopacity indicated remodeling without central necrosis.(Fig. 4J)

DISCUSSION

The reason why grafts are required for cystic defects is that we can get rapid bone healing to minimize the possibility of pathological fractures and morphologic deformities. In addition, the another purpose of graft is to allow radiological evaluation of post-operative defects whether the recurrence. Chmitz and Hollinger suggested for the necessity for bone grafts if the remaining walls of cystic defects are not stable⁷⁾. However, there has been controversy about the efficiency of bone graft after cyst enucleation. The cost-effectiveness should be considered in clinical practice and there is also a consideration against grafts due to the risk of infection. In the present patient, extensive defects on the maxilla into the maxillary sinus and instability of bone structure surrounding the defect were identified. In this large defect case, there was a high risk of central necrosis due to delayed vascularization of grafted materials which do not have osteoinductivity. In addition, the military hospital decided bone graft because there was no financial burden on the patient. Therefore, the patient was used mainly DBM/rhBMP-2 products, well known high potency of osteoinductivity, for rapid healing and for preventing to central necrosis for the grafts.

About twenty bone morphogenetic protein (BMP) families have been revealed so far, BMP-2 and BMP-7 have been proved to have the most potent induction ability of bone and cartilage. BMPs show limited solubility at physiological pH, which is thought to be related to their pharmacological action⁸⁾. Rapid disappearance is also a common property of BMP⁹⁾. Diffusion into nearby tissues can lead to unwanted ectopic bone formation, intrinsic bone absorption and edema of soft tissues¹⁰⁾. On the other

hand, the graft material mainly used for this patient is Bio BMP2 (Cellumed, Seoul, Korea), characterized by the use DBM and natural polymer as a carrier. Long-term binding of DBM and rhBMP-2 could allow to maintain the osteoinduction properties of rhBMP-2 at the center of bone defects and to consistent high bone regeneration ability over time. Studies about the release of rhBMP-2 in the DBM have shown that releasing of rhBMP-2 in the DBM mostly appears up to 4 days and it still has high osteoinductivity until 14 days, including a constant release. After 56 days, rhBMP-2 is still retained in DBM, probably due to affinity with the original extracellular matrix component⁵⁾.

When complications occur after using with rhBMP-2, the exposure dose is high as equivalent to one million times of the amount of the proteins applied physiologically¹¹⁾. Because rhBMP-2 interacts with various cytokines and chemokines¹²⁾, There are some clinical findings that the high doses of rhBMP-2 applied locally are associated with side effects such as soft tissue hematoma¹³⁾, excessive inflammatory reaction¹⁴⁾ and infection¹⁵⁾. The release kinetics of the delivery system of rhBMP-2 has been showed that the choice of carrier material affects not only the physiological structure of the carrier but also the protein integration method and interaction type between proteins and carrier¹⁶⁾. Encapsulating rhBMP-2 into the nanoparticles can bypass most of the problems resulting from fast release, but many encapsulation techniques involve hardly controlled conditions such as the use of organic solvents, interfacial exposure and acidic environments¹⁷⁾. The chemical and physical instability, caused by host conditions such as change of temperature and pH, could decrease the activity of rhBMP-2 and causes side effects¹⁸⁾. As well known, an efficacy of rhBMP-2 exhibits proportional to dose and complications of rhBMP-2 are caused proportional to releasing concentration.

The authors concerned a burst releasing that a large amount of rhBMP-2 had been released immediately after surgery. However, it is difficult to define whether the intraoral swelling, observed in the patient from the third day after surgery, and the fluidic aspect, observed at CT, were due to released rhBMP-2 solution or due to inflammatory reaction of rhBMP-2. There was no liquid collection during aspiration on intraoral swelling site and ec-

topic bone formation which indicated leasing of rhBMP-2 to adjacent soft tissue. The radiopacity on grafted site was not rapidly increased within three months but gradually increased at six months after operation without central necrosis of the grafts. This the result may be suggesting that osteoinductive potency could maintain until six months postoperatively without central necrotizing. This result could be affected by the initial angiogenetic efficacy of rhBMP-2 or the osteoinductive properties of DBM carrier itself. Consequently, DBM/rhBMP-2 products could be effectively used for large cystic defects without severe complications but it could be necessary to improve rhBMP-2 loading method to reducing initial inflammatory complications and to maintaining consistent local releasing concentrations over the long term period for more efficient results.

CONFLICT OF INTEREST

The authors have no financial relationship to disclose.

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