Application of Regenerative Medicine to Mandibular Reconstruction

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Abstract

Among the various methods of mandibular reconstruction, regeneration using poly-L-lactic acid mesh and particulate cancellous bone and marrow attained good efficacy and safety in a multi-institution prospective clinical study in Japan (Project No. GM941). This mandibular reconstruction method is not difficult to perform and is minimally invasive to the patient. If the use of this surgical technique spreads worldwide, elimination of disparities among medical treatment outcomes is expected.

Keywords: Mandibular reconstruction; PLLA mesh; Regenerative medicine

Abbreviations: PCBM: Particulate Cancellous Bone and Marrow; PLLA: Poly-L-Lactic Acid; bFGF-GMs: Basic Fibroblastic Growth Factor-Incorporated Gelatin Sponges; iPS cells: Induced Pluripotent Stem Cells

Current Status of Mandibular Reconstruction

Mandibular defects due to various conditions such as amputations excisions or injury are generally reconstructed using free bone grafts, pedicle bone grafts, microvascular free flaps, reconstruction plates, and Particulate Cancellous Bone and Marrow (PCBM) grafts [1]. These methods have advantages and disadvantages in terms of morphological and functional recovery. Among these techniques, microvascular free bone grafts such as those involving the fibula or scapula are often used for a wide range of defects after resection of malignant tumors. However, these methods require specialized surgical expertise and hospital resources, and donor site morbidity is significant. There are also limitations in restoration of the complex shape of the mandible, particularly in terms of maintaining symmetry of the curve of the mental region. The goal of mandibular reconstruction is to recover the patient’s aesthetics and occlusal and masticatory functions so that the use of dentures and dental implants is possible. This implies the need to regenerate a mandible of the desired shape and sufficient strength.

In 1944, Mowlem [2] demonstrated the superior osteogenic potential of cancellous bone grafts. However, sufficient global application of jawbone reconstruction in the clinical setting has not occurred. In 1964, Burwell [3] reported that the cells capable of bone formation are included in PCBM originated from undifferentiated mesenchymal cells. The necessary elements for bone formation are the presence of 1) osteogenic cells (osteoprogenitor cells/stem cells), 2) a scaffold for bone formation, and 3) bioactive factors (biologically active substances) or genes that induce proliferation and differentiation of osteoblasts while guiding the tissue-repairing function of the subject [4]. To apply PCBM to jawbone regeneration, it is essential to provide a scaffold (framework) that guides the bone formation from the PCBM into the desired shape while withstanding external force until completion of the intended bone formation. At present, such a scaffold is available in the form of either titanium mesh tray [5] or an absorbable tray [6,7]. However, the former demonstrates very limited molding at the time of the operation and requires a second operation for removal [8]. In addition, evaluation of a sufficient number of cases is required to elucidate the efficacy of the latter.

Weaving PLLA Mesh with PCBM

Kinoshita et al. [9] have developed a scaffold of poly-L-lactic Acid (PLLA) mesh and established a method for jawbone regeneration, using PCBM as a cellular reservoir. The PLLA mesh is composed of 0.56 mm- and 0.6 mm-diameter PLLA monofilaments (Gunze Ltd., Kyoto, Japan) that are fabricated by spinning at 245°C and drawing at 80°C to obtain a filaments of a molecular weight of 20.5 x 10^4 Da.

These filaments can be woven into a sheet-type or tray-type PLLA mesh. The tray-type mesh can be prepared into a mandibular shape of various sizes using specific molds.

Woven PLLA mesh has sufficient pliability, adequate strength, and good maneuverability. Its conformity is excellent; a PLLA mesh sheet or tray can be adjusted to the shape of the bone defect with scissors and molding at about 70°C. In particular, it is preferable that bone regeneration results in a symmetrical mentum arch. Furthermore, the capillary vascularization required for bone regeneration is abundant in the gaps between the filaments. Our PLLA mesh can achieve a larger contact surface with the surrounding tissue compared with the porous PLLA plate, which may maintain a better balance of fragmentation and absorption. PCBM is harvested from either the anterior or posterior iliac bone, then injected and densely packed into the mesh tray, which is consequently consolidated [10].

PLLA is gradually absorbed during 4 to 5 years by non-enzymatic hydrolysis and phagocytosis by macrophages. The PLLA mesh tray does not require surgical removal and thus facilitates denture application and dental implant placement. The PLLA mesh tray is 21 mm high and 12 mm wide, so dentures or dental implants can be placed at any site when sufficient bone regeneration has been achieved (Figure 1).

Project No. GM941 of Gunze, Ltd: Sixty-two mandibular reconstruction surgeries (22 malignant tumors, 30 benign tumors, 5 cysts, 2 osteomyelitis lesions, 2 trauma lesions, and 1 lesion due to

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function was not achieved because of his unstable dentures. The surplus gradually matured (Figure 1C); however, sufficient masticatory using stainless steel wire. Postoperatively, the regenerated bone (Figure 1A and 1B). The mesh tray was fixed to the remaining bone reconstruction using a PLLA mesh tray and PCBM was performed using a free forearm flap and titanium plate. The titanium plate was removed at 19 months postoperatively, and mandibular resection method, use of irradiation, and combination with soft tissue reconstruction. The results showed that mandibular reconstruction combined with soft tissue reconstruction resulted in significantly less bone regeneration compared with mandibular reconstruction alone (p = 0.0305). Therefore, it was thought that mandibular reconstruction should be performed after soft tissue reconstruction to reduce the risk of infection of the PLLA mesh. In six of the cases with poor outcomes, the PLLA mesh was removed due to local infection early after surgery. Bone resorption of >20% was observed in only 1 of 46 cases with a follow-up period of >1 year. There were no signs of any other adverse effects with the exception of one case in which a section of the tray broke off late in the follow-up period.

Based on the above results, bone regeneration using PLLA mesh and PCBM appears to be a useful mandibular reconstruction method because good bone regeneration was obtained and only small amounts of bone resorption occurred in the long-term follow-up.

Case Report

A 55-year-old male patient underwent irradiation of a right mandibular gingival squamous cell carcinoma (stage IV). After irradiation, mandibular segmental resection and reconstruction were performed using a free forearm flap and titanium plate. The titanium plate was removed at 19 months postoperatively, and mandibular reconstruction using a PLLA mesh tray and PCBM was performed (Figure 1A and 1B). The mesh tray was fixed to the remaining bone using stainless steel wire. Postoperatively, the regenerated bone gradually matured (Figure 1C); however, sufficient masticatory function was not achieved because of his unstable dentures. The surplus reconstruction flap was resected followed by vestibular extension using a full-thickness skin graft, three dental implant placements (PO137-19FN, 10 mm; Japan Medical Materials), and fabrication and placement of the overdenture incorporating a magnet (Figure 1D and 1E). Masticatory function markedly improved. A satisfactory mentum arch was observed on a computed tomographic image taken 13 years after the reconstruction surgery (Figure 1F).

Future Outlook for Mandibular Regeneration

The current disadvantages in mandibular reconstruction using PLLA mesh and PCBM include limited indication for certain patients and an increased risk of infection. This method is contraindicated in patients with an extensive bilateral defect, poor regional blood circulation, those of an advanced age with poor bone regenerative capacity or those who have received a full-dose irradiation. Infection can be prevented by: 1) dense closure of the oral wound; 2) strict and immediate initial fixation; 3) avoidance of simultaneous reconstruction of soft tissue and bone; and 4) strict patient selection.

To overcome these disadvantages, surgical treatment combined with growth factors that enhance vascularization and bone formation may be a promising strategy. Many reports on the pros and cons of platelet-rich plasma have been published. Kinoshita et al. [12] reported that basic fibroblastic growth factor (bFGF)-incorporated gelatin sponges (bFGF-GMs) promoted bone regeneration in a model of alveolar ridge reconstruction. The addition of bFGF-GMs to PCBM may overcome the inherent disadvantages of using a PLLA mesh tray and PCBM in mandibular reconstruction. However, the only growth factors approved by the Food and Drug Administration are BMP-2, 7 for augmentation of the sinus floor (sinus lift) and PDGF/beta-tricalcium phosphate for periodontal tissue reproduction; no growth factors are currently approved for mandibular bone regeneration. Therefore, the following fundamental techniques are necessary to obtain sufficient bone regeneration by the present method: 1) dense closing of the wound in the mouth, 2) preservation of a sufficient quantity of PCBM by harvesting from the posterior iliac crest or both anterior iliac crests, 3) insertion of the blood vessel into the PCBM to ensure abundant blood circulation [13], 4) strict initial fixation immediately after...
the operation using intermandibular fixation or other methods, and 5) bone maturation by the masticatory load after bone regeneration [14,15].

Since Professor Shinya Yamanaka of Kyoto University in Japan won the Nobel Prize in Physiology or Medicine for his research on induced pluripotent stem cells (iPS cells) in 2012, the field of regenerative medicine has attracted increasingly more attention. In the future, iPS cells may be used as the cellular sources of mandibular bone regeneration instead of PCBM.

However, in such cases, a scaffold to serve as a framework is indispensable. It is hoped that this mandibular regeneration technique will also attract attention from domestic and global targets, accelerating its utilization. Bone regeneration using a PLLA mesh tray is not a surgically difficult method. If the use of this mesh tray is disseminated, it is expected that patients’ surgical stress as well as disparities among medical treatment outcomes will decrease.

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References