Ridge Preservation Using Demineralized Bone Matrix Gel With Recombinant Human Bone Morphogenetic Protein-2 After Tooth Extraction: A Randomized Controlled Clinical Trial

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Purpose: The aim of the present randomized controlled trial was to determine the safety and efficacy of injectable demineralized bone matrix (DBM) gel combined with recombinant human bone morphogenetic protein-2 (rhBMP-2) on alveolar ridge preservation after tooth extraction.

Materials and Methods: A total of 69 patients were randomly assigned to either a test group (n = 35) or a control group (n = 34). In the test group, DBM, together with rhBMP-2 (0.05 mg/mL; rhBMP-2/DBM) was transplanted into the extraction sockets. The control group received DBM alone. The safety of rhBMP-2/DBM was evaluated by oral examination, serum chemistry, and hematologic examination. The radiographic changes in alveolar bone height and width were measured using computed tomography scans performed immediately after transplant and again 3 months thereafter.

Results: Healing was uneventful in all subjects, with no anticipated adverse events and no clinically significant changes in the serum chemistry and hematologic findings. No meaningful immune response was found among the study groups. No significant difference was found in the radiographic changes of alveolar bone height and width ($P > .05$).

Conclusions: This new injectable biomaterial can be used easily and safely in clinical applications.
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Demineralized bone matrix (DBM) is made from donated human bone from which the inorganic mineral has been removed, leaving behind the organic collagen matrix.[1] During this process, a group of proteins becomes sequestered in the residual inorganic bone matrix; these proteins have been termed "bone

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morphogenetic proteins" (BMPs) by Urist.[2] Owing to the osteogenetic characteristics of native BMPs, DBM has been classified as an osteoinductive material,[3] and it has been routinely used to promote bone regeneration, not only in orthopedic surgery, but also in dental implant surgery.[4,5]

However, controversy exists regarding the osteoinductive potential of DBM. Although it has been shown in animal studies that DBM implants placed in middiaphyseal defects and extraction sockets have failed to induce new bone formation,[6,7] Landsberg et al[8] found that DBM did promote bone formation in defects adjacent to dental implants. Even the results of meta-analyses of previous clinical trials have been controversial. Reynolds et al[9] reported a beneficial effect of DBM, and Laurell et al[10] stated that its use might not be beneficial. This apparent lack of consistency in the ability of DBM to induce bone regeneration could be attributable to variations in the donor characteristics. A few studies have found that donor age, physiology, and pharmacologic status[11,12] could be contributing factors to the variable osteoinductive capacity of DBM. Furthermore, the processing and sterilization protocols used have differed according to the bone bank used, which might have influenced the quality of the final product by affecting the DBM particle size,[13] just as would the acid exposure times during the demineralization procedure. Therefore, the use of DBM in clinics, with the associated beneficial release of native BMPs, has been limited owing to their variable concentration within, or inadequate recovery from, bone.

Recombinant technologies have been used to provide controlled concentrations of BMPs, resulting in the development of recombinant human BMP (rhBMP), which expresses osteoinductive properties.[14-16] It has been shown that when rhBMP-2 is successfully loaded into inactive DBM, the addition of rhBMP-2 directly to inactive DBM provides consistent bone induction.[17] Furthermore, a few other studies have found that DBM is a suitable carrier for rhBMP-2.[18] The mechanism underlying these useful effects of DBM as a carrier for rhBMP-2 is not clear; however, it seems that the collagenous substrate that remains after hydrochloric acid extraction of the mineral fraction[2] might provide a sustained pattern of release of the osteoinductive protein[19] and serve as a scaffold for the proliferation and differentiation of osteoprogenitor cells.[20] Moreover, the manufacture of DBM into a putty- or paste-type form provides easy handling without scattering, which might facilitate its retention in the grafted area.

To the best of our knowledge, no well-controlled, randomized clinical trials (RCTs) of the utility of DBM combined with rhBMP-2 and modified into an injectable gel form for ridge preservation after tooth extraction have been performed. Hence, the present study was designed to determine the effect of DBM combined with rhBMP-2 in an injectable gel form (rhBMP-2/DBM) for alveolar ridge preservation after exodontia. The aims of our RCT were to assess the safety of rhBMP-2/DBM in human subjects; and to evaluate the radiographic changes in the alveolar ridge after transplantation of either DBM alone or rhBMP-2/DBM gel into extraction sockets.

Materials and Methods

STUDY POPULATION AND DESIGN

The present single-blind, prospective, and parallel-arm RCT was conducted at 2 centers in the Republic of Korea from April 2011 to March 2013, and the study protocol was approved by the institutional review board at each of the 2 study centers (approval nos. 2-2010-0004, MD09019). The present study was conducted with the approval of the Korean Food and Drug Association. This clinical trial was registered at http://cris.nih.go.kr/cris/index.jsp.

All patients aged 20 to 70 years, who required single tooth extraction in the anterior region and alveolar ridge preservation were candidates for the present study. At the first visit, the patients were asked for their informed consent before enrollment in our study.

The inclusion criteria were systemically healthy subjects who required extraction of a single-rooted nonmolar tooth and residual extraction sockets with less than 50% bone loss in all dimensions. The exclusion criteria were the presence of severe periodontitis or acute infections at tooth extraction; pregnancy or planning to become pregnant within 1 year of the experiment; recent myocardial infarction or uncontrolled bleeding disorders; the presence of mental illnesses or suspected mental illnesses; hypersensitivity to bone graft materials; and the presence of clinically significant or unstable systemic diseases affecting bone or soft tissue growth, or other renal, hepatic, endocrine, hematologic, and autoimmune diseases.

Randomization was performed using a computer-generated randomization list. The randomization code was opened only at surgery (visit 2), and the patients were randomly allocated to either the test or the control group. The test group received rhBMP-2/DBM (Rafugen DBM Gel plus rhBMP-2, 0.05 mg/mL; Korea Bone Bank, Seoul, Korea). The control group received DBM alone into the extraction socket immediately after tooth removal.

PREPARATION OF RHBMP-2/DBM

After cleaning the cortical bones with distilled water and grinding them to a particle size of 0.5 to 1.0 mm, the lipid and fat were removed in 70% ethanol and 3%

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