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Evaluation of the clinical and radiographic effectiveness of treating peri-implant bone defects with a new biphasic calcium phosphate bone graft: a prospective, multicenter randomized controlled trial

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ABSTRACT

Purpose: Biphasic calcium phosphate (BCP), a widely used biomaterial for bone regeneration, contains synthetic hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), the ratio of which can be adjusted to modulate the rate of degradation. The aim of this study was to evaluate the clinical and radiographic benefits of reconstructing peri-implant bone defects with a newly developed BCP consisting of 40% β-TCP and 60% HA compared to demineralized bovine bone mineral (DBBM).
Methods: This prospective, multicenter, parallel, single-blind randomized controlled trial was conducted at the periodontology departments of 3 different dental hospitals. Changes in clinical (defect width and height) and radiographic (augmented horizontal bone thickness) parameters were measured between implant surgery with guided bone regeneration (GBR) and re-entry surgery. Postoperative discomfort (severity and duration of pain and swelling) and early soft-tissue wound healing (dehiscence and inflammation) were also assessed. Data were compared between the BCP (test) and DBBM (control) groups using the independent t-test and the χ^2 test.
Results: Of the 53 cases included, 27 were in the test group and 26 were in the control group. After a healing period of 18 weeks, the full and mean resolution of buccal dehiscence defects were 59.3% (n=16) and 71.3% in the test group and 42.3% (n=11) and 57.9% in the control group, respectively. There were no significant differences between the groups in terms of the change in mean horizontal bone augmentation (test group: −0.50±0.66 mm vs. control groups: −0.66±0.83 mm, P=0.133), postoperative discomfort, or early wound healing. No adverse or fatal complications occurred in either group.
Conclusions: The GBR procedure with the newly developed BCP showed favorable clinical, radiographic, postoperative discomfort-related, and early wound healing outcomes for peri-implant dehiscence defects that were similar to those for DBBM.

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Keywords: Allografts; Bone regeneration; Bone substitutes; Dental implants; Randomized controlled trial

INTRODUCTION

In recent decades, guided bone regeneration (GBR) has been a predictable and reliable treatment modality for horizontal and vertical bone augmentation around dental implants [1]. Although various bone graft biomaterials (including autografts, allografts, xenografts, and alloplasts) are widely used as scaffolds for GBR procedures, debate continues and there is a lack of scientific evidence regarding which bone graft materials are superior or comparable to other bone graft substitutes [2].

Autologous bone has favorable physical and biological properties, such as osteogenesis, osteoinduction, and osteoconduction, and is therefore considered the gold standard among bone graft materials [3]. However, because several surgery-related disadvantages and critical complications are associated with autologous bone grafts, including severe acute pain and swelling, a long rehabilitation period, limited availability, and significant donor site morbidity, alternative bone materials are increasingly being used in current clinical practice [3,4]. In particular, demineralized bovine bone mineral (DBBM), a xenograft bone material, has been successfully applied to horizontal and vertical peri-implant bone defects in many pre-clinical and clinical trials, and the effectiveness and biocompatibility of DBBM have also been confirmed in recent systematic and consensus reviews [5,6].

Since the use of synthetic bone graft materials was first reported in 1892, synthetic materials have been actively and increasingly applied for the treatment of various types of bone defects [7]. Among them, alloplastic and synthetic biphasic calcium phosphate (BCP), which contains synthetic hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), the ratio of which can be adjusted to modulate the rate of degradation, has emerged as a promising graft material for bone regeneration [8]. Through numerous *in vitro*, experimental, animal, and clinical studies using BCP over the past 20 years, BCP-based scaffolds have been shown to facilitate cell attachment, proliferation, and differentiation through porous and bioactive surfaces, and consequently improve biocompatibility, osteoconductivity, and new bone formation [9-12].

HA provides a platform and scaffold for new bone formation, whereas β-TCP is advantageous for accelerating bone tissue regeneration based on its rapid and uncontrollable rate of degradation [13]. Although BCP combines the structural advantages and physiobiological properties of the biomaterials of both HA and β-TCP, the ideal HA/β-TCP ratio remains unclear and continues to be the topic of research [14]. The purpose of this study was to evaluate the clinical and radiographic effectiveness of GBR techniques for the reconstruction of peri-implant dehiscence defects with a newly developed BCP consisting of 40% β-TCP and 60% HA compared to DBBM through a randomized controlled clinical trial.

MATERIALS AND METHODS

Study design and ethics

This prospective, multicenter, parallel, and single-blind randomized controlled trial was conducted at the periodontology departments of 3 dental hospitals (Jeonbuk National University Dental Hospital, Yonsei University Gangnam Severance Hospital, and Wonkwang University Daejeon Dental Hospital) from November 2020 to November 2022. All procedures and materials were approved by the Institutional Review Board (IRB) of Jeonbuk National University Hospital (approval No. CUH 2020-09-058-007), Yonsei University Gangnam Severance Hospital (approval No. 3-2020-0441), and Wonkwang University Daejeon Dental Hospital (approval No. W2011/001-001), and registered with the Republic of Korea Clinical Trials Registry (Identifier Number: KCT0006428). This study was conducted in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice, and the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials were followed [15,16].

Participants and eligibility criteria

Patients treated with implant surgery in combination with GBR who met the following inclusion criteria were included: 1) age >20 years, 2) presence of intrabony and buccal dehiscence defects (≥1 mm of both horizontal and vertical defects) after implant placement, 3) proper oral hygiene and stable periodontal status suitable for implant surgery, and 4) agreement to provide informed consent in accordance with IRB guidelines.

Patients who met any of the following criteria were excluded: 1) current heavy smoking (≥20 cigarettes/day), 2) the use of any medicines within 2 weeks of screening that could interfere with bone formation, 3) the use of oral or injectable rheumatoid arthritis medication, including immunosuppressants, within 2 weeks of screening, 4) the use of oral or injectable bisphosphonate therapy for more than 3 months before screening, 5) a history of hypersensitivity to HA or DBBM, 6) uncontrolled diabetes or hypertension, 7) a history of radiation therapy for head and neck cancers, 8) pregnancy or breastfeeding, 9) dependence on alcohol or drugs, and 10) poor oral hygiene or uncontrolled periodontal disease.

Interventions

Implant surgery with GBR was conducted by 3 board-certified periodontists (JHL, DWL, and JHY) at the 3 participating dental hospitals. After mucoperiosteal flaps were fully elevated under local anesthesia (2% lidocaine HCl with 1:100,000 epinephrine), dental implants (Anyone®, MegaGen Implant Co., Ltd., Daegu, Korea; Astra OsseoSpeed Tx®, Dentsply Sirona Implants, Mannheim, Germany; Superline®, Dentium, Seoul, Korea; Roxolid®, Straumann, Basel, Switzerland; or TS III®, Osstem, Seoul, Korea) were placed in the correct prosthetic position according to the manufacturer's instructions.

- Test group: Buccal dehiscence defects around the implant were filled with the alloplastic BCP bone graft material (Bone Matrix I® 0.25 g, MegaGen Implant Co., Ltd.) consisting of HA and β-TCP at a ratio of 60:40 (with pure raw materials) that was then covered with an appropriately trimmed cross-linked resorbable membrane (Ossix Plus® 15×25/25×30 mm, Datum Dental Biotech, Lod, Israel).
- Control group: Buccal dehiscence defects were filled with DBBM (Bio-Oss® 0.25 g, Geistlich Pharma AG, Wolhusen, Switzerland), after which the augmentation site was covered with the same cross-linked resorbable membrane as that used in the test group.

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Primary wound closure of the flap was achieved using interrupted and horizontal mattress suture techniques with or without vertical releasing incisions with non-absorbable (4–0 Biotex®, Purgo, Seongnam, Korea; 4–0 Dafilon®, Braun Surgical, Tuttlingen, Germany) and absorbable (5–0 and 6–0 Vicryl®, Johnson & Johnson, New Brunswick, NJ, USA; 5–0 Monosyn®, B. Braun, Melsungen, Germany) sutures. All enrolled patients were instructed on proper oral hygiene and were provided with analgesics (amoxicillin [500 mg], 3 times daily) and antibiotics (ibuprofen [200 mg], 3 times daily) for 5 days, as well as mouthwash containing 0.12% chlorhexidine gluconate. The sutures were removed 2 weeks after implant placement (**Figure 1**).

Primary and secondary outcomes

- Primary outcomes: 1) defect width (DW, measured as the linear distance between the widest points to the left and right of the buccal dehiscence defect), and 2) defect height (DH, measured as the linear distance from the top of the implant shoulder to the initial bone-to-implant contact at the buccal dehiscence defect), which were assessed after implant placement and during re-entry surgery using a periodontal probe (CP 15 UNC periodontal probe, Hu-Friedy, Chicago, IL, USA).
- Secondary outcomes: 1) lines perpendicular to the implant's long axis at the implant shoulder (HT0) and 1 mm (HT1), 2 mm (HT2), and 3 mm (HT3) below the coronal portion of the implant were drawn on sagittal cone-beam computed tomography (CBCT) images. CBCT (CS 8100 3D®, Carestream, Rochester, NY, USA; Alphard-3030®, Asahi Roentgen, Kyoto, Japan; Planmeca ProMax 3D Classic®, Planmeca, Helsinki, Finland) images were obtained and measured by calibrated examiners not involved in the surgical procedures using medical image analysis software (OnDemand 3D version 1.0.10.7510, Cybermed, Seoul, Korea) at baseline, after implant surgery with GBR, and before re-entry surgery; and 2) early subjective postoperative discomfort (including severity and duration of pain and swelling) and wound healing (including dehiscence and inflammatory reactions [e.g., suppuration, abscess, and severe swelling]), which were evaluated 2 weeks after implant surgery with GBR using a self-reported questionnaire and clinical examination. The severity of pain and swelling was assessed using a visual analog scale (VAS) (range, 0–10).

Sample size

G*Power software (version 3.1.9.6, Franz Faul, Christian-Albrechts-Universität Kiel, Kiel, Germany) was used to determine the sample size necessary to assess differences between the test and control groups. By referring to previous studies (non-inferiority limit of 0.06 mm and standard deviation of 0.085 mm), to achieve an 80% statistical power and a type 1 error probability of 0.05, we determined that 25 cases were required per group [17,18]. Adjusting for a dropout rate of 20%, a sample size of at least 30 cases per group was required for the study.

Randomization and allocation

After obtaining informed consent, each patient was randomized using a computer-generated randomization list in permuted blocks of 2 and 4 (1:1 allocation ratio). The randomization and allocation concealment processes were carried out by an independent research assistant who did not participate in the implant surgery. None of the patients knew whether they had received the test or control bone materials until the end of the study.

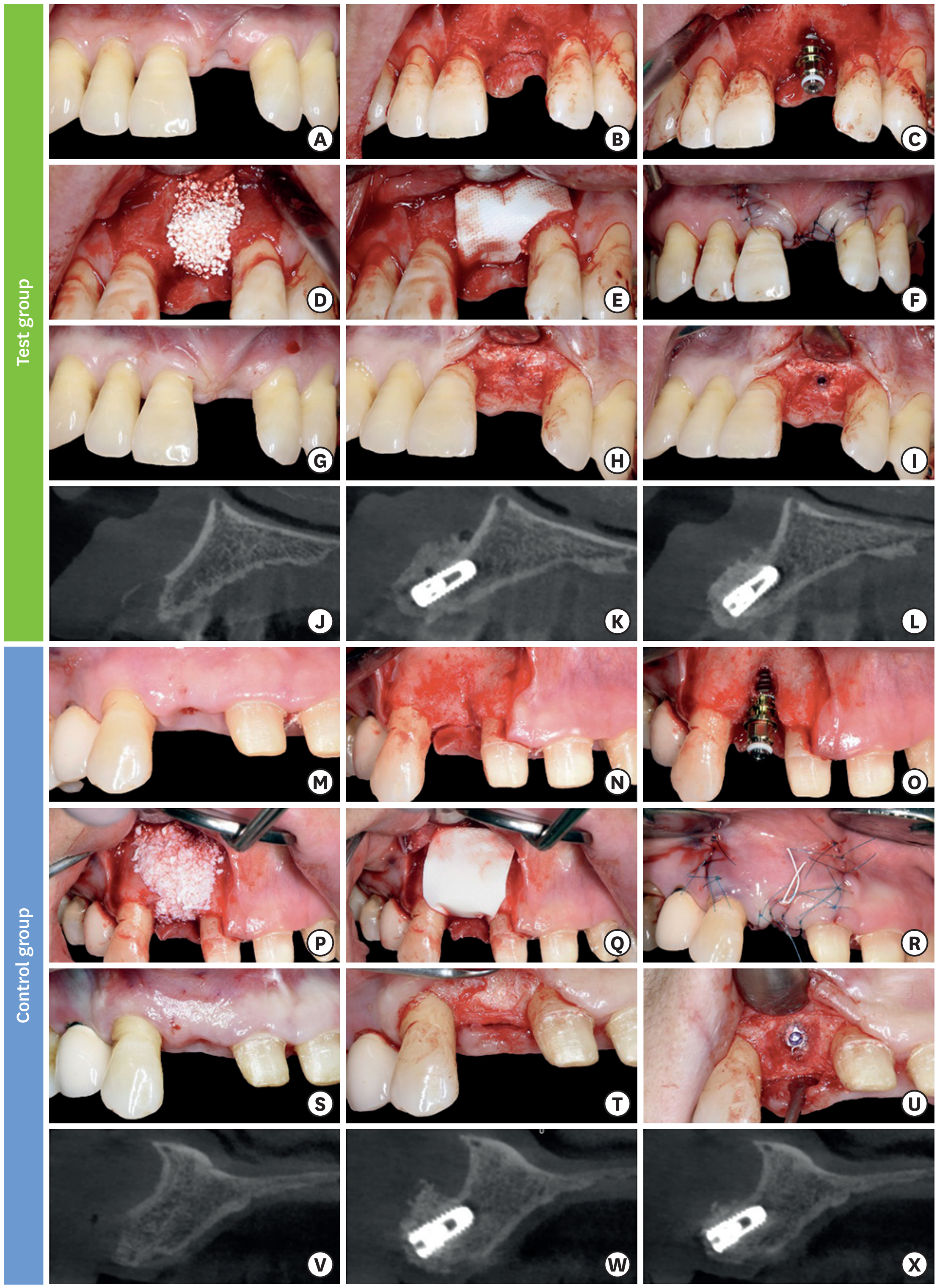

Figure 1. Representative clinical and radiographic images of the surgical sequence. (A and M) Facial view before implant surgery. (B and N) Full-thickness mucosal flap elevation. (C and O) Peri-implant dehiscence defect after implant placement. (D and P) Bone augmentation with alloplastic biphasic calcium phosphate and with demineralized bovine bone mineral. (E and Q) Coverage with a resorbable collagen membrane. (F and R) Suture with primary and tension-free closure. (G and S) Facial view before re-entry surgery. (H–I and T–U) Facial view during re-entry surgery. (J and V) Sagittal CBCT images before implant surgery. (K and W) CBCT images after implant surgery with guided bone regeneration. (L and X) CBCT images before re-entry surgery.
CBCT: cone-beam computed tomography.

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Statistical analysis

Descriptive statistics were expressed as frequencies, proportions, means, medians, quartiles, and standard deviations. Ten CBCT images were randomly selected and scored twice to evaluate the reliability and validity of the measured values, and intra- and inter-correlation coefficients >0.85 were obtained. The clinical and radiographic outcomes were assessed for normal distribution and equality of variance using the Shapiro–Wilk and Levene tests. For comparisons between the 2 groups, we used the independent *t*-test for comparisons of continuous variables and the χ^2 and Fisher exact tests for comparisons of categorical variables. All calculations were performed using SPSS version 28 (IBM Corp, Armonk, NY, USA), and the level of significance was set at 0.05.

RESULTS

Sixty-one cases were screened and randomly assigned at a 1:1 allocation ratio to the test and control groups at baseline. After 8 cases were excluded based on the inclusion and exclusion criteria, 53 cases were ultimately included, 27 (mean age 57.9±9.3 years; 18 males and 9 females) in the test group and 26 (mean age 63.2±9.3 years; 13 males and 13 females) in the control group. No statistically significant differences in the baseline characteristics between the 2 groups, including sex, age, smoking status, diabetes mellitus, and implant location, were observed. Detailed baseline characteristics and a flowchart of the participants are presented in **Table 1** and **Figure 2**, respectively.

Clinical and radiographic outcomes

No statistically significant differences were found in any of the clinical or radiographic parameters investigated between the test and control groups at baseline. After a hard tissue healing period of 18 weeks, significant improvements in clinical and radiographic outcomes were observed in the test and control groups (P<0.001). In the assessment of changes in clinical and radiographic parameters after implant surgery with GBR and before re-entry surgery, the test group showed significant changes in mean DW, DH, and HT0–3, from 3.41±1.64 mm to 0.88±1.16 mm (P<0.001), 3.02±1.68 mm to 0.41±0.54 mm (P<0.001), and 2.65±0.74 mm to 2.15±0.70 mm (P<0.001), respectively; likewise, the control group showed significant changes in mean DW, DH, and HT0–3 from 3.63±1.42 mm to 1.01±1.26 mm

Table 1. Baseline characteristics of the participants

Variables	Test group (n=27)	Control group (n=26)	*P* value
Sex			0.222
Male	18 (66.7)	13 (50.0)	
Female	9 (33.3)	13 (50.0)	
Age (yr)	57.9±9.3	63.2±9.3	0.708
Smoking status			0.413
Non-smoker	24 (88.9)	21 (80.8)	
Smoker (<20 cigarettes/day)	3 (11.1)	5 (19.2)	
Diabetes mellitus			0.482
Yes	5 (18.5)	3 (11.5)	
Location			0.553
Maxillary anterior region	7 (25.9)	3 (11.5)	
Maxillary premolar region	4 (14.8)	3 (11.5)	
Maxillary molar region	2 (7.4)	3 (11.5)	
Mandibular anterior region	0 (0.0)	2 (7.7)	
Mandibular premolar region	4 (14.8)	4 (15.4)	
Mandibular molar region	10 (37.0)	11 (42.3)	

Values are presented as mean ± standard deviation or number (%).

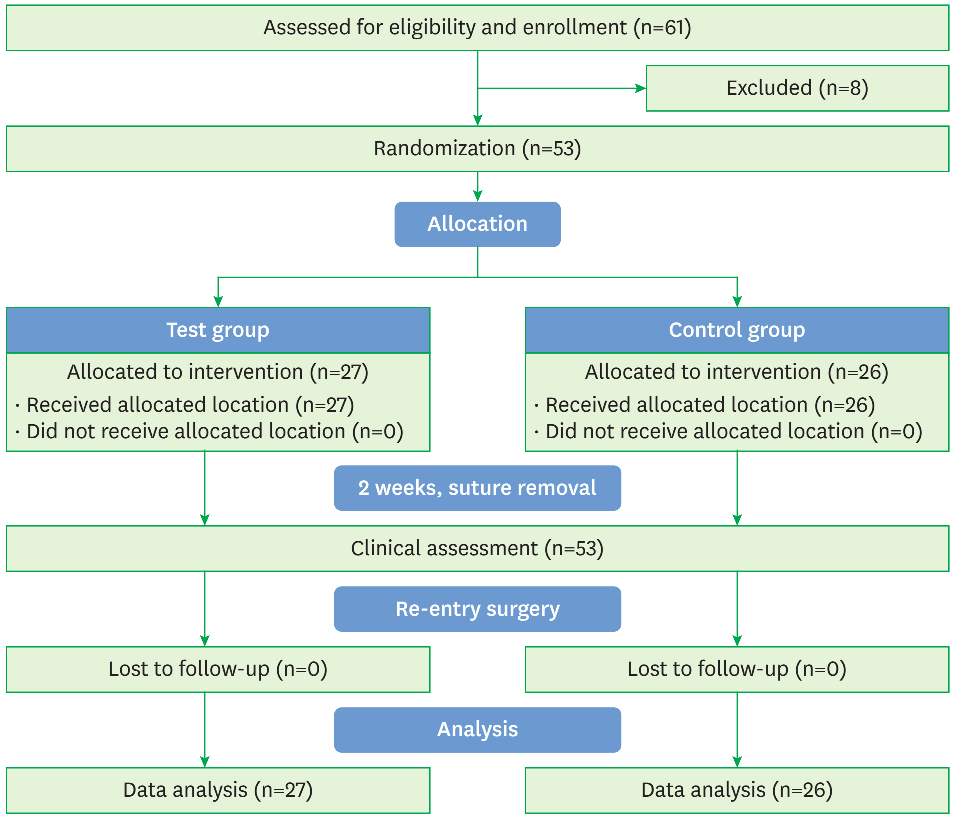

Figure 2. Flow chart of the study cases.

(*P*<0.001), 2.97±2.06 mm to 0.55±0.70 mm (*P*<0.001), and 3.19±1.43 mm to 2.54±1.17 mm (*P*=0.001), respectively. Detailed comparisons of the clinical and radiographic outcomes between the 2 groups are presented in **Table 2** and **Figure 3**.

Postoperative discomfort and early wound healing outcomes

In 13 of the 53 cases, postoperative discomfort-related questionnaires were not administered owing to time constraints. The severity of pain (test group: 4.4±2.4 vs. control group: 4.5±3.0, *P*=0.909) and swelling (test group: 6.4±2.1 vs. control group: 6.4±2.8, *P*=0.992) and the duration of pain (test group: 4.3±2.6 days vs. control group: 3.5±2.1 days, *P*=0.920) and swelling (test group: 6.0±2.1 days vs. control group: 6.4±2.5 days, *P*=0.522) did not differ significantly between the 2 compared groups (**Figure 4A**). In the test group, dehiscence and

Table 2. Changes in clinical and radiographic results from implant surgery with guided bone regeneration to re-entry surgery

Parameters (mm)	Test group				*P* value	Control group				*P* value
	Implant surgery with GBR		Re-entry surgery			Implant surgery with GBR		Re-entry surgery		
	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	
Clinical outcomes										
DW	3.41±1.64	3.10 (2.50, 4.00)	0.88±1.16	0.00 (0.00, 1.75)	<0.001	3.63±1.42	3.50 (2.70, 4.38)	1.01±1.26	0.25 (0.00, 1.95)	<0.001
DH	3.02±1.68	3.00 (1.55, 4.15)	0.41±0.54	0.00 (0.00, 1.00)	<0.001	2.97±2.06	2.90 (1.50, 3.58)	0.55±0.70	0.50 (0.00, 0.90)	<0.001
Radiographic outcomes										
HT0	2.27±0.72	2.30 (1.79, 2.79)	1.81±0.69	1.79 (1.47, 2.14)	0.003	2.56±1.25	2.01 (1.80, 3.60)	1.92±1.07	1.60 (1.02, 2.71)	<0.001
HT1	2.48±0.76	2.52 (1.98, 2.82)	1.97±0.56	1.91 (1.65, 2.27)	0.001	3.02±1.40	2.78 (1.80, 4.15)	2.35±1.19	2.06 (1.35, 3.11)	0.002
HT2	2.74±0.73	2.38 (2.28, 3.23)	2.27±0.71	2.14 (1.72, 2.73)	0.002	3.42±1.47	3.20 (2.25, 4.21)	2.76±1.15	2.60 (1.90, 3.47)	<0.001
HT3	3.10±0.77	3.24 (2.72, 3.56)	2.54±0.86	2.46 (1.91, 3.27)	<0.001	3.77±1.61	3.58 (2.84, 4.36)	3.12±1.26	3.00 (2.20, 3.86)	0.002

GBR: guided bone regeneration; SD: standard deviation, Q1: first quartile, Q3: third quartile, DW: defect width; DH: defect height; HT: hard-tissue thickness at the implant shoulder (HT0), 1 mm (HT1), 2 mm (HT2), and 3 mm (ΔHT3), respectively.

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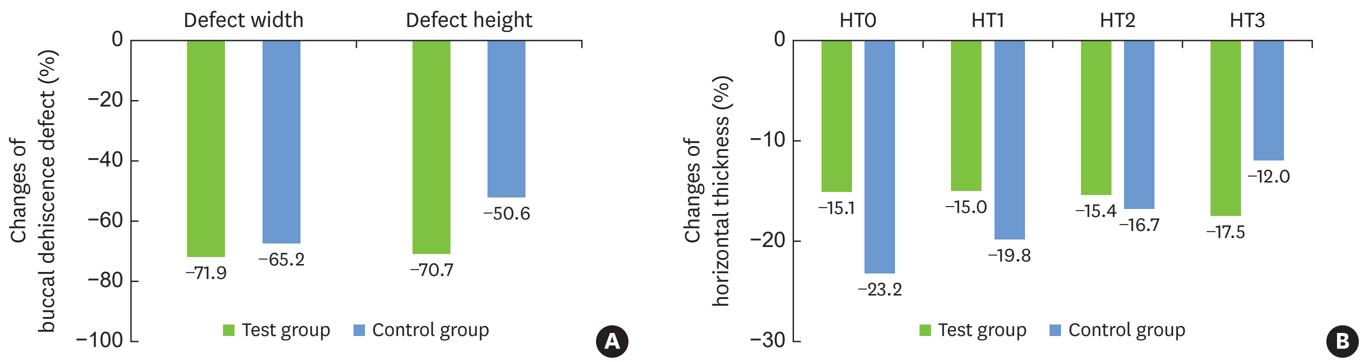

Figure 3. Changes in (A) clinical and (B) radiographic results from the implant surgery with guided bone regeneration to re-entry surgery. None of the measured clinical and radiographic parameters differed significantly between the 2 groups.

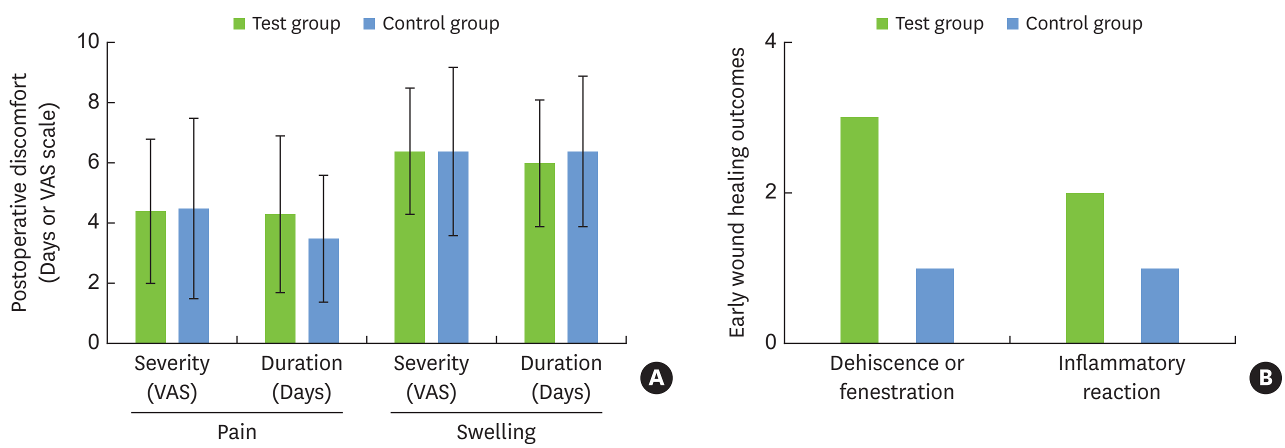

Figure 4. Comparative assessment of postoperative discomfort and early wound healing outcomes. (A) Severity and duration of pain and swelling. (B) Clinical evaluation of early wound healing outcomes. None of the measured parameters differed significantly between the 2 groups.

inflammatory reactions occurred in 3 (11.1%) and 2 (7.4%) cases, respectively, while in the control group, dehiscence and inflammatory reactions occurred in 1 (3.7%) and 1 (3.7%) case, respectively. No statistically significant differences in wound healing complications between the 2 groups were observed, and no severe adverse or fatal complications occurred (**Figure 4B**).

DISCUSSION

The present study prospectively investigated the clinical and radiographic outcomes of implants placed with GBR using 2 different types of bone graft biomaterials. The following observations were made: 1) no significant differences were found in the resolution of peri-implant dehiscence defects between the test and control groups, and 2) both groups showed acceptable postoperative discomfort levels and good early wound healing outcomes without any severe adverse complications. In summary, this clinical trial provided scientific evidence that biocompatibility and osteoconductivity were similar between the newly developed BCP and DBBM, which has been used as a gold standard xenograft for GBR for several decades [19,20].

Various physical and mechanical properties such as composition, crystallinity, and macropore and micropore size significantly influence the bioactive or biodegradable nature

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of bone graft materials [21,22]. The material properties of BCP can be intentionally varied by altering the ratio of HA to β-TCP [23]. The novel BCP used in this study had a mixed pore structure of macropores (100–500 µm) and micropores (10–50 µm) and consisted of 60% β-TCP and 40% HA. This ratio allows high blood wettability and the potential to maintain sufficient space for new bone formation, and also has a higher compressive strength (34.3 kgf/cm^2) than DBBM (23.5 kgf/cm^2), along with a relatively large and specific surface area (mean 3.97 m^2/g) [24-26].

Additionally, the newly developed BCP has the unique morphological feature of a very smooth surface finish and clear edge definition. By refining the rough and sharp edges of the BCP particles, the loss of bone chips could potentially be reduced not only before the GBR procedure, but also after surgery, and the rate of new bone formation and bone mass could also be increased [27,28]. This additional manufacturing process has been shown to minimize mucosal cell irritation and residual debris during the hard tissue healing period and may also reduce the likelihood of additional postoperative complications, such as soft tissue dehiscence or perforation [10,11].

A previous clinical trial reported a 20.8% rate of wound dehiscence and membrane exposure after GBR with DBBM for peri-implant dehiscence defects [29]. Another study comparing DBBM and deproteinized porcine bone mineral as the bone graft materials reported that membrane perforation occurred in 9.1% and 15.0% of cases, respectively, and no statistically significant differences in early wound healing outcomes were found between the two groups (P=0.348) [30]. Similar to these previous studies, our results showed wound dehiscence and membrane exposure at rates of 11.1% (n=3) in the test group and 3.8% (n=1) in the control group and no adverse or fatal complications. In terms of early postoperative discomfort, the severity of pain and swelling was 4 and 3, respectively, and the duration was 6 days in both groups. These results are consistent with previous clinical trials of implant surgery with simultaneous GBR procedures [29,30].

A recent randomized clinical study using BCP (consisting of 60% β-TCP and 40% HA) and a resorbable collagen membrane reported that the percentage of buccal bone thickness reduction at the level of the implant platform and at 2 mm, 4 mm, and 6 mm below the platform was 34.80%, 24.06%, 19.52%, and 20.45%, respectively, at the 6-month follow-up [31]. Our study showed similar results, with mean changes of horizontal bone augmentation (mean HT0–3) of −0.50±0.66 (−15.75%) in the test group and −0.66±0.83 mm (−17.92%) in the control group after a healing period of 18 weeks. Although it was not statistically significant, at HT0, the mean changes of buccal bone thickness in the test and control groups were −0.46±0.69 mm (−15.08%) and −0.64±0.72 mm (−23.15%), respectively, which were the largest differences (P=0.358). These results are consistent with those of previous studies, which have shown a reduction in the augmented bone graft in the coronal portion of the implant. Soft block bone substitutes and L-shaped bone graft trimming have recently been attempted in GBR and have been reported to have significantly better augmentation stability, pressure resistance, and occluso-buccal space maintenance than general particle bone grafts [29,30,32].

Another randomized comparative study using particulate DBBM and a resorbable collagen membrane during GBR reported that 85% of buccal dehiscence and fenestration-type defects were resolved, whereas in the current study, the full and mean resolution of buccal dehiscence defects was 59.3% (n=16) and 71.3% in the test group and 42.3% (n=11) and 57.9% in the control group, respectively, with no significant differences between the 2 groups

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[33]. These inferior results seem to be associated with the lack of using additional fixation methods (such as a pin or screw) to maintain hard tissue integrity.

This study had several potential and actual limitations. First, long-term functional outcomes were not included in our analyses. While DBBM, which was used as the control group, has favorable long-term clinical and radiographic outcomes, the BCP used in the current study only has very short-term research results available [34,35]. Therefore, future studies are needed to assess the long-term biocompatibility and clinical efficacy of the BCP used in this study. Second, although the physical and structural properties of alveolar bone differ between the maxillary and mandibular regions, this study did not consider anatomical differences according to the surgical site. The heterogeneity of all clinical and radiographic outcomes, including changes in hard tissue and the resolution of peri-implant dehiscence defects, should therefore be interpreted with caution. Third, given the multicenter study design, potential differences in the board-certified periodontists' proficiency and skill with the GBR technique are another limitation. Finally, profilometric, histologic, histomorphometric, and immunohistochemical analyses were not included, which constitutes a major limitation of this study.

Within the limitations of this study, GBR with BCP consisting of 60% β-TCP and 40% HA showed favorable clinical and radiographic outcomes for peri-implant dehiscence defects. No statistically significant differences were found in any clinical, radiographic, postoperative discomfort-related, or early wound healing outcomes between the BCP and DBBM groups.

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