Original Article

# Safety and feasibility assessment of biodegradable poly (L-lactic acid/ε-caprolactone) membrane for guided bone regeneration: A case series of first-in-human pilot study

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**Abstract** *Background/purpose*: Guided bone regeneration (GBR) is the most popular technique for alveolar ridge augmentation in implant dentistry, and resorbable cell barrier membrane, made of collagen, is widely used. We tried to develop a new resorbable cell barrier membrane from an animal-free product. This study aimed to investigate the safety and feasibility for clinical application of poly (L-lactic acid/ε-caprolactone) [P (LA/CL)] membrane, a novel biodegradable synthetic material used for GBR.

*Materials and methods*: Patients who required horizontal bone augmentation (≥3 mm implant exposure) for implant treatment were included in the study. P (LA/CL) membrane was used simultaneously with implant placement to achieve bone augmentation by GBR. The occurrence of adverse events was assessed until the follow-up period of a second surgical procedure. The amount of bone augmentation was assessed by means of cone-beam computed tomography, and implant stability was assessed by measuring the implant stability quotient (ISQ). Student's *t*-test was used and the level of significance was set at p < 0.05.

*Results*: This first-in-human study comprised five participants. Adverse events were observed in three of five patients, and a cause-and-effect relationship of the membrane could not be denied in one of them. Good bone formation was observed in the GBR region of all five

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patients. The ISQ during the second surgical procedure indicated good osseointegration in all the patients.

*Conclusion:* The application of P (LA/CL) membrane for bone augmentation with GBR made it possible to maintain the augmented bone volume without causing any irreversible adverse events. However, further investigations on humans are required to confirm the safety of this biomaterial.

## Introduction

Dental implant treatments are considered one of the most feasible options for prosthetic treatment of dental defects. In recent years, restoration-driven implant treatment has gained popularity because it ensures functionality, esthetics, and long-term stability. However, it is not uncommon to encounter a lack of sufficient alveolar bone at the implant placement site during treatment, thereby necessitating simultaneous guided bone regeneration (GBR) around the implant site during the implant placement. In GBR, bone substitute materials are used to fill the bone defect region at the implant placement site and are covered by a cell barrier membrane to prevent the entry of fibroblasts that originate in the connective tissue and to secure space for bone regeneration by osteoblasts, thereby encouraging bone augmentation around the implant site.[1] The use of GBR has widely increased the indications for dental implant treatment.[2]

Cell barrier membranes are classified as either resorbable or non-resorbable. Non-resorbable membranes are strong and can reliably block fibroblast entry into the area during the bone regeneration period to enable sufficient bone formation.[3] Expanded polytetrafluoroethylene (e-PTFE) membrane had first been developed as a cell barrier membrane and was regarded as the gold standard for GBR owing to its early and successful application.[4] However, the associated disadvantages include the need for a second surgical invasion to remove the membrane and the risk of infection from membrane exposure.[5] Becker et al. reported survival rates of 79.4% for implants with dehiscence/fenestration defects treated with e-PTFE membranes and 93.3% for implants in extraction sites treated with e-PTFE membranes.[6] Subsequently, the inflammatory reaction of the surrounding soft tissues may necessitate early removal of the membrane.[7] e-PTFE membranes have 5—100 μm pores that are permeable to liquids and nutrients, but bacteria also pass through this pore size.[8] Nonexpanded dense PTFE (d-PTFE) membranes, which achieved wider use after e-PTFE membranes were withdrawn from the market, have 0.2 μm pores that are impermeable to bacteria. Thus, d-PTFE membranes can be utilized without primary closure to achieve bone regeneration because they are more resistant to infection.[9] Nevertheless, in a previous study, 10% of participants were infected after exposure of d-PTFE membrane.[10] In contrast, resorbable membranes are absorbed within the body and therefore do not require removal; hence, they are widely used for GBR. Most of the resorbable membranes that are currently available are made from animal collagen.[11] Common complications of all animal-derived products include the risk of transmitting unknown pathogenic material and issues regarding the product quality. Furthermore, the rate of breakdown and resorption of resorbable membranes generated from collagen can be difficult to predict; there are also concerns regarding whether the cell barrier function can be maintained, without the cell barrier being absorbed, over the bone formation period.[12] In addition, the enzymatic activity of macrophages and neutrophils causes the membrane to rapidly degrade and decreases barrier function when resorbable membranes are exposed and/or associated with inflammatory reactions in the adjacent tissue.[8] To overcome these disadvantages, the development of a GBR membrane requires a clear composition and a stable supply and requires to be made from a chemical, synthetic, biodegradable polymer that has been modified to offer all the characteristics required for use in GBR.

Kawasaki et al. used polylactide-co-glycoside acid (PLGA) membrane (GC membrane; GC Corporation, Tokyo, Japan), a bioabsorbable synthetic material used for guided tissue regeneration, in GBR and reported its usefulness as a cell barrier membrane.[13] However, PLGA is not able to sufficiently maintain the cell barrier function for bone regeneration during GBR and there were no significant differences reported in the resorption and decomposition of PLGA when compared with conventional resorbable membranes made from biological collagen. More recently, poly (ʟ-lactic acid/ε-caprolactone) [P (LA/CL)], a new biodegradable membrane composed of poly (lactic acid) (PLA) and poly (ε-caprolactone) (PCL) has been developed.[14] The decomposition rate of P (LA/CL) can be adjusted by altering the amount of PCL.[15] Abe et al. reported that 80% and 82% of PLGA is decomposed and degraded in phosphate buffered saline at 12 and 26 weeks, respectively, whereas only 40% and 55% of refined P (LA/CL) is degraded at 12 and 26 weeks, respectively.[14] Thus, it has been demonstrated that P (LA/CL) membrane can act as a cell barrier membrane during bone generation using the GBR method.

In the present study, P (LA/CL) membrane was clinically applied to GBR to assess its safety and feasibility and to partially investigate its efficacy.

## Materials and methods

This study was approved by the certified review board at Nagasaki University Hospital (approval no.: CRB7180001) and

registered in the Ministry of Health, Labour and Welfare clinical study database (registration no.: jRCTs07219012). We performed this study in accordance with the tenets of the Declaration of Helsinki. The written informed consent was obtained from all participants in the current study.

## The medical device

A bilayer P (LA/CL) membrane (GMEM-B2; GC Corporation, Tokyo, Japan) was used as the cell barrier membrane for GBR. GMEM-B2 consists of a compact layer and a multi-porous layer. The compact layer on the soft tissue side blocks fibroblasts from entering the bone defect site, while the multi-porous layer, which is on the bone defect side, promotes the differentiation of undifferentiated cells into osteoblasts and allows for flexible operability due to its multi-porous structure.[14] The GMEM-B2 used in this study was supplied by GC Corporation.

## Study subjects

The subjects in this study were patients who were being treated at the Nagasaki University Hospital Oral and Maxillofacial Implant Center and had requested dental implant treatment for missing teeth. Patients who required horizontal bone augmentation with GBR to compensate for a lack of bone volume at the implant placement site were included in the study. The other selection and exclusion criteria are shown in Table 1. Subjects who met the other selection criteria were enrolled in this study.

This was the first known clinical application of GMEM-B2 in humans; therefore, the number of patients enrolled in the study was set at five to evaluate the safety of the membrane as a first-in-human pilot study.

## Endpoints

The primary endpoint was as follows: the adverse events observed over the course of this study, for which a cause-and-effect relationship for the materials investigated could not be denied, were identified in order to evaluate the safety of the membrane. The secondary endpoints were the bone regeneration status, which was evaluated based on the amount of bone generated as determined by computed tomography (CT) images, and the implant stability quotient (ISQ) obtained during the second surgical procedure.

## Surgical procedure

A two-stage surgery was performed in all five patients. Based on the cone-beam CT (CBCT; 3D Accuitomo F17D, Morita, Kyoto, Japan) images taken before the first surgical procedure, prosthetically ideal implant positions and directions were simulated using the Simplant Pro 18.0 system (Materialise, Leuven, Belgium). At least 3 mm of vertical bone augmentation was required for the patients. Implant placement was performed under local anesthesia either alone or in combination with intravenous sedation using guided assistance (Simplant Universal Guide; Materialise, Leuven, Belgium). Straumann bone level implants (Straumann, Basel, Switzerland) were implanted into the

**Table 1** Selection and exclusion criteria.

| Selection criteria | Exclusion criteria |
|---|---|
| 1. Lack of bone for dental implant placement, bone augmentation with GBR deemed necessary for the area surrounding the dental implant to ensure a stable prognosis<br>2. Horizontal bone defect to augment 3 mm or larger vertical hight exposure of implant<br>3. Initial fixation deemed possible during dental implant placement<br>4. Aged 20 years or older but younger than 80 years<br>5. Understood the informed consent form and provided consent for the study. | 1. Severe blood disease<br>2. Presence of or suspected calcium metabolism abnormality such as kidney/gastrointestinal disease, or collagen disease<br>3. Undergoing hemodialysis<br>4. Using steroids<br>5. Presence of a malignant tumor and undergoing radiotherapy at present or in the past<br>6. Undergoing treatment with bisphosphonates<br>7. Severe concomitant disease (infection, immunodeficiency disease, heart disease, etc.), or concomitant disease which prevents adherence to the requirements of this study<br>8. Alcohol/drug dependency<br>9. Possibility of pregnancy, pregnant or lactating<br>10. Potential difficulty visiting hospitals for follow-up due to distance.<br>11. Cannot adhere to the requirements of this study due to social or household environment<br>12. Smoker<br>13. Requires a legal proxy<br>14. Deemed ineligible to participate in the study for any other reason by the principal investigator or a sub-investigator |

GBR: guided bone regeneration.

designated site achieving an adequate stability (insertion torque >25 Ncm), following which GBR was performed. Carbonate apatite (Cytrans Granules; GG Corporation, Tokyo, Japan) and autologous bone collected with a bone collecting device (Safescraper; META, Reggio Emilia, Italy) were mixed at a ratio of 1:1 and combined with peripheral blood to form the bone graft material. The mixed graft material was transferred to the implant exposure site, covered with GMEM-B2, and fixated with a titanium tack pin (Q-Bone Pin Kit; Trinon, Karlsruhe, Germany) before the wound was closed in a tension-free state (Fig. 1a−c). CBCT was performed to evaluate the status of bone augmentation. An antibiotic agent (amoxicillin hydrate; 750 mg/day) was administered for 5 days postoperatively. The wound was confirmed and sutures were removed on postoperative day 10 ± 4. On postoperative day 150 ± 30, the ISQ measurement was implemented while performing the second surgical procedure under local anesthesia (Fig. 1d). Additionally, postoperative CBCT was performed. The sutures were removed and the final follow-up
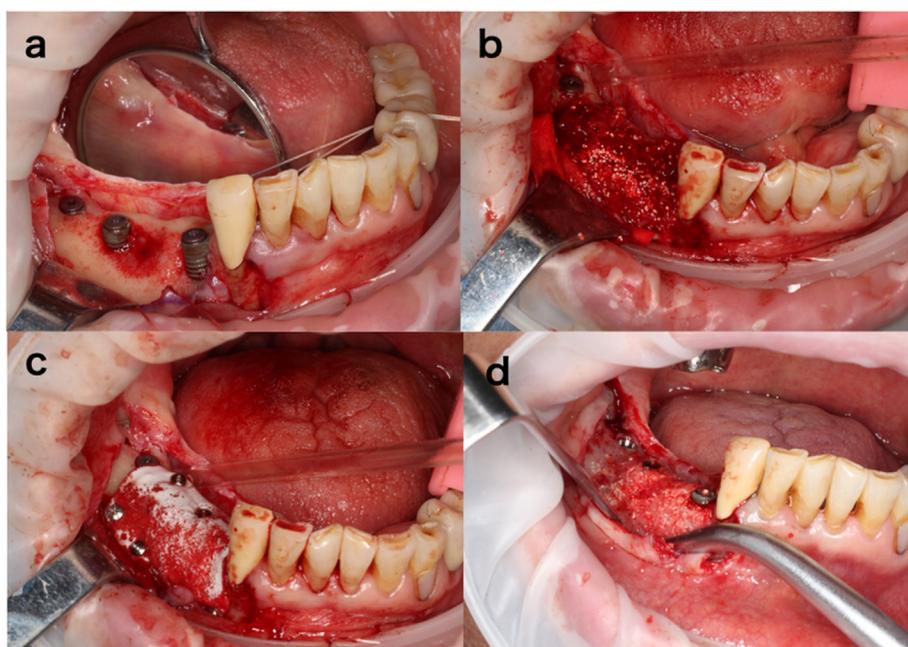
**Figure 1** Intraoperative findings (Patient 3). a. After implant placement. b. During the first surgical procedure. Carbonate apatite and autologous bone were mixed at a ratio of 1:1 and combined with peripheral blood prior to bone augmentation. c. The grafted bone was strongly retained by fixating the GMEM-G2 with tension. d. Good bone formation was observed during the second surgical procedure.

observation was performed at $10 \pm 4$ days after the second surgical procedure.

## Assessment

### Safety assessment
Wound follow-up observations were conducted at $10 \pm 4$ days, $60 \pm 7$ days, $90 \pm 7$ days, and $150 \pm 30$ days (second surgical procedure) after the first surgical procedure and at $10 \pm 4$ days after the second surgical procedure. Subsequently, inflammation symptoms (pain, swelling, and fever), infection (pus and fistula), shock, and wound dehiscence/rupture were assessed.

### Bone augmentation volume
CBCT images taken before and after the first and second surgical procedures were used to compare the amount of bone generated. The evaluation methods were used based on previous studies.[13] Cross-sectional images crossing through the center of the implant body were prepared using image analysis software (Osirix MD; Pixmeo, Geneva, Switzerland). A line crossing through the platform perpendicular to the implant body axis was used as a reference line, and a line parallel to the baseline was set at 1, 3, and 5 mm in the direction of the root apex from the reference line. The horizontal bone augmentation volume (horizontal width; HW) at these sites were set as HW1, HW3, and HW5, respectively (Fig. 2). Distance was then measured.

To statistically analyze the bone regeneration volume, we tested for the presence of significant differences between the first and second surgical procedures. Student's $t$-test was used and the level of significance was set at $p < 0.05$.

### Implant stability quotient (ISQ)
ISQ was measured during the second surgical procedure using the Osstell ISQ Scale (Osstell, Gothenburg, Sweden). Measurements were taken from the labial/buccal side and lingual/palatal side, and mean values were calculated.

## Monitoring

To ensure that this study was appropriately implemented, a third-party (not involved in the study) performed monitoring in accordance with Detailed Enforcement Regulations for Clinical Trial Act.[16]

## Study period

This study was performed between July 2019 and April 2020.

## Results

### Subjects

A total of five patients, including three men and two women (age range, 25—71 years; mean age, $49 \pm 18.9$ years) were enrolled in this study. None of them had any particular oral habits. The details of the patients are as follows:

Patient 1: 63 years old, male. Defects were observed at #24, #25, #26 and #27. Two implants were placed at #24 and #26, and the evaluated implant was #24.
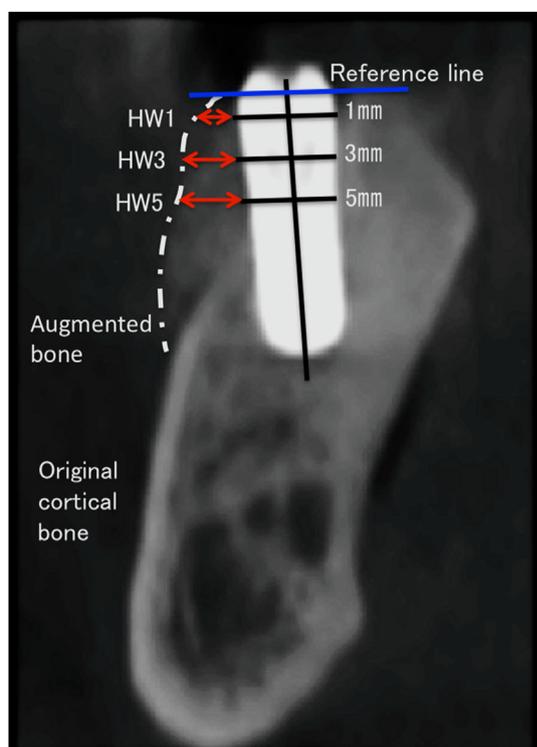
**Figure 2** Evaluation of augmented bone volume. The horizontal distance (horizontal width; HW) of bone augmentation volume in the root apex side at 1, 3, and 5 mm from the reference line was set as HW1, HW2, and HW3, respectively. Distance was then measured.

Patient 2: 58 years old, male. Defects were observed at #35, #36, and #37. Three implants were placed at #35, #36 and #37, and the evaluated implant was #36.

Patient 3: 71 years old, male. Defects were observed at #47, #46, #45 and #44. Three implants were placed at #47, #46, and #44, and the evaluated implant was #44.

Patient 4: 28 years old, female. A defect was observed at #11. One implant was placed at #11 and the evaluated implant was #11.

Patient 5: 25 years old, female. Defects were observed at #11, #21, and #22. Two implants were placed at #11 and #22, and the evaluated implant was #11.

Each subject had one to four missing teeth, and one to three dental implants placed. Then the implant sites for which a horizontal bone augmentation was required to cover 3 mm or more height of implant surface exposure were targeted for observation. The bone augmentation volume ranged from 3.8 to 7.0 mm in vertical height, and the mean value was 5.3 mm (Table 2).

## Safety assessment

Although mucosal rubefaction, thought to be caused by surgical invasion, was observed in patient 1 at 1 week postoperatively, the condition had improved by week 2 (Fig. 3a). Rubefaction and fistula formation were observed in the mucosa behind the subject site 30 days postoperatively in patient 2, though the date was not the

observation day on the protocol (Fig. 3b). In addition, discharge consisting of a small amount of artificial bone substitute granules from the fistula was noted. Consequently, an antibiotic was administered for four days, after which the symptoms improved. In patient 3, the formation of a small mass with a diameter of approximately 2 mm was observed on the alveolar mucosa of the alveolar ridge at the subject site approximately 2 months postoperatively (Fig. 3c). Puncture and resection were performed, but no pus was observed and the site spontaneously healed 1 week later.

Postoperative pain was controlled for all patients using analgesics administered for approximately 3 days postoperatively. No postoperative abnormal bleeding, fever, or shock was observed in any of the patients. In addition, no wound dehiscence/rupture and membrane or implant/fixture exposure was observed in any of the five patients (Table 3).

## Bone augmentation volume

The macroscopic findings during the second surgical procedure indicated good bone formation at the GBR site in all patients (Fig. 1d).

The amount of augmented bone during GBR was as follows: HW1, 2.01 ± 0.57 mm; HW3, 2.48 ± 0.65 mm, and HW5, 3.10 ± 0.86 mm. The corresponding amounts measured during the second surgical procedure were as follows: HW1, 1.74 ± 0.53 mm, HW3, 2.23 ± 0.67 mm, and HW5, 2.59 ± 0.66 mm, with significant decreases at HW3 and HW5 ($p$ = 0.0368 and 0.0279, respectively). The waiting period between the first and second surgical procedures was 20.2 weeks (19—22 weeks; Table 4).

Fig. 4 shows individual changes in bone augmentation volume at HW1, HW3, and HW5. The augmented volume in the mandibular posterior region (patients 2 and 3) tended to be larger than that in the maxillary anterior region (patients 4 and 5). The amount of the decreased volume was small in all except one subject (patient 4, at HW5). Those patterns of decline were similar in the same augmented regions (mandibular posterior vs. maxillary anterior).

## Implant stability quotient (ISQ)

The mean ISQ value at the second surgical procedure 20.2 (19—22) weeks after the first surgical procedure was 78.5 ± 4.31 (74—85), indicating sufficient osseointegration in all five patients.

## Discussion

The GMEM-B2 used in this study had a single composition of P (LA/CL). P (LA/CL) has been previously used as source of raw material for artificial dura mater.[17] It is resorbed within the body after undergoing hydrolysis when it comes in contact with liquid.[18,19] Prior to the present clinical study, GC Corporation conducted non-clinical studies including mock trials for animal use, which confirmed that this material has appropriate flexibility and physical properties for use as a GBR membrane. At the same time, a study was

**Table 2** Registered patients and targeted implant with GBR. Three men and two women (age range, 25−71 years; mean age, 49 ± 18.9 years) were enrolled in this study. The bone augmentation volume of the targeted implant ranged from 3.8 to 7.0 mm in vertical height, and the mean value was 5.3 mm. Mean ISQ value at the second surgical procedure was 78.5 ± 4.31 (74−85).

| Patient No. | Age (years) | Gender | Deficiency | Placement of implants | Region of interest | Implant size (mm)[a] (diameter × length) | Augmented size[b] (mm) | Healing term[c] (weeks) | ISQ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 63 | M | 24,25,26,27 | 24,26 | 24 | 4.1 × 10.0 | 5.0 | 19 | 74.0 |
| 2 | 58 | M | 35,36,37 | 35,36,37 | 36 | 4.1 × 8.0 | 5.4 | 20 | 85.0 |
| 3 | 71 | M | 44,45,46,47 | 44,46,47 | 44 | 4.1 × 12.0 | 3.8 | 22 | 82.0 |
| 4 | 28 | F | 11 | 11 | 11 | 4.1 × 12.0 | 7.0 | 20 | 77.0 |
| 5 | 25 | F | 11,12 | 11,12 | 11 | 4.1 × 12.0 | 5.5 | 20 | 74.5 |
| Mean | 49.0 | | | | | | 5.3 | 20.2 | 78.5 |

ISQ: implant stability quotient.
[a] Bone level tapered Roxolid Implant (Straumann) used in all cases.
[b] Vertical height of the implant exposure (mm).
[c] Waiting period between the first and second surgical procedures.
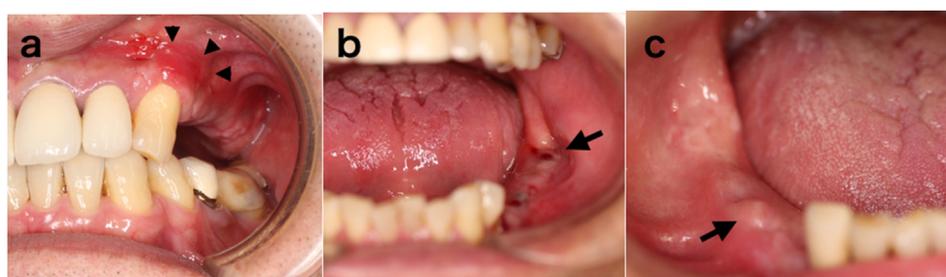


**Figure 3** Adverse events. a. Patient 1 at 1 week postoperatively, Arrow heads indicate mucosal rubefaction. b. Patient 2 at 30 days postoperatively, Arrow indicates fistula. c. Patient 3 at 2 months postoperatively, Arrow indicates tumorous mass.

**Table 3** Postoperative complications. At postoperative day 10 ± 7 and 60 ± 7, slight inflammatory findings were observed in case 1 and 3. At postoperative day 90 ± 7 and 150 ± 30 (at the time of second surgical procedure), no abnormal findings were noted in any of the cases.

| Patient | Postoperative day 10 ± 4 | | | Postoperative day 60 ± 7 | | | 10 ± 4 days after secondly surgery | | |
|---|---|---|---|---|---|---|---|---|---|
| | Inflammatory findings | Infection | Dehiscence /rupture | Inflammatory findings | Infection | Dehiscence /rupture | Inflammatory findings | Infection | Dehiscence/rupture |
| 1 | Rubefaction | − | − | − | − | − | − | − | − |
| 2 | − | − | − | − | − | − | − | − | − |
| 3 | − | − | − | Swelling[a] | − | − | − | − | − |
| 4 | − | − | − | − | − | − | − | − | − |
| 5 | − | − | − | − | − | − | − | − | − |

[a] Resection performed. Natural resolution with no pus discharge.

conducted in accordance with the basic concept and assessment of biological safety assessment required for manufacturing and marketing approval of dental medical equipment, a notification by regulatory authorities (Ministry of Health, Labour and Welfare) regarding biological safety testing, thereby confirming the safety of this product.[20] The aim of the present study was to confirm the safety of GMEM-B2 for use in humans (including the occurrence of defects) using a small sample size, i.e., five patients.

While some minor adverse events were noted throughout the study period, no implant or membrane exposure was observed in any of the cases, and no irreversible adverse events had occurred. Although mucosal rubefaction was observed in one patient (patient 1), it appeared to be an inflammatory symptom of delayed recovery including swelling and pain that occur temporarily as a result of surgical invasion. No persistent mucosal rubefaction was observed in any of the other patients for up to 10 days postoperatively; therefore, it was not considered to be a cause of GMEM-B2. Adverse events were observed in two of the five patients after mucosal wound healing. While clear symptoms of infection were observed in patient 2, they improved with the discharge of artificial bone substitute

**Table 4** Bone augmentation volume (mm). All the values were decreased at 2nd surgery, but the volume at HW1 was maintained with no significant difference.

|  | HW1 | HW3 | HW5 |
|---|---|---|---|
| After 1st surgical procedure | 2.01 ± 0.57 | 2.48 ± 0.65 | 3.10 ± 0.86 |
| After 2nd surgical procedure | 1.74 ± 0.53 | 2.23 ± 0.67 | 2.59 ± 0.66 |
| P value | 0.0513 | 0.0368[a] | 0.0279* |

HW: Horizontal width of the augmented bone.
   [a] Statistically significant difference.

from the formed fistula. Hence, the infection was believed to have arisen in the artificial bone substitute that had erroneously entered the mucosa and was not considered to be caused by GMEM-B2. The formation of a small mass was observed at the subject site 2 months postoperatively in patient 3. This was suspected to be caused by either the erroneous entry of artificial bone substitute into the mucosa, similar to that in patient 2, or an inflammatory reaction to damage caused by food. However, while P (LA/CL) has a slower resorption rate than PLGA, it rapidly starts to resorb in 6—12 weeks.[14] This may be caused by noninfectious inflammation that accompanies membrane resorption. Delayed foreign body reactions caused by plates made from PLGA have been reported and, while the material may need to be removed if the symptoms persist, they are normally expected to improve with no treatment within 2—4 weeks.[21—23] This suggests the need for careful follow-up observation during this period when rapid resorption of the material occurs.

Although no clear presence of the membrane was confirmed when the second surgical procedure was performed approximately 5 months after the first surgical procedure, the artificial bone substitute that had been grafted exhibited good bone regeneration with no invasion of soft tissue in all patients. Although we did not confirm histologically that the augmented alveolar ridges consisted of regenerated new bone, macroscopic evaluation revealed that the amalgamated tissue consisted of bone-like tissue and the bone substitute. We subsequently evaluated the augmented bone volume based on CT images, which indicated resorption of the grafted materials at HW1 (14%), HW3 (10%), and HW5 (16%) (Table 4). While statistically

significant differences between the first and second procedures were observed at HW3 and HW5, the amount of resorption appeared to be reasonable considering that the autologous bone and artificial bone substitute were mixed at a ratio of 1:1 and that 20%—50% of autologous bone grafts are said to undergo resorption.[24] The augmented volume in the mandibular posterior region tended to be larger than that in the maxillary anterior region. The apparent reason being that base of the posterior mandibular bone is wider than that of the anterior maxillary bone. Lager decrease of bone volume at HW5 might be affected by higher labial pressure. Patient 4 showed exceptional decrease at HW5. The excess bone augmentation in the first surgical procedure could have caused the larger resorption to result in a physiological structure of alveolar bone in the anterior maxillary region (Fig. 4).

The volume of regenerated tissue formation at the implant collar (HW1), considered to be the most important site in terms of long-term implant stability, was maintained with no significant differences, thereby confirming that GMEM-B2 offers sufficient functionality as a GBR membrane. Barrier membranes used for GBR must protect the site to enable bone formation by preventing the entry of fibroblasts, which quickly proliferate. Conventional resorbable barrier membranes can be resorbed before the grafted bone is able to mature and does not function sufficiently as a space-maker.[12] Although no reports on the time taken for GMEM-B2 to be resorbed and decomposed within the body have been published thus far, Abe et al. reported that approximately 50% of GMEM-B2 was resorbed and decomposed *in vitro* by 26 weeks compared with 80% of PLGA membrane during that period, thereby indicating that there is sufficient time for bone maturation.[14] The slow degradation of GMEM-B2 can be attributed to the PCL component. Hydrolysis of PCL occurs by end-chain scission because of its highly crystalline chain structure. On the other hand, hydrolysis of PLA occurs at random points.[14] GMEM-B2 has a two-layer structure; the compact layer adjacent to the periosteum prevents the entry of fibroblasts, whereas in the multi-porous layer adjacent to the formed bone surface, strong cell-to-cell interaction is observed and extracellular matrix secretion is promoted. Moreover, infiltration and proliferation of mesenchymal stem cells are also promoted and the adherence of various growth factors is observed in the multi-porous layer, thereby inducing the proliferation and differentiation of cells.[25] As a result, a large number of growth factors enter
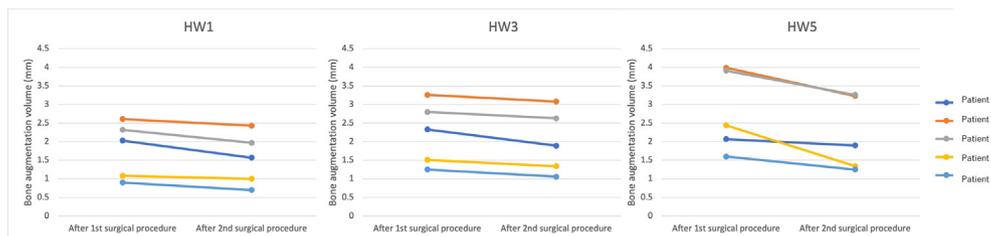


**Figure 4** Individual changes between 1st and 2nd surgical procedure in horizontal bone augmentation volume at HW1, HW3, and HW5 measured by CBCT. HW1, HW5, HW5 indicate the horizontal distance at 1, 3,and 5 mm, respectively, from the top of the implant.

the area, promoting differentiation into osteoblasts.[14] These processes are thought to contribute to early maturation of the generated bone and help in maintaining its volume. The presence of a multi-porous layer indicates that the material is highly flexible and has excellent operability; therefore, it can be easily used to cover the grafted material. A major feature of GMEM-B2 is its elasticity. In the present study, relatively large alveolar bone defects with a mean required bone augmentation height of 5.3 mm were treated. Consequently, tack pin fixation of the membrane was performed to stretch the membrane in all five patients (Fig. 2), which may have enabled sufficient fixation of the grafted material and increased the reliability of bone formation by immobilizing the grafted materials. Thus, GMEM-B2 could also be applied to the sausage technique using a collagen membrane as proposed by Urban.[26]

GMEM-B2 has the following five features proposed by Rakhmatia et al. that are required for a GBR membrane: biocompatibility, ability to create space, blockage of cellular infiltration, tissue integration, and operability.[27] In addition to these features, it is a biodegradable synthetic material. Hence, there is no risk of unknown pathogenic material transmission and a stable quality can be ensured. Moreover, it is a useful shielding membrane for GBR because surgical invasion for membrane removal is not required. However, this study had limitations. The most critical limitation was that the number of participants was limited, and also there was no control group. Although we believe that two of the three adverse events were not related to the membrane used, a 60% incidence of adverse events is very high. The cause of the adverse event in case 2 seemed evident, but we could not clearly prove the causes of the adverse events in the other two patients. Furthermore, we did not confirm that the regenerated alveolar tissue consisted of newly formed bone. To prove the nature of the regenerated tissue, bone biopsy with histological evaluation is necessary. Therefore, to confirm the safety and feasibility of the present biomaterial, further clinical studies with a larger number of participants and analysis of harvested samples should be conducted.

In conclusion, although the included subjects were limited to only 5 patients for a first-in-human pilot study, the results of the present study demonstrated that using P (LA/CL) for GBR did not cause any irreversible adverse events and showed sufficient performance to regenerate alveolar bone as a GBR membrane. Then, the outcome of this study enables us to proceed further investigations on humans in order to confirm the safety and the efficacy of this material using a larger sample size and control group.

## Declaration of competing interest

The authors declare there is no conflict of interest concerning this study.

## Acknowledgments

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