



Complications arising from clinical application of composite polycaprolactone/bioactive glass ceramic implants for craniofacial reconstruction: A prospective study

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ABSTRACT

This study aimed to demonstrate the in vitro performance of a novel polymer-ceramic composite incorporating polycaprolactone (PCL) and bioactive glass (BGS-7), and investigate its clinical outcomes in craniofacial reconstruction. After preparation of the material, the biochemical properties of the composite PCL/BGS-7 implant were tested to evaluate apatite formation in simulated body fluid (SBF). Changes in the implant surface after soaking in the SBF were determined using field-emission scanning electron microscopy. For clinical application of the implant, patients with craniofacial defects were prospectively enrolled to receive three-dimensional (3D)-printed PCL/BGS-7 implants. Clinical outcomes were investigated by reviewing postoperative complications, including wound problems, allergic responses, hematoma, seroma, implant displacement, and bone union. The accuracy of reconstruction was assessed by measuring the surface error between the reconstructed and mirrored models. Upon exposure of the PCL/BGS-7 implant to SBF, apatite particles were actively developed on the surface of the PCL/BGS-7 sample, showing favorable bone-binding capacity. Regarding the clinical application, seven patients with craniofacial defects were included. The clinical outcome was favorable in terms of complications, except in one patient, who presented with delayed wound healing due to previous irradiation. The patients showed improvements in symmetry, with a significant change in mean $\pm$ SD surface error between preoperative (5 ± 3 mm) and postoperative (1.5 ± 0.65 mm) status ($p = 0.018$). Within the limitations of the study it seems that the PCL/BGS-7 implants might be a relevant option for repairing craniofacial bone defects, owing to its favorable bone-binding property and clinical safety, with few complications.

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1. Introduction

Reconstruction of craniofacial bone defects is challenging, especially given the difficulties in restoring bone symmetry and the requirement for an appropriate bone substitute. Although autologous tissue has traditionally been used as a gold standard option, it is difficult to achieve accurate three-dimensional (3D) restoration of the skeletal contour. Advances in the field of biomaterials mark

the beginning of a new era in reconstructive surgery, expanding reconstructive options with various alternatives, and improving surgical outcomes (Matassi et al., 2011; Sohn and Oh, 2019). With the development of new fabrication techniques and computer-assisted technologies, customized implants with better designs and biomechanical properties have been realized in clinical applications (Chia and Wu, 2015; Choi and Kim, 2015).

Contemporary tissue engineering techniques have allowed the production of biomaterials that mimic the physical and biological properties of normal bone tissue as alternatives to autogenous bone grafts. Various biomaterials, ranging from metals to polymers, have been proposed as bone substitutes, with diverse compositions, mechanical strengths, and biological properties (Matassi et al.,

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2011; Sohn and Oh, 2019). An ideal bone substitute should have the ability to provide a scaffold for osteoconduction, growth factors for osteoinduction, and similar structural properties. There is no material that can completely replace autogenous bone, and therefore the development of ideal biosynthetic materials has drawn significant attention. Ceramic bone substitutes are one such biomaterial, constructed using hydroxyapatite (HA) and β -tricalcium phosphate (β -TCP), and their compounds (Flatley et al., 1983; Bianco and Robey, 2001; Sohn and Oh, 2019). These ceramics can be clinically used as bone-repair materials owing to their ability to produce bone-like apatite surface layers in body fluids (Jonášová et al., 2002). However, these materials cannot replace load-bearing bones, owing to their mechanical vulnerability and low fracture toughness (Eliaz and Metoki, 2017).

To overcome the intrinsic fragility of ceramic, a composite bio-ceramic material can be produced through combination with biodegradable polymers with desirable mechanical properties, using 3D printing or coating techniques (De Santis et al., 2019). In our study, a novel composite material of bioactive glass ceramics (BGS-7, $\text{CaO-SiO}_2\text{-P}_2\text{O}_5\text{-B}_2\text{O}_3$) and polycaprolactone (PCL) was used, which has favorable mechanical properties of strength and toughness, and optimal cellular activities with osteoconductive potential. With computer-assisted design (CAD) and 3D-printing techniques, patient-specific, prefabricated, bioceramic polymers can be manufactured and clinically administered.

The aim of this study was to test the *in vitro* properties of PCL/BGS-7 implant in terms of reproducing apatite formation in simulated body fluid (SBF), and to investigate the clinical outcomes of using 3D-printed PCL/BGS-7 implants to reconstruct craniofacial defects.

2. Methods

2.1. Material preparation

Medical-grade polycaprolactone (PCL, #PURASORB PC12, CorbionPurac, Netherlands) and $\text{CaO-SiO}_2\text{-P}_2\text{O}_5\text{-B}_2\text{O}_3$ bioactive glass ceramics (BGS-7, CGBIO Co., Ltd, South Korea) were used as raw materials. The sintered BGS-7 powder was mixed with PCL pellets by freeze-milling at a ratio of 20 wt % of the composite. The average particle size of the BGS-7 and PCL composite after freeze-milling was $2.1 \pm 0.2 \mu\text{m}$.

2.2. SBF soaking test

An *in vitro* experiment was performed with the PCL/BGS-7 implant to evaluate its biomineralization properties in SBF. Samples intended for exposure in the SBF were prepared by printing disk-shaped specimens, 10 mm in diameter and 2 mm in height, using a mixture of PCL/BGS-7 and pure PCL, with a 3D printer (LUCA 300, CGBIO, Seongnam, South Korea). Each mixture was printed using a 400- μm (inner diameter) nozzle.

Next, the disks were immersed in a 1X SBF solution composed of NaCl (7.995 g), KCl (0.224 g), $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (0.368 g), $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (0.305 g), K_2HPO_4 (0.174 g), NaHCO_3 (0.349 g), and $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (0.161 g) in 1 L of distilled water. The pH of the solution was adjusted to 7.4 by the addition of tris-HCl. The disks were immersed in SBF and preserved at 36.5 °C during CO_2 incubation. After 7 and 14 days, the disks were washed with deionized water to remove adsorbed minerals and lyophilized.

Changes in the implant surface after soaking in SBF were determined using field-emission scanning electron microscopy (FE-SEM; S-4700, Hitachi, Chiyoda, Tokyo, Japan). To evaluate the rate of apatite formation on the sample surface, the changes in the concentrations of calcium, phosphorus, and silicon were analyzed using energy-dispersive spectroscopy (EDS).

2.3. Design and manufacturing of patient-specific implants

Implants were designed using Geomagic Freeforms Plus 3D modeling software (3D Systems, Washington, USA). The anticipated bone defect was marked on a stereolithography (STL) skull model, followed by mirroring of the normal bone contour. Patient-specific implants were designed over the region of interest, fabricated, and refined.

The patient-specific implants (EASYMADE-CF, CGBIO, Korea) were manufactured in the Korea Good Manufacturing Practice (KGMP) facility, according to the process parameters used in a prior study (Fig. 1) (Kim et al., 2019). Considering the PCL/BGS-7 composite rheology, a 3D printer equipped with an extrusion mode was used. The printed implant was washed, dried at room temperature, and packed by thermal sealing of the PET tray and Tyvek. The final product was sterilized using gamma-ray irradiation.

2.4. Clinical application

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board. All patients provided written informed consent to participate in the study (approval number: 2021-1292).

Patients with craniofacial bone defects were recruited prospectively and underwent hard-tissue reconstruction with a 3D-printed PCL/BGS-7 implant between October 2021 and January 2022. The inclusion criteria were as follows: (1) age between 19 and 79; (2) presence of craniofacial bone defect; (3) bony defects resulting from cancer ablation, trauma, or congenital causes of bony atrophy; and (4) a follow-up period of at least 6 months. Pregnant women and patients with critical infectious disease or immune deficiency, or with anticipated immunosuppressive treatment, were excluded from the study. Demographic data, including age at surgery, sex, underlying disease, location and cause of defect, operation history, combined operation, timing of reconstruction (immediate or delayed), previous radiation treatment, underlying disease, and follow-up period, were collected. All patients underwent computed tomography (CT) scans with a slice thickness of 1 mm preoperatively, immediately postoperatively, and in the 6-month postoperative period.

2.5. Surgical techniques

The bone defect was exposed in a conventional manner, with notable modifications to hide scars using intraoral, trans-conjunctival, and bicoronal incisions. Prior to implantation, the implant was submerged in betadine solution for 10 min. The bone defect was covered with a 3D-printed implant with or without soft tissue coverage using fasciocutaneous free flaps. After fitting the implant into the existing defect, it was fixed with titanium mini-plates and 6–8-mm screws. Immediate adverse reactions, such as allergic responses, were monitored during surgery.

2.6. Assessment of clinical outcome

The clinical outcomes of adverse events, including wound breakdown, allergic responses, hematoma, seroma, implant displacement, reoperation, and implant–bone fusion status, were reviewed. Wound problems included any dehiscence of the surgical wound, infection, peri-implant enhancement of the soft tissue, and bone tissue in the CT scans. Allergic responses included acute and chronic reactions, with erythema, urticaria, and eczema in the skin or mucosal tissues. Implant status was assessed with CT scans taken 6 months postoperatively. Implant displacement or malunion was defined as an implant mobilized more than 1 mm from the original position. Implant–bone fusion was defined as complete contact

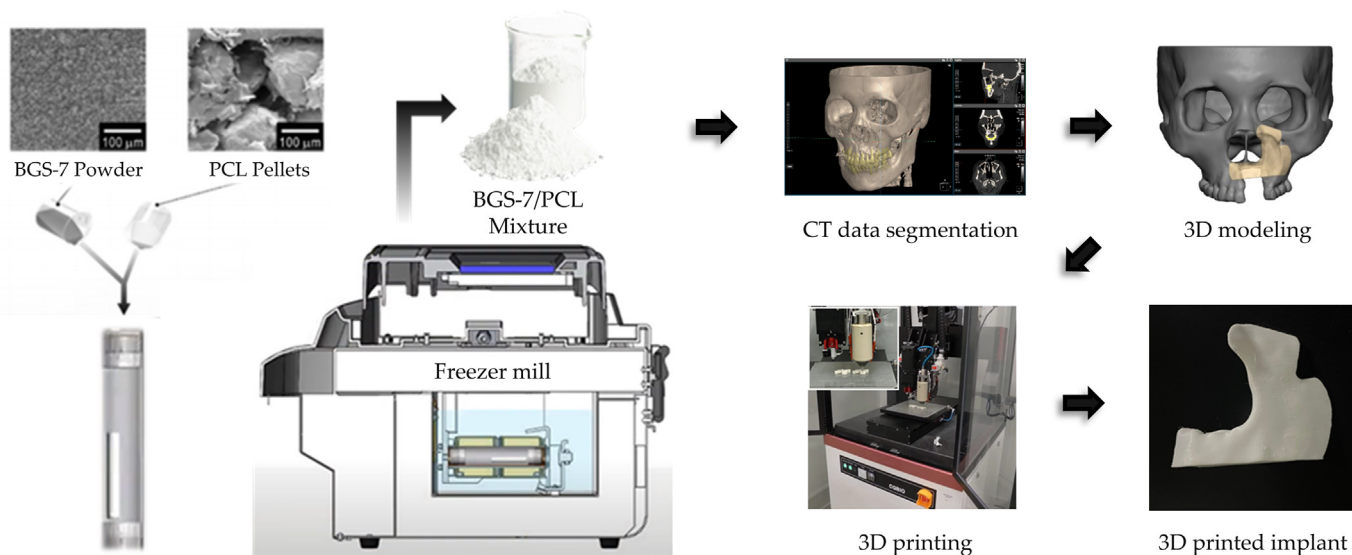


Fig. 1. Fabrication process for composite PCL/BGS-7 implant using a 3D printing system.

between the implant and bone of at least 50% of the intersurface area, without a bony gap or osteolysis.

2.7. Assessment of reconstructive accuracy

To assess the reconstructive accuracy, the symmetry of the bone contour was analyzed using a 3D volume-rendering model. CT scans for each period were obtained and processed using computer modeling software (3-Matics, Materialise N.V., Leuven, Belgium). This software transformed the digital imaging and communications in medicine (DICOM) files into a 3D model, and the axial skull plane was oriented parallel to the sella–nasion horizontal plane. The midsagittal plane was created by drawing a plane based on three landmarks: the midpoint between the canthi, nasal tip, and center of the upper lip vermilion–cutaneous junction. Subsequently, 3D segmentation was performed based on the manual selection of facial and cranial bones, including the zygomaticomaxillary bone, mandible, and frontal bone, on the affected and unaffected sides. The normal part was flipped over the midsagittal plane using a mirror tool, and then alignment between the newly created part and the original part was ensured. After registration of the original and mirrored images, quantitative error analysis was performed using a part comparison tool in the analysis module of the software (3-Matics, Materialise N.V., Leuven, Belgium). The entity was selected from the actual patient model, and the target entity was selected from the mirrored model. This approach allowed the calculation of the mean and root mean square (RMS) errors, which represented estimates of the average distance between the two selected models. Mathematically, RMS equals $\sqrt{(\sum_{x=1}^N x^2)/N}$, where x is the measured distance between the surfaces at a single point and N is the total number of points used. An RMS of zero indicates perfect symmetry, with increasing values indicating increasing asymmetry. A representative image showing the procedure for symmetry assessment by calculating the mean and RMS error, and the discrepancy between the models, is displayed as a heatmap in millimeters guided by a distribution of error bars (Fig. 2).

2.8. Statistical analysis

Demographic data and surgical variables were described using descriptive methods, with numbers, means, and standard

deviations. The method error was checked by repeating the entire procedure, including segmentation, mirroring, and calculation of the mean and RMS, by the same operator 1 week after the first assessment, and by another operator to assess the intra-rater and inter-rater errors. Changes in the mean and RMS errors between the preoperative and postoperative periods were compared using the Wilcoxon signed-rank test for nonparametric testing of paired data. Statistical significance was defined as $p < 0.05$ in multivariate analysis. Statistical analyses were performed using SPSS v.20 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. SEM and EDS analysis

Upon exposure of the PCL/BGS-7 disks to SBF, spherical clusters composed of needle-like crystals precipitated on the surface. As the soaking time in SBF increased, the number of clusters also increased, and covered the disk surface. However, there were no differences on the surface of the 100% PCL disks, even though they were soaked in the SBF solution for the same period (Fig. 3).

The components of the surface clusters were analyzed using EDS of the SEM images (Fig. 4). Before the PCL/BGS-7 disk was soaked in SBF solution, the carbon and silicon on the surface accounted for about 66.73 and 5.14 atomic %, while calcium and phosphorous accounted for 6.66 and 2.04 atomic %, respectively. As the soaking period increased, the carbon and silicon contents decreased, and the calcium and phosphorous contents increased. In particular, the calcium and phosphorous ratios were similar to those of hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$), with a Ca/P ratio of 1.67.

The formation of a hydroxyapatite layer on a bioactive glass ceramic surface is an intrinsic property. Even though the BGS-7 content was only 20% of the final composite, a needle-like hydroxyapatite layer was formed on the PCL/BGS-7 surface within 7 days of SBF soaking, and grew as time progressed.

3.2. Demographic information

Seven patients (four male and three female), with a mean age at surgery of 47 years (range 19–65 years) were included in this study. The mean follow-up period was 9 months (range 7–11 months), and the patients presented with craniofacial bone defects in various

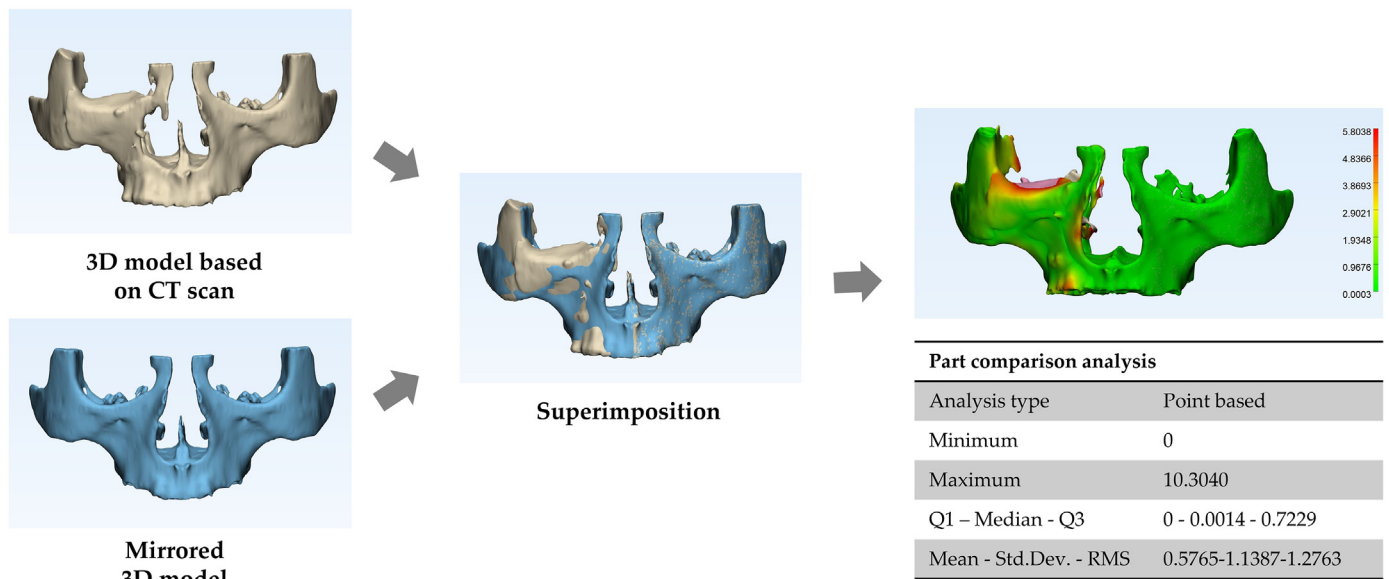


Fig. 2. Procedures for symmetry assessment. The mirrored 3D model is obtained by flipping the normal left zygomaticomaxillary bone with respect to the sagittal plane. The original and mirrored 3D model are then aligned according to the least point-to-point distance between the two models. Quantitative errors between the original and mirrored models are measured automatically using the part comparison tool of the software. The error between the overlaid segments is depicted as a heatmap, guided by a distribution of error bar.

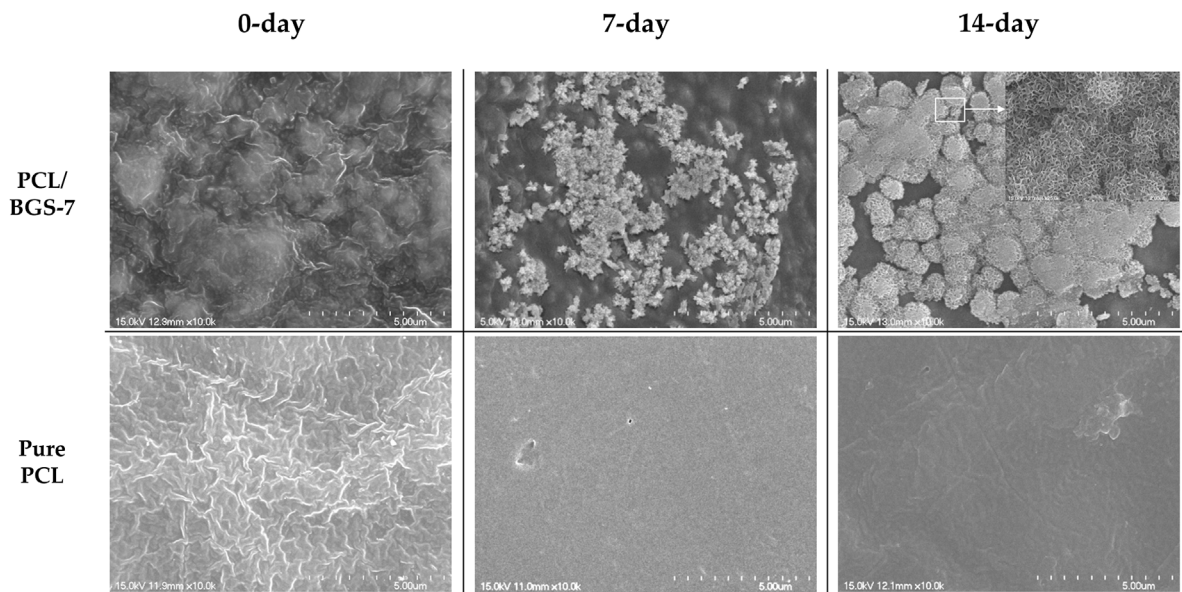


Fig. 3. SEM micrographs of the PCL/BGS-7 and pure PCL disks soaked in SBF for 0, 7, and 14 days. The development of apatite particles occurred more actively on the surface of the PCL/BGS-7 disk than on the pure PCL specimen.

regions, including the zygoma, maxilla, nasal bone, mandible, and frontal bone. The causes of defects were as follows: maxillectomy for tumor ablation, including suprastructure ($n = 2$), infrastructure ($n = 1$), total maxillectomy ($n = 1$); traumatic frontal bone depression ($n = 1$); unilateral mandibular hypoplasia due to hemifacial microsomia ($n = 1$); and chronic osteomyelitis of the chin region ($n = 1$). Radial forearm free flaps were used for soft-tissue reconstruction in three cases. All cases were reconstructed in the delayed stages, except for those who underwent simultaneous infrastructural maxillectomy and implant reconstruction. Three patients had underlying diseases, such as hypertension and diabetes mellitus, and one patient had a history of previous radiation treatment in the maxilla (Table 1).

3.3. Clinical outcomes

All the patients underwent successful implant reconstruction without any events during surgery. The mean $\pm$ standard deviation (SD) operation time for all patients was 3.54 ± 2.5 h. When confined to patients who had only implant reconstruction, however, the mean operation time was 1.58 ± 0.3 h. During surgery, none of the patients required blood transfusion. There were no cases of wound breakdown, allergic response, hematoma, seroma, implant displacement, or reoperation in the study group, except for one patient (patient #2), who developed a palatal fistula by the post-operative 1-month follow-up, and required a buccal fat graft for

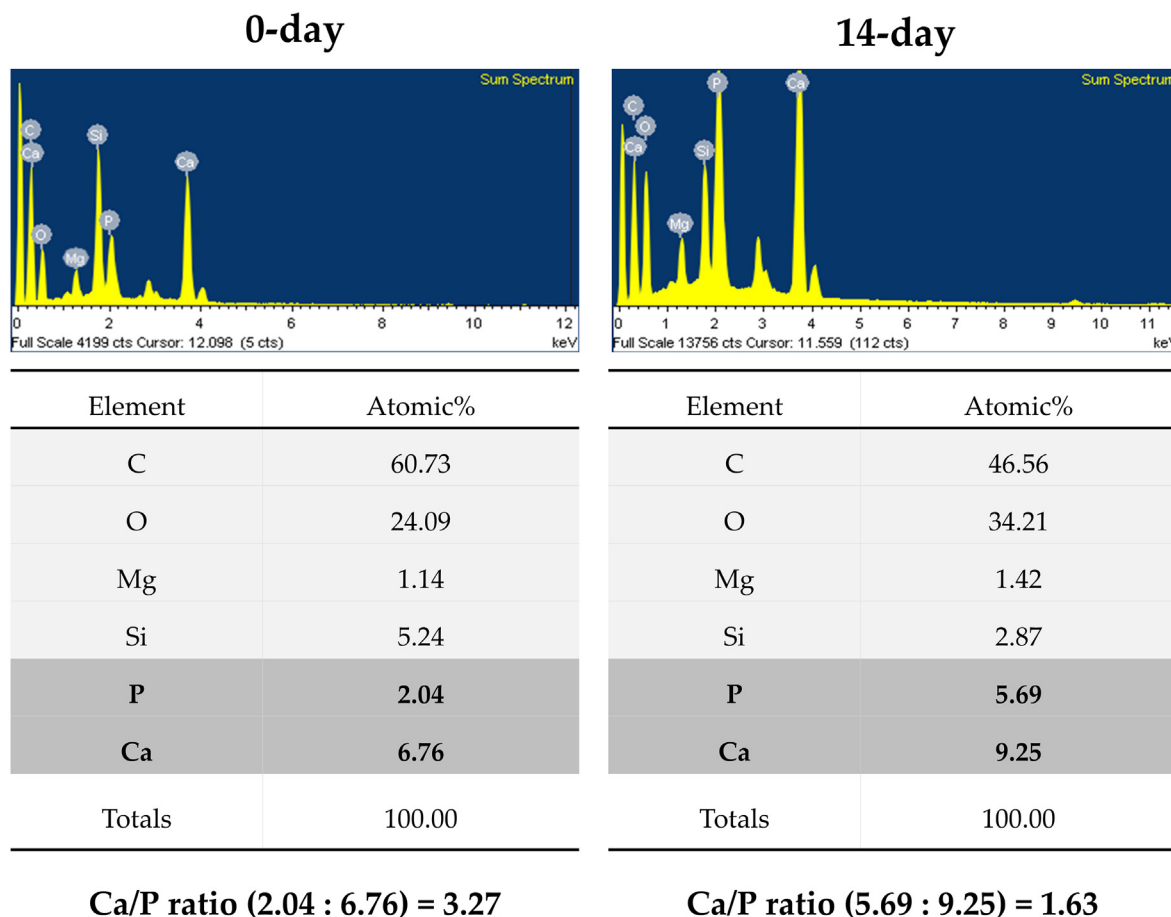


Fig. 4. EDS analysis of the PCL/BCS-7 sample soaked in SBF for 0 and 14 days. The Ca/P ratio of surface particles changed towards the ideal ratio, from 3.27 (day 0) to 1.63 (day 14), as the specimen was immersed longer in SBF solution.

Table 1

Demographics of the patients.

Patient number	Age at surgery	Sex	Location of defect	Cause of defect	Previous surgery	Combined operation	Timing of reconstruction	Previous Radiation	Underlying disease	Follow-up period (months)
1	64	Male	Rt. zygoma, maxilla	Squamous cell carcinoma	Suprastructure maxillectomy	RFFF	Delayed		DM, HTN	12
2	57	Female	Lt. maxilla, alveolar bone	NK/T cell lymphoma	Infrastructure maxillectomy	RFFF	Immediate	Yes	DM	14
3	65	Male	Rt. maxilla, zygoma, nasal bone	NK/T cell lymphoma	Suprastructure maxillectomy		Delayed			8
4	54	Male	Rt. maxilla, zygoma, alveolar bone	Squamous cell carcinoma	Total maxillectomy	RFFF	Delayed			10
5	48	Female	Symphysis, and bilateral parasymphysis of mandible	Chronic osteomyelitis	Mandibuloplasty		Delayed		HTN	8
6	19	Female	Both frontal bones	Previous cranioplasty	Cranioplasty		Delayed			10
7	22	Male	Right mandible angle, body and ramus	Hemifacial microsomia	Two-jaw surgery		Delayed			12

RFFF, radial forearm free flap; DM, diabetes mellitus; HTN, hypertension.

wound coverage. All patients showed favorable implant-to-bone fusion on the 6-month postoperative CT scans (Table 2).

3.4. Method error and symmetry outcome

The repeatability of the mean and RMS was more than 80% for all measurement data, indicating that there was no significant error in terms of intra-rater or inter-rater validity.

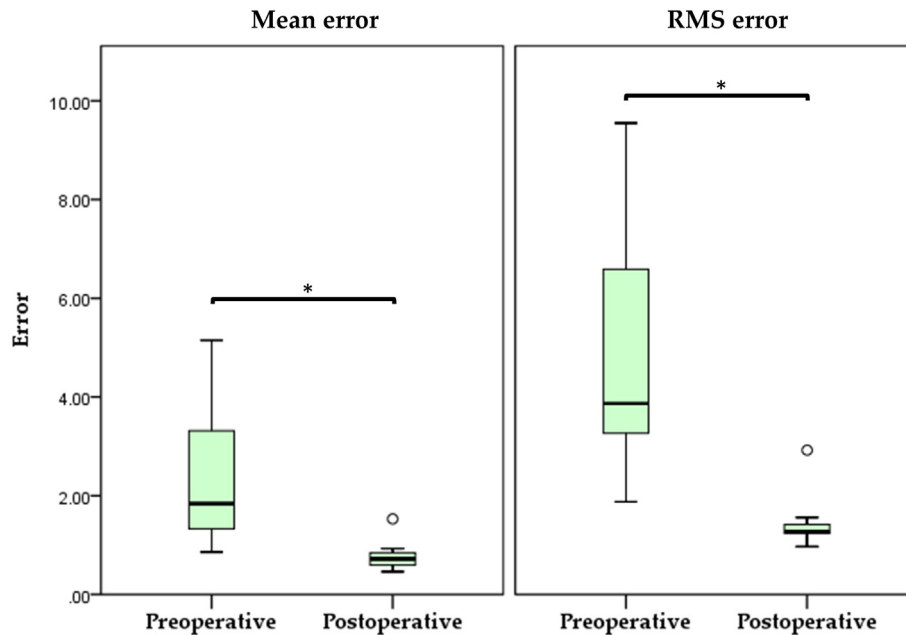
Patients showed variable degrees of asymmetry preoperatively, with average error values from the calculated mean (SD) and RMS (SD) of 2.45 (1.71), and 5.00 (3.00), respectively. Postoperatively, the average error values from the calculated mean (SD) and RMS (SD) were significantly decreased to 0.80 (0.36) and 1.50 (0.65), respectively ($p = 0.028$ and 0.018) (Fig. 5 and Table 3).

Preoperative CT, simulation, and postoperative CT images are presented in Fig. 6. A representative case is shown in Fig. 7.

Table 2
Surgical details and clinical outcomes.

Patient number	Operation hours	Blood transfusion	Implant–bone fusion	Complication ^a	Reoperation
1	5.5	No	Intact	No	No
2	6	No	Intact	Palatal fistula	Buccal fat graft
3	3.5	No	Intact	No	No
4	7	No	Intact	No	No
5	2	No	Intact	No	No
6	4	No	Intact	No	No
7	1.3	No	Intact	No	No

3D, three-dimensional; CT, computed tomography.

^a Wound breakdown, allergic response, hematoma, seroma, and implant displacement were reviewed.**Fig. 5.** The symmetry outcome represented by the mean and RMS error between the original and mirrored models. A significant decrease was observed in both errors between the preoperative and postoperative status.

4. Discussion

Bioglass, or bioactive glass, first manufactured by Hench et al., has favorable interfacial bond properties, with bone and angiogenic potential in the presence of vascular endothelial growth factor (Hench et al., 1971; Rawlings, 1993). Compared with other bioceramics, the dissolution of silica and calcium from bioglass stimulates the deposition of bone matrix and facilitates faster integration between the scaffold and surrounding bone tissue (Zhou and Grayson, 2022). However, the pure bioglass scaffold is limited by its intrinsic brittleness, which causes frequent fractures

in the load-bearing region (Jones, 2013; Kim et al., 2019). The mechanical properties of bioceramics can be improved by mixing biodegradable polymers, using 3D printing techniques (Taboas et al., 2003; Motealleh et al., 2017; Zhou and Grayson, 2022). To overcome the disadvantage of pure bioceramic scaffolds, which have poor mechanical vulnerability, tough PCL material can be added (Kim et al., 2019). In mechanical property tests, the fracture toughness of the composite PCL/BGS-7 scaffold was found to be 129-fold greater than that of pure bioglass, while the mechanical stiffness was 2.3-fold greater than that of the pure PCL scaffold (Kim et al., 2019).

Table 3
Calculation of mean and RMS error between original and mirrored image.

Patient number	Preoperative		Postoperative	
	Mean error (mm)	RMS error (mm)	Mean error (mm)	RMS error (mm)
1	2.01	4.26	0.58	1.28
2	1.38	3.87	0.72	1.56
3	5.15	9.55	0.61	1.27
4	4.62	8.92	0.46	0.97
5	0.86	1.88	0.93	1.24
6	1.84	3.77	1.53	2.92
7	1.28	2.76	0.76	1.23
Average	2.449	5.001	0.799	1.496

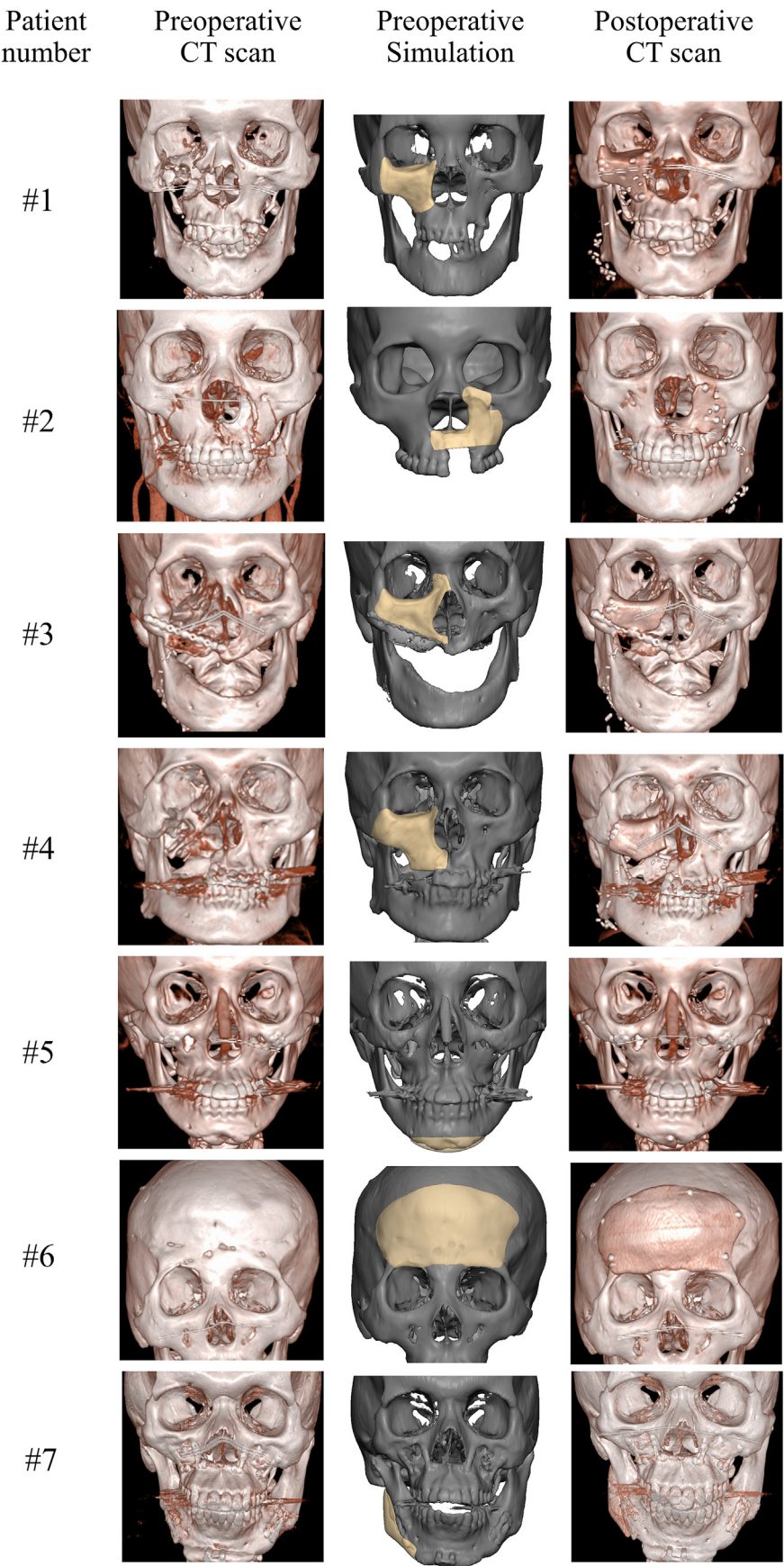


Fig. 6. Preoperative CT, simulation, and postoperative CT images.



Fig. 7. Clinical photographs of patient #3. (A, B) Preoperative and 6-month postoperative frontal photographs. (C, D) Preoperative and 6-month postoperative lateral photographs, showing improved symmetry in the zygomaticomaxillary contour. (E, F) Intraoperative photographs depicting bone defects in the right zygomaticomaxillary region and placement of the 3D-printed PCL/BGS-implant.

In the in vitro experiments, the composite material showed bioactivity to produce apatite layer formation on the surface of the specimen, even though the amount of BGS-7 was only 20%, and it was covered with PCL. When bioactive glass reacts in the SBF, a silica gel layer is formed on the glass surface during the first few hours, followed by precipitation and crystallization of Ca/P to form an apatite layer (Rich et al., 2002). This silicon layer has osteogenic potential, promoting organic matrix formation and activation of osteoblasts (Karlsson et al., 1989). The Ca/P layer plays a role in chemical bonding with living bone, and promoting osteoblast activation (Kokubo, 1990). It is similar to the inorganic component of human bone, facilitating bone growth on its surface. In addition, the fabricated geometrical structure with a cross-layered arrangement may increase the cell seeding efficiency by preventing the cells from falling through the pores, while promoting bone ingrowth through the complex interconnected pore structure (Habibovic et al., 2008; Bose et al., 2013; Lee et al., 2013).

The strength of the 3D PCL/BGS-7 implant lies in its ability to reproduce the complex geometric contour of the craniofacial bone. The maxilla and mandible have 3D structures with variable degrees of thickness. Previous reports on cortical bone thickness have found values ranging from 1.09 mm to 2.12 mm in the maxilla and from 1.59 mm to 3.03 mm in the mandible (Ono et al., 2008). 3D printing allows the formation of a product with a minimum thickness of 1–1.5 mm, which is a sufficient threshold for restoring thin bony areas, such as the orbital, nasal, and anterior maxillary regions (Bose et al., 2013).

The symmetry outcome was found to have significantly improved postoperatively in the 3D contour analysis. This method is suitable for assessing the complex bony contours of the facial region, even where no anatomical landmark exists, or when determination of reliable landmarks proves difficult during point-based analysis (Gong et al., 2014; Gibelli et al., 2018). The RMS is a unique measure in 3D imaging systems, in which it acts as an indicator of volumetric change by calculating the mean value of aggregated distances between surfaces (Moghaddam et al., 2014). By using RMS as an indicator of asymmetry, significant improvements were found in various facial regions, of which the maxillary region showed the greatest change.

The intrinsic limitation of this implant is the risk of unfavorable wound healing and the resultant exposure of the material. In patients included in this study, one who had undergone previous radiation in the maxilla developed implant exposure, resulting from postoperative wound breakdown in the hard palate. This patient also presented with a residual bone gap due to unfavorable bone ingrowth around the surface of the implant. If radiation-induced fibrosis occurs, delayed wound healing can lead to fistula formation even when free tissue transfer with good vascularity is used for reconstruction (Choi et al., 2021). It is highly recommended that when implant reconstruction is planned for craniofacial bone defects, aggressive debridement should be performed to confirm fresh bleeding from both the soft tissue and bony surfaces. In addition, the implant should be covered with highly vascularized tissue to ensure tissue ingrowth into the implant.

This study had some limitations. First, it comprised a small cohort and reported only short-term results; future studies with a larger number of patients and long-term follow-up are required to verify these results. Considering that the total time for complete degradation of PCL takes 2–3 years, and that more rapid degradation is anticipated in the PCL/BGS composite implant, a minimum of 2 years is recommended for long-term follow-up (Soni et al., 2019). Regarding bone formation, however, a minimum postoperative period of 6 months was found to be sufficient for bony ingrowth into the implant. The second limitation of this study was the lack of clinical comparisons among different proportions of the

composite material. Of the various combinations of PCL and BGS-7 materials, a ratio of 8:2 was found to be the most suitable for 3D printing in order to obtain similar strut and pore sizes in the composite scaffold (Kim et al., 2019). Although the composite implant mixed with 6:4 PCL:BGS-7 showed favorable outcomes in terms of toughness and bioactivities, it was difficult to form a complex 3D structure due to printing errors. Further studies should focus on comparing various implants with different composite proportions to identify the most feasible and applicable composites.

5. Conclusion

Within the limitations of the study it seems that PCL/BGS-7 implants might be a relevant option for repairing craniofacial bone defects, owing to its favorable bone-binding properties and clinical safety, accompanied with fewer complications.

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Declaration of competing interest

None to disclose.

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