Regenerative Therapy 26 (2024) 767–774

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Original Article

Clinical outcomes of guided tissue regeneration with carbonate apatite granules and poly(lactic acid/caprolactone) membrane for the treatment of intrabony defects and mandibular Class II furcation involvements: A 12-month prospective pilot clinical study

Munehiro Okada, Shunsuke Fukuba[*, 1], Daichi Yamaki, Takanori Iwata[**, 1]

Department of Periodontology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan

ARTICLE INFO

Article history:
Received 25 July 2024
Received in revised form
13 August 2024
Accepted 21 August 2024

Keywords:
Periodontal regeneration
Carbonate apatite
Poly(lactic acid/caprolactone) bilayer membrane
Intrabony defect
Furcation involvement
Clinical study

ABSTRACT

Introduction: For deep intrabony defects or Class II furcation involvements (FI), periodontal tissue regenerative therapy combined with bone graft materials and a barrier membrane is recommended. The objective of this study was to assess the safety and efficacy of using carbonate apatite (CO_3Ap) granules and absorbable poly(lactic acid/caprolactone) (PLCL) membranes for periodontal regeneration in the treatment of intrabony defects and mandibular Class II FI.

Methods: This prospective pilot clinical study, conducted at a single center with a single-arm design, aimed to assess the safety and efficacy of CO_3Ap and PLCL membranes in patients with periodontitis. A total of 9 patients with 10 teeth, including seven deep intrabony defects and three Class II FI, were treated with CO_3Ap granules and PLCL membranes. Clinical parameters such as probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), tooth mobility (Mo), Plaque Index (PI), and Gingival Index (GI) were assessed at baseline, 6 and 12 months post-surgery. Radiographic analysis was performed using dental X-rays and cone beam computed tomography (CBCT) images taken at baseline, 6, and 12 months post-surgery.

Results: Postoperative healing was uneventful in most of the cases. In some cases, membrane exposures were observed. However, there were no signs of inflammation, such as abnormal bleeding, pain, swelling, or pus. These exposures eventually healed well in the end. The mean reductions in PPD at 6 and 12 months were 4.5 ± 1.6 mm and 4.9 ± 1.4 mm, respectively, while the mean gains in CAL were 4.4 ± 1.7 mm at 6 months and 4.6 ± 1.2 mm at 12 months. Radiographic analysis showed improvements in linear bone height within intrabony defects and in the vertical subclassification of FI in Class II FI.

Conclusions: Despite the limitations of this study, periodontal regenerative therapy using CO_3Ap granules and a PLCL membrane demonstrated promising clinical safety and efficacy for treating intrabony defects and mandibular Class II furcation involvement.

Abbreviations: CO_3Ap, Carbonated apatite; PLCL, Poly(lactic acid/caprolactone); FI, Furcation involvement; PPD, Probing pocket depth; CAL, Clinical attachment level; BOP, Bleeding on probing; Mo, Tooth mobility; CBCT, Cone beam computed tomography; PI, Plaque index; GI, Gingival index; BL, Baseline; CEJ, Cement-enamel junction; COM, Composite outcome measure; DM, Diabetes; MB, Mesial-buccal; DB, Distal-buccal; B, Buccal; M, Mesial; BL, Buccal-lingual; SPPT, Simplified papillae preservation technique; EPPT, Entire papillae preservation technique; SFA, Single flap approach; MPPT, Modified papillae preservation technique.

* Corresponding author. Department of Periodontology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-Ku, Tokyo, 113-8549, Japan.

** Corresponding author. Department of Periodontology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-Ku, Tokyo, 113-8549, Japan.

E-mail addresses: sfukuba.peri@tmd.ac.jp (S. Fukuba), iwata.peri@tmd.ac.jp (T. Iwata).

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

[1] Shunsuke Fukuba and Takanori Iwata contributed equally as corresponding authors and should be considered as joint corresponding authors.

https://doi.org/10.1016/j.reth.2024.08.017

1. Introduction

Periodontitis is characterized by inflammation around the periodontal tissues, resulting in bone resorption that can lead to tooth loss if untreated [1]. The extent and morphology of bone resorption around the root can vary, with defects categorized based on the number of remaining bone walls—ranging from one-wall to three-wall defects, as well as circumferential defects [2]. In cases where bone resorption reaches the entrance of the furcation in multi-rooted teeth, furcation involvement (FI) can be diagnosed. The classification of FI ranges from Class I to Class III, representing different stages of progression until the defect fully penetrates the furcation area [3].

Previous systematic reviews and consensus reports have highlighted that periodontal regenerative therapy yields favorable clinical outcomes, particularly in cases of deep intrabony defects and Class II FI [4–9].

To support periodontal tissue regeneration, various synthetic bone graft substitutes have been applied [10]. Carbonate apatite (CO_3Ap) is one of the components of natural bone in humans and is biodegradable under physiological conditions through absorption by osteoclasts [11–14]. CO_3Ap has recently been clinically employed as a chemically manufactured synthetic bone graft substitute [15,16]. In recent years, the safety and efficacy of periodontal tissue regeneration therapy using CO_3Ap have been reported in both preclinical and clinical trials [17–20].

Barrier membranes are categorized as either resorbable or non-resorbable. Non-resorbable membranes are durable and effectively prevent fibroblast infiltration during the bone regeneration phase, promoting adequate bone formation [21]. Nevertheless, non-resorbable membranes have disadvantages such as requiring a second surgical procedure for their removal and a risk of infection if the membrane becomes exposed [22]. On the other hand, resorbable membranes are naturally absorbed by the body and do not need to be removed surgically, making them a popular choice for guided bone regeneration (GBR) procedures and periodontal regenerative therapies. Most currently available resorbable membranes are composed of animal-derived collagen [23]. However, predicting the breakdown and resorption rate of collagen-based resorbable membranes is difficult. There are also concerns about whether these membranes can maintain their cell barrier function throughout the bone formation period without being prematurely absorbed [24].

To address these challenges, the development of a GBR membrane necessitates a well-defined composition, reliable sourcing, and utilization of a chemically synthesized, biodegradable polymer that has been tailored to possess all the essential characteristics needed for GBR applications.

Recently, a new biodegradable membrane composed of poly(-lactic acid (LA)/caprolactone (CL)) (PLCL), has been developed. The degradation rate of P(LA/CL) can be adjusted by varying the amount of PCL in the composition [25]. This membrane has a bilayer structure consisting of outer compact and inner porous layers. Previous in vivo and in vitro studies indicated that its porous structure of the inner surface promoted bone formation, while its compact structure of the outer surface provided strong barrier effects against bacterial adherence and penetration. A Case report has been published demonstrating the safety and efficacy of bone regeneration using a PLCL membrane during simultaneous implant placement [26]. However, there are currently no prior clinical studies reporting the safety and efficacy of periodontal regeneration using a combination of bone graft material and a PLCL membrane. Therefore, this initial pilot clinical trial in humans aimed to assess the safety and efficacy of using a combination of CO_3Ap granules and PLCL membrane for periodontal regenerative therapy. The study included cases of intrabony defects and mandibular Class II FI to investigate the potential of CO_3Ap granules and PLCL membrane in periodontal regeneration.

2. Methods

2.1. Patient population and study design

This study was conducted as an observational prospective clinical trial at a single center, with a non-blinded, single-arm design. Recruitment took place between April 2022 and January 2023 among patients undergoing non-surgical periodontal therapy at the Periodontal Clinic of Tokyo Medical and Dental University Hospital. Patients were included based on specific criteria: 1) aged 20 years or older with informed consent, 2) diagnosed with severe periodontitis showing a probing pocket depth (PPD) of 4 mm or greater and a bony defect depth of 3 mm or greater on dental x-ray images, specifically intrabony defects or Class II FI in the mandible, and 3) agreed to participate in the study utilizing their pre- and post-treatment examination and medical records and to receive guided tissue regeneration therapy using CO_3Ap granules with a PLCL membrane. After obtaining informed consent for study participation, a preoperative examination was conducted, including a medical interview, periodontal tissue examinations, dental X-ray images, cone-beam computed tomography (CBCT) (3DX FPD, Morita, Japan), and intraoral photos. The clinical trial was conducted in compliance with the World Medical Association's Code of Ethics (Declaration of Helsinki), approved by the ethics committee at Tokyo Medical and Dental University (NR2021-012), and registered in Japan Registry of Clinical Trials (jRCTs032210705).

2.2. Clinical measurements at baseline and follow-up visits

In this study, various clinical measurements of periodontal tissues were conducted, including Clinical Attachment Level (CAL), Probing Pocket Depth (PPD), Bleeding on Probing (BOP), Tooth Mobility (Mo), Plaque Index (PI), and Gingival Index (GI). CAL and PPD were assessed at the deepest sites using a periodontal probe (PCP-UNC-15, Hu-Friedy, Chicago, USA) with a standardized pressure of 25 g. The degree of furcation involvement (FI) was evaluated using a furcation probe (PQ2N6, Hu-Friedy, Chicago, USA). Prior to the trial, examiners underwent calibration to ensure consistent and standardized measurements. Clinical measurements were taken at specific time points: initial visit, 2 months post non-surgical periodontal treatment as baseline (BL), and at 6 and 12 months after the surgical intervention. Fig. 1 provides an overview of the treatment and follow-up sequence depicted in the study.

2.3. Surgical procedures

Before the surgery, periodontal specialists (M.O., S.F.) conducted the initial phase of periodontal treatment, which included providing instructions on oral hygiene and non-surgical periodontal procedures. All periodontal regenerative therapies were carried out by these specialists, and local anesthesia (Xylocaine, GC Showa-Yakuhin Corporation, Tokyo, Japan) was administered. The surgical procedure involved elevating the flap based on the incision design with papillae preservation techniques chosen by the surgeon. Utilizing an ultrasonic scaler and Gracey curettes under a microscope and/or dental loupes, dental plaque, calculus, and granulation tissues were removed. The morphology of intrabony defects and the classification of FI were verified. Particulate bone substitutes, specifically CO_3Ap (Cytranse Granules, GC Corporation, Tokyo, Japan), were soaked in saline solution to improve their handling. The bone defects were then filled with CO_3Ap granules

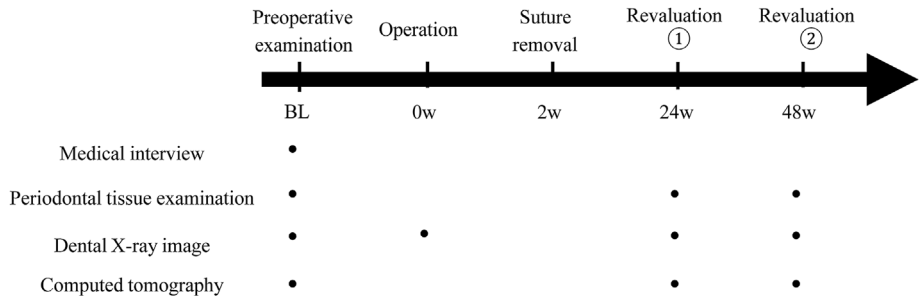

Fig. 1. Overview of the treatment and follow-up sequence.

and covered with trimmed biodegradable bilayered PLCL membranes (Cytranse Erashield; GC Corporation, Tokyo, Japan). When fixation of the membrane was required, it was positioned using absorbable sutures (5-0 Vicryl, Johnson & Johnson, New Jersey, USA) in a sling suture. If the tooth exhibited mobility greater than degree 2 following flap closure, temporary fixed resin cement (Superbond C&B, Clear polymer powder, Sun Medical, Shiga, Japan) was applied to splint the tooth with an adjacent tooth. During the initial revaluation, the cement was removed, and the tooth mobility was reassessed. Irrespective of the incision design in each case, tension-free flap closure was achieved using single interrupted sutures and/or mattress sutures (5-0 Softretch, GC Corporation, Tokyo, Japan). Immediately after the surgery, a dental X-ray image was taken. Postoperative care involved the systemic administration of antibiotics (amoxicillin 750 mg/day for three days), analgesics (Loxoprofen sodium 180 mg/day for 3 days), and 0.2% benzethonium chloride oral rinses (Neostelin Green 0.2% mouthwash solution, Nishika, Yamaguchi, Japan) (three times/day for two weeks). Sutures were removed at the two-week post-surgery.

2.4. Radiographic analysis

Standardized dental X-ray images were captured using the long-cone paralleling technique at baseline (BL), the day of surgery, as well as 6- and 12-months post-operation. The average percent of bone fill in sites with intrabony defects was determined following established procedures [19,20], employing image processing software (ImageJ, U.S. National Institutes of Health, Maryland, USA). Landmarks such as the cement-enamel junction (CEJ), apex, remaining alveolar bone crest, and the bottom of the bone defect were identified. The rate of alveolar bone height increase was calculated using the formula [(A-D at BL) - (A-D' at revaluation)] * 100/(C-D at BL) (Fig. 2a), with the distance between CEJ and root apex serving as a reference for pre- and postoperative correction. To assess new bone formation in intrabony defect, linear bone height was calculated based on a previous study [27]. Cone-beam computed tomography (CBCT) images were obtained at BL, 6- and 12-months post-operation. The length between CEJ and the bottom of the intrabony defect in each two-dimensional CBCT section was measured, again using the distance between CEJ and root apex as a reference for pre- and postoperative correction.

Vertical subclassification of FI was diagnosed using dental CBCT images captured at BL and 12 months post-operation [28]. The two-dimensional CBCT section at the tested FI involved dividing the two roots closest to the FI into two equal parts. Within this section, the area between the apex and flute was divided into coronal (subclass A), middle (subclass B), or apical (subclass C) thirds of the root length. The degree of the worst periodontal attachment was categorized by these three subclasses (Fig. 2b). All radiographic analyses were carried out using image processing software (ImageJ, U.S. National Institutes of Health, Maryland, USA) by the same calibrated blinded examiner (D.Y.), who was not involved in the surgical procedures.

2.5. Statistical analysis

Descriptive statistics, including mean and standard deviations for metric variables, were provided using Microsoft Excel version 2011 from Microsoft, Redmond, WA.

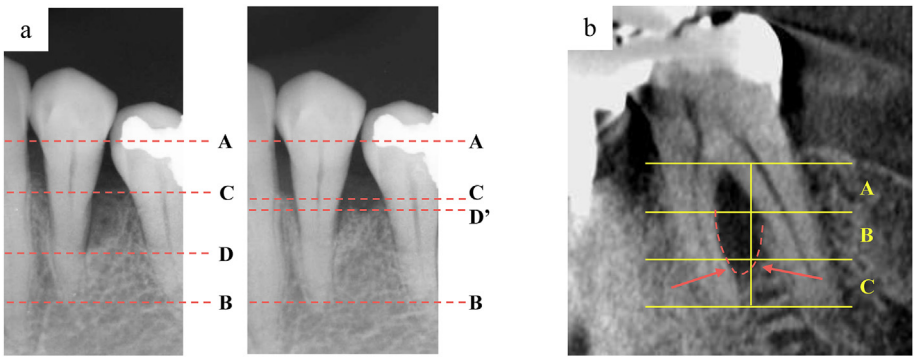

Fig. 2. a. Measurement of the percentage of bone fill is determined using standardized dental x-ray images. Points A, B, C, D, and D′ correspond to the cementoenamel junction (CEJ), the root apex, the remaining alveolar bone crest, and the bottom of the bone defect at baseline and revaluation, respectively. The increase in alveolar bone height is calculated with the formula: (A–D) - (A - D′) × 100/(C–D). The distance between the CEJ and the apex is used as a reference to correct for minor errors. b. The vertical subclassification of furcation involvement (FI) is assessed by examining a two-dimensional cross-section at the FI site. This is done by splitting the two roots nearest to the FI into two equal halves. This cross-section is then divided into three equal segments: the coronal third (subclass A), the middle third (subclass B), and the apical third (subclass C) of the root length. The severity of periodontal support loss is categorized into these three subclasses.

3. Results

3.1. Study population

A total of 9 patients (three males and six females) undergoing treatment at the Department of Periodontology, Tokyo Medical and Dental University Hospital, were included in the study. The patients had an average age of 58.6 ± 15.7 years, with none of them having smoking habits or diabetes. The characteristics of each subject and test site at baseline were presented in Table 1. The study was conducted on 10 sites, with seven patients having intrabony defects at seven sites and two patients with mandibular Class II FI at three sites. Clinical and radiographic images of typical cases for intrabony defects, Class II FI were shown in Figs. 3–5.

3.2. Clinical outcomes

Primary healing without abnormal bleeding, pain, redness, or swelling was achieved at six out of ten sites without any exposure of the grafted materials or PLCL membranes. At four sites, membrane exposures from the gingival sulcus were observed, but there were no signs of inflammation such as bleeding, swelling, or pus, and these sites eventually healed well. The clinical outcomes at each time point; BL, 6 and 12 months after the surgery were

Table 1
Characteristics of patients and tested sites (n = 9 patients, 10 teeth) DM; diabetes, MB; mesial-buccal, DB; distal-buccal, B; buccal, M; mesial, BL; buccal-lingual, SFA; single flap approach, MPPT; modified papillae preservation technique.

	Patient									
Parameter	1		2	3	4	5	6	7	8	9
Age/Sex	63/Female		74/Male	70/Female	47/Female	51/Male	73/Male	27/Female	48/Female	67/Female
Smoking	No		No	No	No	No	No	No	No	No
DM	No		No	No	No	No	No	No	No	No
Tooth location	#37	#46	#14	#34	#37	#47	#36	#36	#14	#46
Tested site	B	B	MB	M	DB, D	DB, D	B	M, D	M	D
Defect type	FI ClassII	FI ClassII	1-2 wall	1-2 wall	2-3 wall	2-3 wall	FI ClassII	1-2 wall	1-2 wall	2-3 wall
Flap design	SFA	SFA	MPPT	MPPT	SFA	Extended Flap	SFA	MPPT	MPPT	Extended Flap
Splinting	−	−	−	−	+	+	−	−	−	−

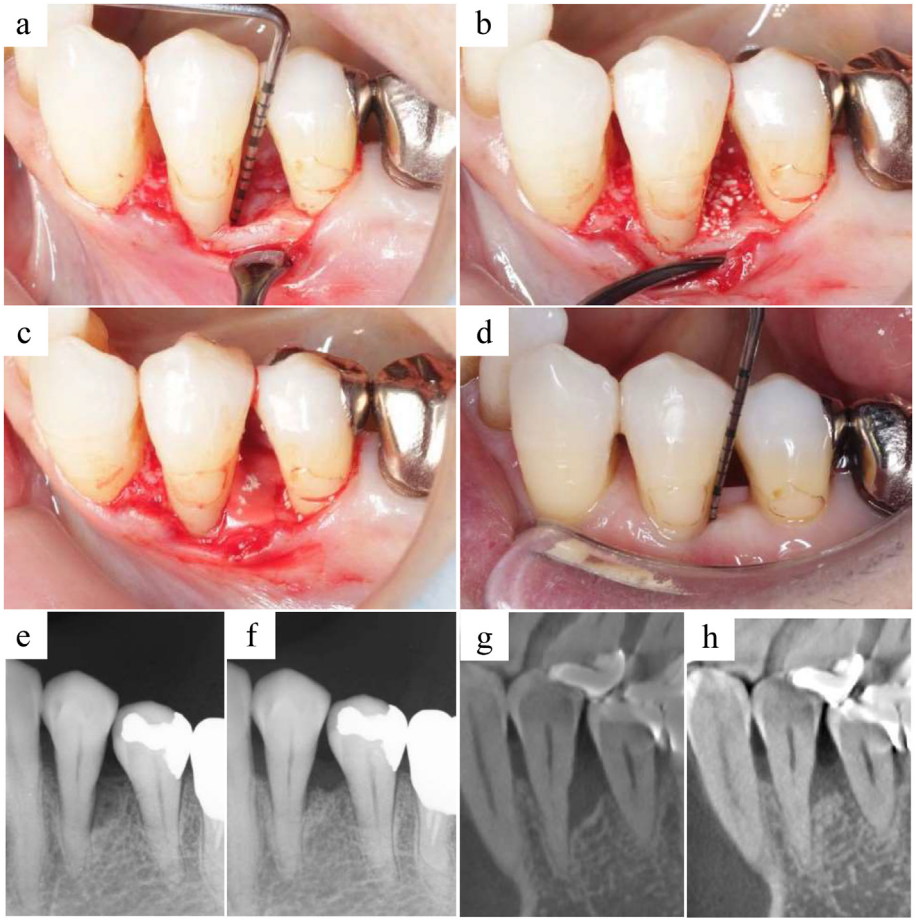

Fig. 3. Case 1; a 70-year-old female. a) After flap elevation of the mandibular left first premolar; #34, 1–2 wall intrabony defect was observed. b) After administration of CO_3Ap granules. c) After administration of a PLCL membrane. d) 48 weeks after the surgery. e, g) Dental x-ray image and two-dimensional section of CBCT at BL. f, h) Dental x-ray image and two-dimensional section of CBCT at 48 weeks post-surgery.

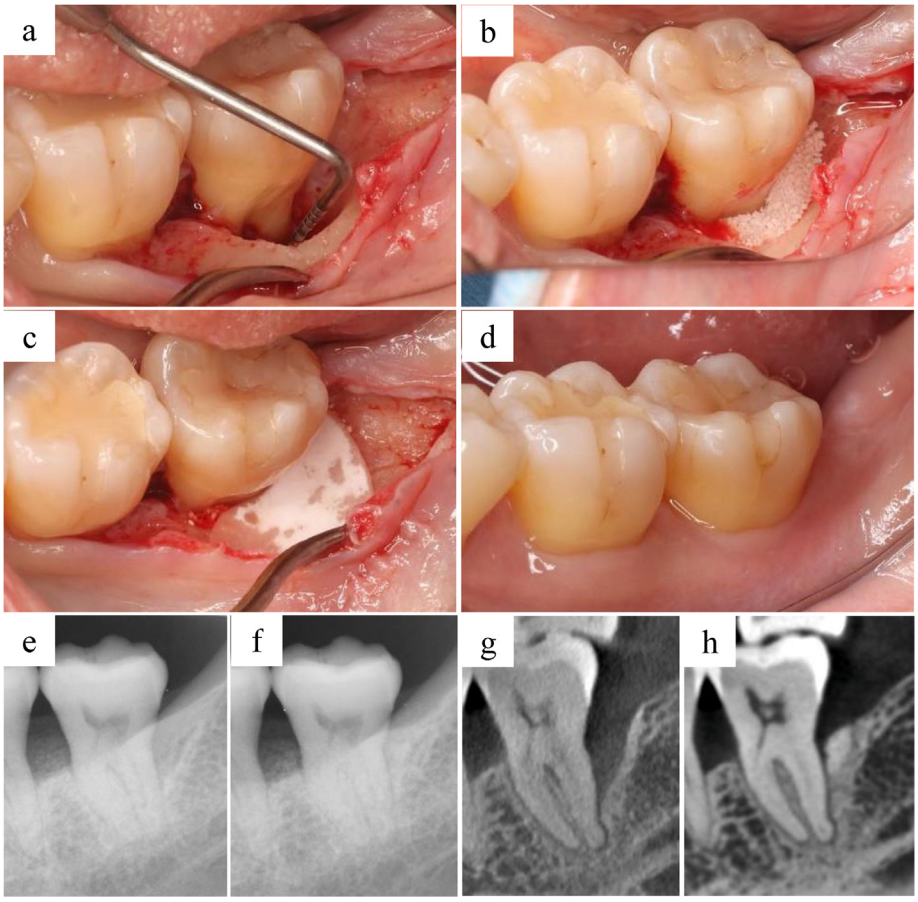

Fig. 4. Case 2; a 47-year-old female. a) After flap elevation of the mandibular left second molar; #37, 3 wall intrabony defect was observed. b) After administration of CO_3Ap granules. c) After administration of a PLCL membrane. d) 48 weeks after the surgery. e, g) Dental x-ray image and two-dimensional section of CBCT at BL. f, h) Dental x-ray image and two-dimensional section of CBCT at 48 weeks post-surgery.

summarized in Table 2. The average gain in CAL at 6- and 12-months post-surgery was 4.4 ± 1.7 mm and 4.6 ± 1.2 mm, respectively. Similarly, the mean reduction in PPD at these time points was 4.5 ± 1.6 mm and 4.9 ± 1.4 mm, respectively. BOP was absent in all tested sites at 24 and 48 weeks after surgery. Tooth mobility remained stable throughout the observational period in this study. Notably, one of the Class II furcation involvements (FI) sites improved to Class I, while the other site successfully resolved the FI.

3.3. Radiographic analysis

The radiographic analysis for each patient is presented in Table 2. The average percentage of bone fill in sites with intrabony defects was 35.89% ± 17.97% at 6 months, and 40.4% ± 20.69% at 12 months post-surgery. Additionally, the mean increase in linear bone height at sites with intrabony defects from BL to 6- and 12-months post-surgery was 3.5 ± 1.9 mm and 3.4 ± 2.0 mm, respectively.

Regarding the vertical subclassification of FI, improvement from Class B to Class A was observed in two cases, and improvement from Class C to Class A was observed in one case.

4. Discussion

This study represents the first human clinical trial aiming to achieve periodontal tissue regeneration using guided tissue regeneration (GTR) with a combination of CO_3Ap granules and a PLCL membrane for intrabony defects and Class II FI in the mandible. Throughout the observation period, no serious adverse events such as postoperative infections were observed.

A combination of CO_3Ap granules and a PLCL membrane in periodontal regenerative therapy proved to be an effective treatment modality. Regarding intrabony defects, a mean CAL gain of 4.6 ± 1.3 mm and a mean PPD reduction of 4.7 ± 1.2 mm were achieved at 12 months after the surgery. The mean % bone fill and the mean gain of liner bone height between BL and 12 months after the surgery amounted to 40.4 ± 20.7 %, and 3.4 ± 2.0 mm, respectively. According to the success criteria for periodontal regenerative therapy suggested in a previous study [31], all tested sites in this study met the composite outcome measure (CAL gain ≥3 mm, pockets ≤4 mm without bleeding). The results of this study can be partly attributed to the initial CAL of each patient with intrabony defects. Previous research has shown that sites with deeper initial intrabony defects tend to exhibit greater CAL gain following periodontal regenerative therapy [32]. Specifically, the mean initial CAL measurements for sites with intrabony defects were 8.1 ± 2.1 mm in this study.

At the tested sites with Class II FI in the mandible, a mean gain of 4.7 ± 1.7 mm in CAL and a mean reduction of 5.3 ± 1.9 mm in PPD were achieved at 12 months post-surgery. At the revaluation in 6 and 12 months after the surgery, all sites were classified as Class A in terms of vertical subclassification of FI. Previous research indicated that improvements in the vertical subclassification of furcation involvement are associated with improved tooth prognosis [28].

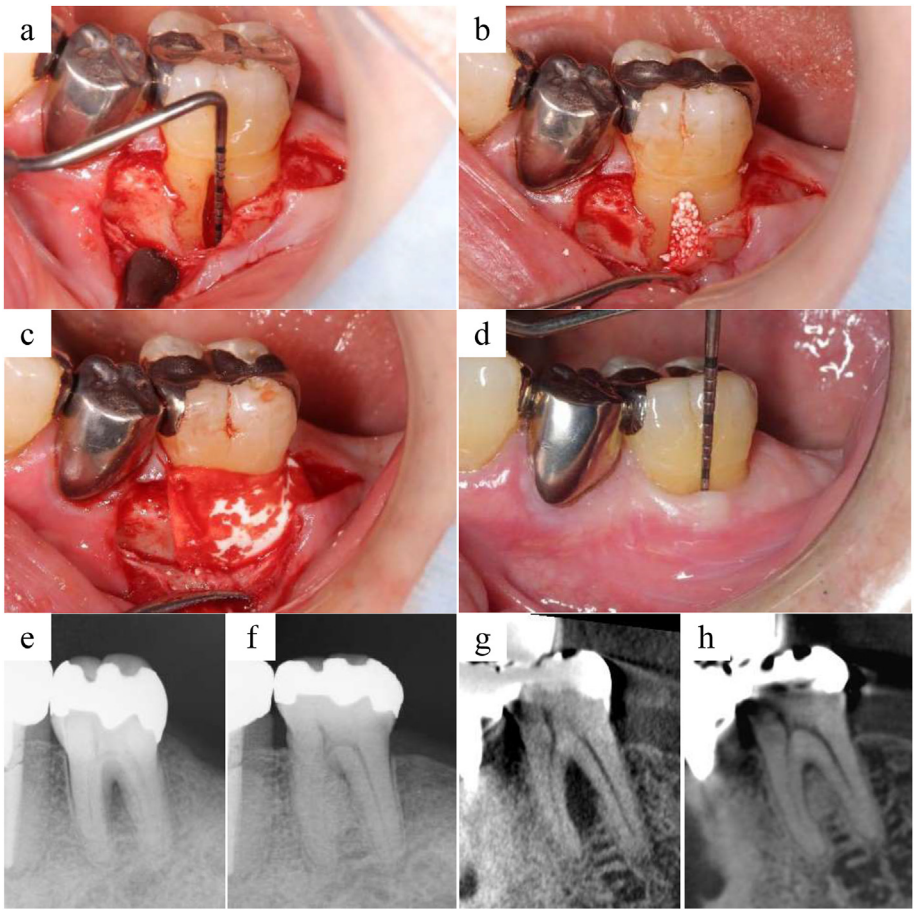

Fig. 5. Case 3; a 73-year-old male. a) After flap elevation of the mandibular left first molar; #36, FI was observed. b) After administration of CO_3Ap granules. c) After administration of a PLCL membrane. d) 48 weeks after the surgery. e, g) Dental x-ray image and two-dimensional section of CBCT at BL. f, h) Dental x-ray image and two-dimensional section of CBCT at 48 weeks post-surgery.

The improvements in CAL, PPD, and bone fill percentages observed in this study are not inferior to the outcomes in previous clinical studies evaluating the efficacy of combining other bone graft substitutes and membranes in periodontal regenerative therapy [29,30]. The favorable clinical outcomes are most likely to be related to the characteristics of CO_3Ap bone substitute and bilayer PLCL membrane.

CO_3Ap, a delayed absorbable bone graft material, exhibit superior space-making capabilities for periodontal tissue regeneration compared to rapidly absorbable bone graft materials like beta-tricalcium phosphate [33]. Additionally, because CO_3Ap is less likely to remain over the long term, as seen with bovine-derived xenografts [34–36], it is expected to reduce the risk of post-operative reinfection [37]. Based on these considerations, CO_3Ap is considered effective as a bone graft material for periodontal regenerative therapy.

For intrabony bone defects with one or two walls, wide intrabony defects, and Class II FI, the additional use of membranes is recommended to facilitate space-making for periodontal tissue regeneration and to prevent epithelial downgrowth. However, complications during the initial healing phase, such as membrane exposure, have been a point of concern. Typically, these complications can lead to decreased clinical outcomes of periodontal regeneration due to rapid membrane resorption and infections of the bone substitutes. In this present study, membrane exposures from the gingival sulcus were observed at a few tested sites regardless of papillae preservation incision design. However, there were no signs of inflammation and these sites eventually healed well and periodontal conditions were clinically improved. These heterogeneous results might be ascribed to the unique properties of the PLCL membrane. A PLCL membrane is characterized by excellent biocompatibility, a slow degradation rate, reduced bacterial adhesion, and blocked bacterial penetration [25,39].

Originally, this PLCL membrane was developed for applications in GBR procedures. For this purpose, the membrane possesses unique stiff and elastic features, which allow it to be stretched and stabilized with fixing pins, facilitating easy handling. An in vitro study evaluating the physicochemical characteristics of PLCL membrane revealed its high tensile strength and breaking strain. In fact, a preclinical study revealed that significantly greater bone regeneration was achieved by treatment with PLCL membrane compared with Col membranes [38]. Furthermore, the previous in vivo study demonstrated that the barrier function of the PLCL membrane was superior to type I collagen (Co) membranes [38]. The PLCL membrane showed slow biodegradation, resulting in an efficient and prolonged barrier function compared with type I Col membranes.

This study was conducted as an exploratory observational prospective clinical trial with a limited number of participants. Larger-scale studies with extended follow-up periods and randomized clinical trial designs are needed to validate the efficacy of periodontal regeneration using a combination of CO_3Ap and PLCL membrane.

Table 2
Results of clinical and radiographic evaluation. CAL; clinical attachment level, PPD; probing pocket depth, Mo; teeth mobility, PI; plaque index, GI; gingival index, FI; furcation involvement, BL, baseline. A; subclass A, B; subclass B.

	Patient									
Parameter	1		2	3	4	5	6	7	8	9
Tooth location	#37	#46	#14	#34	#37	#47	#36	#36	#14	#46
Defect type	FI ClassII	FI ClassII	1-2 wall	1-2 wall	2-3 wall	2-3 wall	FI ClassII	1-2 wall	1-2 wall	2-3 wall
CAL BL (mm)	6	7	8	8	7	13	11	7	8	6
CAL 24w (mm)	3	3	4	4	3	5	4	5	3	3
CAL 48w (mm)	2	3	3	4	2	4	5	4	3	3
PPD BL (mm)	6	7	8	6	7	13	10	7	8	5
PPD 24w (mm)	3	3	4	2	3	5	3	4	3	2
PPD 48w (mm)	2	3	3	2	2	4	2	3	3	2
BOP BL	+	+	+	+	+	+	−	+	+	−
BOP 24w	−	−	−	−	−	+	−	−	−	−
BOP 48w	−	+	+	−	−	−	−	−	−	−
Mo BL	0	0	0	1	0	2	0	0	0	0
Mo 24w	0	0	0	1	0	1	0	0	0	0
Mo 48w	0	0	0	1	0	1	0	0	0	0
PI BL	1	1	1	1	0	1	1	2	1	0
PI 24w	0	1	0	0	0	1	1	1	0	0
PI 48w	0	0	0	0	0	1	1	0	0	0
GI BL	2	2	2	2	2	2	2	2	2	2
GI 24w	0	1	0	0	0	2	0	1	0	0
GI 48w	0	0	0	0	0	1	0	1	0	0
% bone fill 24w (%)			20.6	36.9	63.8	47.7		47.6	37.1	33.5
% bone fill 36w (%)			21.2	42.4	67.4	48.7		53.9	43.5	46.2
Linear bone height (mm) 24w			1.28	3.33	6.35	5.14		3.14	2.24	2.68
Linear bone height (mm) 48w			1.31	3.83	6.72	5.25		3.55	2.62	3.69
Subclassification of FI BL	B	B					C			
Subclassification of FI 24w	A	A					A			
Subclassification of FI 48w	A	A					A			

5. Conclusions

Despite the study's limitations, periodontal regenerative therapy using CO_3Ap granules and a PLCL membrane showed promising clinical safety and efficacy for intrabony defects and mandibular Class II FI.

Author contribution

M.O. S.F., T.I. conceived the study design. M.O., S.F. did the surgical therapies. D.Y. performed data acquisition and analysis. M.O. drafted the manuscript. M.O., S.F., D.Y., and T.I. revised the manuscript. All authors have read and approved the final manuscript.

Declaration of competing interest

This study received funding from GC Corporation (Tokyo, Japan). The funder had an involvement with the study design, interepretation of data.

Acknowledgment

The authors thank the staff of the Department of Periodontology of TMDU, especially Takahiro Naito, DDS, Yugo Ito, DDS, Ryota Kobayashi, DDS, Keita Nakagawa, DDS, for their assistance with data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2024.08.017.

References

[1] Papapanou PN, Wennström JL, Gröndahl K. A 10-year retrospective study of periodontal disease progression. J Clin Periodontol 1989;16(7):403–11.
[2] Reynolds MA, Kao RT, Nares S, et al. Periodontal regeneration – intrabony defects: practical applications from the AAP regeneration workshop. Clin Adv Periodontics 2015;5:21–9.
[3] Aichelmann-Reidy ME, Avila-Ortiz G, Klokkevold PR, et al. Periodontal regeneration - furcation defects: practical applications from the AAP regeneration workshop. Clin Adv Periodontics 2015;5(1):30–9.
[4] Kao RT, Nares S, Reynolds MA. Periodontal regeneration - intrabony defects: a systematic review from the AAP Regeneration Workshop. J Periodontol 2015;86(2 Suppl):S77–104. https://doi.org/10.1902/jop.2015.130685.
[5] Reynolds MA, Kao RT, Camargo PM, et al. Periodontal regeneration - intrabony defects: a consensus report from the AAP Regeneration Workshop. J Periodontol 2015;86(2 Suppl):S105–7. https://doi.org/10.1902/jop.2015.140378.
[6] Nibali L, Koidou VP, Nieri M, Barbato L, Pagliaro U, Cairo F. Regenerative surgery versus access flap for the treatment of intra-bony periodontal defects: a systematic review and meta-analysis. J Clin Periodontol 2020;47(Suppl 22):320–51. https://doi.org/10.1111/jcpe.13237.
[7] Reddy MS, Aichelmann-Reidy ME, Avila-Ortiz G, et al. Periodontal regeneration - furcation defects: a consensus report from the AAP Regeneration Workshop. J Periodontol 2015;86(2 Suppl):S131–3. https://doi.org/10.1902/jop.2015.140379.
[8] Jepsen S, Gennai S, Hirschfeld J, Kalemaj Z, Buti J, Graziani F. Regenerative surgical treatment of furcation defects: a systematic review and Bayesian network meta-analysis of randomized clinical trials. J Clin Periodontol 2020;47(Suppl 22):352–74. https://doi.org/10.1111/jcpe.13238.
[9] Sanz M, Herrera D, Kebschull M, et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. J Clin Periodontol 2020;47(Suppl 22):4–60.

[10] Fukuba S, Okada M, Nohara K, Iwata T. Alloplastic bone substitutes for periodontal and bone regeneration in dentistry: current status and prospects. Materials 2021;26(5):1096. 14.
[11] Ishikawa K. Bone substitute fabrication based on dissolution-precipitation reactions. Materials 2010;3(2):1138–55.
[12] Ishikawa Kunio, Hayashi Koichiro. Carbonate apatite artificial bone. Sci Technol Adv Mater 2021;16(1):683–94. https://doi.org/10.1080/14686996.2021.1947120. 22.
[13] Ishikawa Kunio, Miyamoto Youji, Tsuchiya Akira, Hayashi Koichiro, Tsuru Kanji, Ohe Go. Physical and histological comparison of hydroxyapatite, carbonate apatite, and β-tricalcium phosphate bone substitutes. Materials 2018;16(10):1993. https://doi.org/10.3390/ma11101993. 11.
[14] Muguruza LB, Mäkelä K, Yrjälä T, Jukka Salonen J, Yamashita K, Nakamura M. Surface electric fields increase human osteoclast resorption through improved wettability on carbonate-incorporated apatite. ACS Appl Mater Interfaces 2021;15(49):58270–8. 13.
[15] Nagai H, Kobayashi-Fujioka M, Fujisawa K, et al. Effects of low crystalline carbonate apatite on proliferation and osteoblastic differentiation of human bone marrow cells. J Mater Sci Mater Med 2015;26(2):99. https://doi.org/10.1007/s10856-015-5431-5.
[16] Kobayashi M, Tsuru K, Nagai H, et al. Fabrication and evaluation of carbonate apatite-coated calcium carbonate bone substitutes for bone tissue engineering. J Tissue Eng Regen Med 2018;12(10):2077–87.
[17] Takeuchi S, Fukuba S, Okada M, Nohara K, Sato R, Yamaki D, Matsuura T, Hoshi S, Aoki K, Iwata T. Preclinical evaluation of the effect of periodontal regeneration by carbonate apatite in a canine one-wall intrabony defect model. Regen Ther 2023 Jan 24;22:128–35.
[18] Shirakata Y, Setoguchi F, Sena K, et al. Comparison of periodontal wound healing/regeneration by recombinant human fibroblast growth factor-2 combined with β-tricalcium phosphate, carbonate apatite, or deproteinized bovine bone mineral in a canine one-wall intra-bony defect model. J Clin Periodontol 2022;49(6):599–608.
[19] Kitamura M, Yamashita M, Miki K, et al. An exploratory clinical trial to evaluate the safety and efficacy of combination therapy of REGROTH® and Cytrans® granules for severe periodontitis with intrabony defects. Regen Ther 2022;21:104–13. https://doi.org/10.1016/j.reth.2022.06.001.
[20] Fukuba S, Okada M, Iwata T. Clinical outcomes of periodontal regenerative therapy with carbonate apatite granules for treatments of intrabony defects, Class II and Class III furcation involvements: a 9-month prospective pilot clinical study. Regen Ther 2023 Aug 28;24:343–50.
[21] Konstantinidis I, Kumar T, Kher U, Stanitsas PD, Hinrichs JE, Kotsakis GA. Clinical results of implant placement in resorbed ridges using simultaneous guided bone regeneration: a multicenter case series. Clin Oral Invest 2015 Mar;19(2):553–9. Epub 2014 Jun 8.
[22] Dahlin C, Andersson L, Linde A. Bone augmentation at fenestrated implants by an osteopromotive membrane technique. A controlled clinical study. Clin Oral Implants Res 1991;2(4):159–65.
[23] Bunyaratavej P, Wang HL. Collagen membranes: a review. J Periodontol 2001 Feb;72(2):215–29.
[24] Cucchi A, Chierico A, Fontana F, Mazzocco F, Cinquegrana C, Belleggia F, Rossetti P, Soardi CM, Todisco M, Luongo R, Signorini L, Ronda M, Pistilli R. Statements and recommendations for guided bone regeneration: consensus report of the guided bone regeneration symposium held in bologna, october 15 to 16, 2016. Implant Dent 2019 Aug;28(4):388–99.
[25] Abe GL, Sasaki JI, Katata C, Kohno T, Tsuboi R, Kitagawa H, Imazato S. Fabrication of novel poly (lactic acid/caprolactone) bilayer membrane for GBR application. Dent Mater 2020 May;36(5):626–34.
[26] Ogata K, Ohba S, Sumita Y, Ashahina I. 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. J Dent Sci 2022 Jan;17(1):368–76.
[27] Iwata T, Yamato M, Washio K, et al. Periodontal regeneration with autologous periodontal ligament-derived cell sheets - a safety and efficacy study in ten patients. Regen Ther 2018;24(9):38–44.
[28] Tonetti MS, Christiansen AL, Cortellini P. Vertical subclassification predicts survival of molars with class II furcation involvement during supportive periodontal care. J Clin Periodontol 2017;44(11):1140–4.
[29] Venkatesan N, Lavu V, Balaji SK. Clinical efficacy of amniotic membrane with biphasic calcium phosphate in guided tissue regeneration of intrabony defects- a randomized controlled clinical trial. Biomater Res 2021;25:15.
[30] Camelo M, Nevins ML, Schenk RK, et al. Clinical, radiographic, and histologic evaluation of human periodontal defects treated with Bio-Oss and Bio-Gide. Int J Periodontics Restor Dent 1998;18(4):321–31.
[31] Trombelli L, Farina R, Vecchiatini R, Maietti E, Simonelli A. A simplified composite outcome measure to assess the effect of periodontal regenerative treatment in intraosseous defects. J Periodontol 2020;91(6):723–31. https://doi.org/10.1002/JPER.19-0127.
[32] Mikami R, Mizutani K, Shioyama H, et al. Influence of aging on periodontal regenerative therapy using enamel matrix derivative: a 3-year prospective cohort study. J Clin Periodontol 2022;49(2):123–33.
[33] Kwon SH, Jun YK, Hong SH, Lee IS, Kim HE, Won YY. Calcium phosphate bioceramics with various porosities and dissolution rates. J Am Ceram Soc 2002;85:3129e31.
[34] Fujisawa K, Akita K, Fukuda N, et al. Compositional and histological comparison of carbonate apatite fabricated by dissolution–precipitation reaction and Bio-Oss. J Mater Sci Mater Med 2018;121(8):121. 21;29.
[35] Handschel J, Simonowska M, Naujoks C, et al. A histomorphometric meta-analysis of sinus elevation with various grafting materials. Head Face Med 2009;11(5):12.
[36] Orsini G, Traini T, Scarano A, et al. Maxillary sinus augmentation with Bio-Oss particles: a light, scanning, and transmission electron microscopy study in man. J Biomed Mater Res B Appl Biomater 2005;74(1):448–57.
[37] Sato R, Matsuura T, Akizuki T, et al. Influence of the bone graft materials used for guided bone regeneration on subsequent peri-implant inflammation: an experimental ligature-induced peri-implantitis model in Beagle dogs. Int J Implant Dent 2022;21(1):3. 8.
[38] Abe GL, Sasaki JI, Tsuboi R, Kohno T, Kitagawa H, Imazato S. Poly (lactic acid/caprolactone) bilayer membrane achieves bone regeneration through a prolonged barrier function. J Biomed Mater Res B Appl Biomater 2024 Jan;112(1).
[39] L Abe G, Tsuboi R, Kitagawa H, Sasaki JI, Li A, Kohno T, Imazato S. Poly (lactic acid/caprolactone) bilayer membrane blocks bacterial penetration. J Periodontal Res 2022 Jun;57(3):510–8.