Original Articles

CBCT Evaluation of 3D-porous Dual-Leached Polycaprolactone (PCL) Scaffold in Socket Healing

Chanvit Tangsantigulanon[1], Phonkit Sinpitaksakul[2], Pisha Pittayapat[2], Prasit Pavasant[3], Panunn Sastravaha[1]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand
[2]Department of Radiology, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand
[3]The Center of Excellence in Regenerative Dentistry (CERD), Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand

Abstract

Optimal and rapid bone healing is a desired outcome for any surgery. Thus, biodegradable three-dimensional scaffold was developed as a space filler and a support for bone cell attachment and differentiation. A previous study revealed that the dual leached PCL scaffold (DL-PCL) could offer promising results. The aims of this study were to evaluate the ability of the DL-PCL scaffold as a bone filler in tooth sockets after impacted teeth removal by using cone-beam computed radiograph (CBCT) and its effect on the patients' responses. A randomized, split-mouth study was performed. Bilateral mandibular third molars were surgically removed in the same appointment (N=19). DL-PCL scaffold was placed in the experimental site. CBCT images were taken at 1 week (T1) and 2 months (T2) post-operatively to evaluate new bone formation. The socket bone gain at 8, 10 and 12 mm from the deepest point of the socket and the vertical socket bone fill were measured in Ondemand3D software. All patients were assessed for post-operative pain and swelling. Results showed statistically significant difference of socket bone fill (P=0.001) between the control (6.55±2.46 mm) and the experimental groups (3.57±1.77 mm). Statistically significant difference of socket bone gain was found with higher bone gain in the control group at all levels (Bucco-Lingual: P = 0.044, 0.002 and 0.023) (Mesio-Distal: P = 0.001, 0.004 and 0.012). The experimental side revealed significantly lesser post-operative pain score on the first, second and the third days (P<0.05), whereas no significant difference in swelling was found between the two groups. It can be concluded that the use of DL-PCL scaffold as socket filling material is still questionable within the two-month follow-up period. Although the findings did not show benefits for new bone formation, the DL-PCL scaffold is undoubtedly compatible with the human body within the two-month observation period.

Keywords : Cone-beam computed tomography, Dual-leached scaffold, 3-dimensional porous scaffold, Impacted tooth, Polycaprolactone, Split-mouth study

Received Date: May 30, 2021 **Revised Date:** Jun 29, 2021 **Accepted Date:** Aug 15, 2022
doi: 10.14456/jdat.2022.55

Correspondence to :
Pisha Pittayapat, Department of Radiology, Faculty of Dentistry, Chulalongkorn University, 34 Henri-Dunant Road, Pathumwan, Bangkok 10330, Thailand. Tel: 081-8142656 Email: p.pittayapat@gmail.com

Introduction

The concept of tissue engineering is assigned to the use of a combination of cells, engineering materials or scaffold to support cell growth and differentiation and appropriate biochemical factors to improve or replace biological functions.[1,2] The approach of tissue engineering is potentially attractive for the repair of bony defects given its widespread adaptability.[3] The engineering materials or bone scaffold is the primary requirement needed to facilitate the integration of tissue into skeletal defect. The 3D porous scaffold will serve as a template for the attachment, proliferation and differentiation of bone cells. Porous structure with interconnected channels has been noted to be a crucial factor in cell migration, nutrient diffusion and bone matrix development *in vitro.*[4]

The potential use of biodegradable porous scaffolds as 3D templates to stimulate initial cell attachment and subsequent tissue formation was studied both *in vitro* and *in vivo.* We have previously fabricated a 3D porous scaffold by mixing water soluble poragen in the solution of biodegradable polymer in organic solvent. After leaching the poragen, 3D porous scaffold was obtained. Adding another polyether compound that could be leached out with water further created a 3-dimensional dual-leached (DL) scaffold with high interconnectivity between the pores. An *in vitro* analysis suggested that this DL scaffold had an excellent support for the proliferation and differentiation of bone cells.[5] An *in vivo* study using calvarial model in Wistar rats demonstrated that this newly synthesized DL scaffold could support bone growth inside the scaffold with still unknown mechanism. Interestingly, this newly synthesized scaffold was partially degraded within 8 weeks, based on histomorphometric analysis, and was replaced by new bone or provisional matrices. No evidence of leukocyte accumulation was detected. The level of serum IgG as well as the number of CD3, CD4 and CD8 cells in the adjacent lymph nodes were comparable to those of the sham control.[6]

The PCL-based material has been approved by FDA and widely used in the medical and dental fields, for example, as a part of wound dressing application, degradable staples, long-term absorbable sutures[7,8], 3D scaffolds for tissue engineering applications[8-10], drug delivery devices[11-13], root canal filler (Resilon™) to replacing gutta percha[14], a matrix for odontogenesis of human dental pulp cells[15], and a scaffold for ridge preservation.[16] Nevertheless, the use of the dual-leached PCL-based scaffold has not been reported in human. Our study was the on-going part of the previous *in vivo* study[6], and the clinical trial was required for the assessment of DL-PCL scaffold prior to use in humans. Therefore, the aims of this study were to evaluate the ability of the DL-PCL scaffold as a bone filler in tooth sockets and the patients' responses. A cone-beam computed tomography (CBCT) was used to quantitate the volume of new bone formation, compared to the control using a split-mouth technique and the patients' responses to the scaffold were assessed as degrees of pain and facial swelling.

Materials and methods

The present study was approved by the Human Research and Ethics Committee, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand under study code HREC-DCU 2020-011

Preparation of the (DL-PCL) scaffold

PCL (80,000 g/mol) was purchased from Sigma-Aldrich (St. Louis, MO), and PEG (MW5200, 600, and 1000 g/mol) was purchased from Merck (Germany). Chloroform (Labscan Asia, Thailand) was used as a solvent for these polyesters, whereas sodium chloride (Ajax Finechem, Australia) was used as a porogen.

The 3-dimensional porous scaffolds were fabricated as previously reported by Pratchayaporn Aksorn *et al.* 2021.[6] The scaffold was cut into the designed size and then treated with NaOH by soaking in 1 M NaOH solution at 37 °C for

1 hour and washed extensively with deionized water. Before use, the scaffold was sterilized by shaking in 70% v/v ethanol for 15-30 minutes , washed with sterile PBS 3 times, 2-3 minutes each time and then dried at room temperature (in the culture hood) for 1-2 hours before packing in a sterilized bag.

Study design and methods

This randomized, split-mouth study was performed on healthy Thai patients aged 16-30 years with ASA I-II patients attending the Oral Surgery Unit of the Chulalongkorn University, Bangkok, Thailand for surgical removal of bilateral mandibular third molar teeth in the same appointment. The patients must have bilateral unerupted mandibular third molars categorized as Pell and Gregory classification class I-II and position A-B without sign of inflammation or pathologic conditions. Patients with undesirable habits such as smoking were also excluded. During the operation, the patients were excluded if the buccal bone of the mandibular second molar was removed more than half of the crown width, intra-operative bleeding occurred and required application of local haemostatic agent into the socket, or other inadvertent complications such as lingual plate fracture, tooth dislodgement ,etc. After the operations, if the patients failed to attend the required follow-up session at 1 week and 2 months post-operatively, they were also excluded from the study. Twenty-three subjects in total who met the inclusion criteria were recruited, and their informed consents were obtained.

Surgical procedure

Bilateral impacted mandibular third molars of each subject were removed simultaneously by oral and maxillofacial surgeon with 30 years of experience. Randomized table was prepared prior to the operation. Thus, one side was considered as a control group, the other was a DL-PCL experimental group. The procedures were performed in the same sequence. Amoxicillin 1 gm was given to non-penicillin allergic subjects and clindamycin 600 mg was given to penicillin-allergic subjects for oral premedication. Then a standard surgical procedure was performed as detachment of muco-periosteal flap, osteotomy, odontoectomy, removal of the impacted tooth, curettage, copious irrigation and wound closure. Pieces of DL-PCL scaffold were applied into a tooth socket to fill the cavity at the level of marginal bone in the DL-PCL group. They were steadily contained in the socket by absorbing blood through the porous structure of the scaffold. The surgical wound was closed by primary intention with a 4-0 vicryl suture. All patients were blinded from the knowledge of which side the DL-PCL scaffold was applied. NSAIDs, paracetamol and chlorhexidine mouthwash were prescribed, and home care instructions were given to all of the subjects post-operatively. Sutures were removed on the 7th post-operative day. The patient's information as well as treatment were coded confidentially so that the side of the experiment was unknown to the patients and for the data analysis.

Post-operative clinical evaluation

All subjects were clinically evaluated for facial swelling and signs of infection on the post-operative day 7, whereas pain was assessed on the post-operative days 1, 2, 3 and 7. The assessment of facial swelling and signs of infection was referred to the study of Mantovai *et al.*[17] The same oral and maxillofacial surgery resident used 2-0 black silk to measure the distance from the angle of the mandible to four reference points (tragus of the ear, lateral canthus of the eye, subnasale and pogonion) before and seven days after the surgery. The degree of facial swelling was calculated as $E = [Sd_i^2/4]^{0.5}$ where Sd_i is sum of the facial reference measurements (A-B, A-C, A-D, A-E) (Fig. 1). Signs of infection were indicated as erythematous swelling, tenderness, or pain due to palpation and purulent discharge. Post-operative pain was determined by using a visual analogue scale (VAS) with a 10-point numeric scale in which one extreme end point represented "no pain" (score of 0) and the other end represented "unbearable pain" (score of 10). In case of infection, the wound was irrigated and debrided and the subject was prescribed antibiotics and excluded from the radiographic analysis.

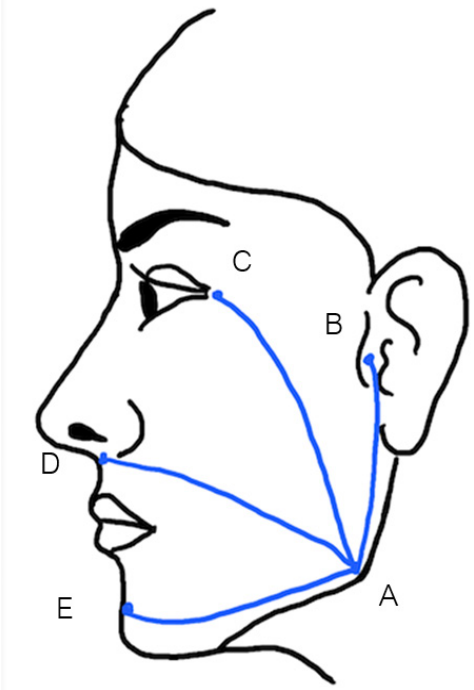

Figure 1 *Five reference points on the face for facial swelling evaluation (modified from Mantovani et al., 2014) A, angle of mandible; B, tragus; C, lateral canthus; D, subnasal; E, pogonion*

CBCT evaluation

At one week after surgical removal of the impacted teeth, patients were scheduled for a visit to remove sutures and post-operative evaluation of clinical conditions. CBCT scans were acquired using the 3D Accuitomo 170® (Morita, Osaka Japan) with a resolution of 0.25 mm, 90 kVp, 5mA, standard mode, field of view (FOV) 14x5 cm. The second CBCT scan were taken at 2 months after the surgery using the same parameters as the first scan.

All CBCT data were exported as digital and communication in medicine (DICOM) format and were imported into OnDemand3D® software (Cybermed, Seoul, Korea) for image analysis. For one patient, there were two CBCT datasets: 1st CBCT at suture off visit (T1) and 2nd CBCT at 2 months after the surgery (T2). In the Ondemand3D software, T1 and T2 dataset were opened together using the "Fusion module". Auto-registration tool in the software was used to superimpose T1 and T2 dataset together (Fig. 2). The fused datasets were saved as DICOM for each patient.

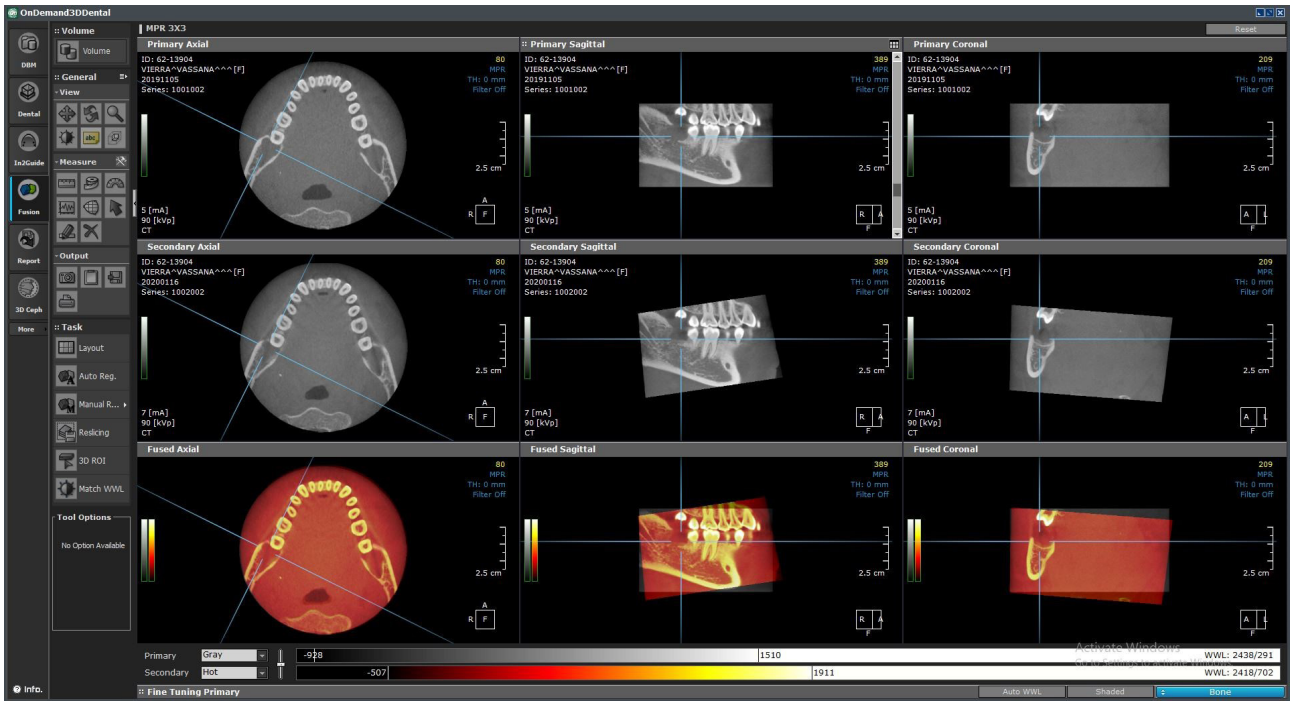

Figure 2 *Radiographic evaluation on OnDemand3D® software. The upper row showed CBCT at T1, the middle row showed CBCT at T2 and the lower row showed the superimposition of T1 and T2 by this software.*

Socket bone fill and socket dimension of both the control and the DL-PCL groups were measured with the "profile linear measurements tools" in the OnDemand3D® software. Socket bone fill was defined as a visible vertical new bone formation that was measured from the apex along the long axis of tooth socket (Table 1). The socket dimension of T1 and T2 were measured and the change in dimension between the two periods of time was considered as bone gain. Socket dimensions were measured at 3 levels: 8, 10 and 12 mm from the deepest point in the socket. The true sagittal plane of the impacted mandibular third molar socket was set and the CBCT slices were scrolled through to find the deepest point of the socket. When the deepest point was established, the measurement was performed on the coronal plane that was perpendicular to this true sagittal plane. At each level, measurements were done in two directions: bucco-lingual and mesio-distal (Figure 3). Any calcified area inside the socket area was noted. (Fig 3). All measurements were done by one oral and maxillofacial resident, twice with 2-week time interval. The main investigator was trained and calibrated with an oral and maxillofacial radiologist with 17 years of experience prior to performing the actual measurement.

Table 1 *Definitions of measured parameters: socket diameter, socket bone fill and bone gain*

Measurement	*Definition*
Socket bone fill	Visible vertical new bone formation that was measured from the apex along the long axis of tooth socket with "profile linear measurements tools" in the OnDemand3D® software
Socket diameter	Socket width is a measured in coronal plane that was perpendicular to this sagittal plane of tooth with "profile linear measurements tools" in the OnDemand3D® software
Bone gain	Difference between the socket diameter in T1 and T2

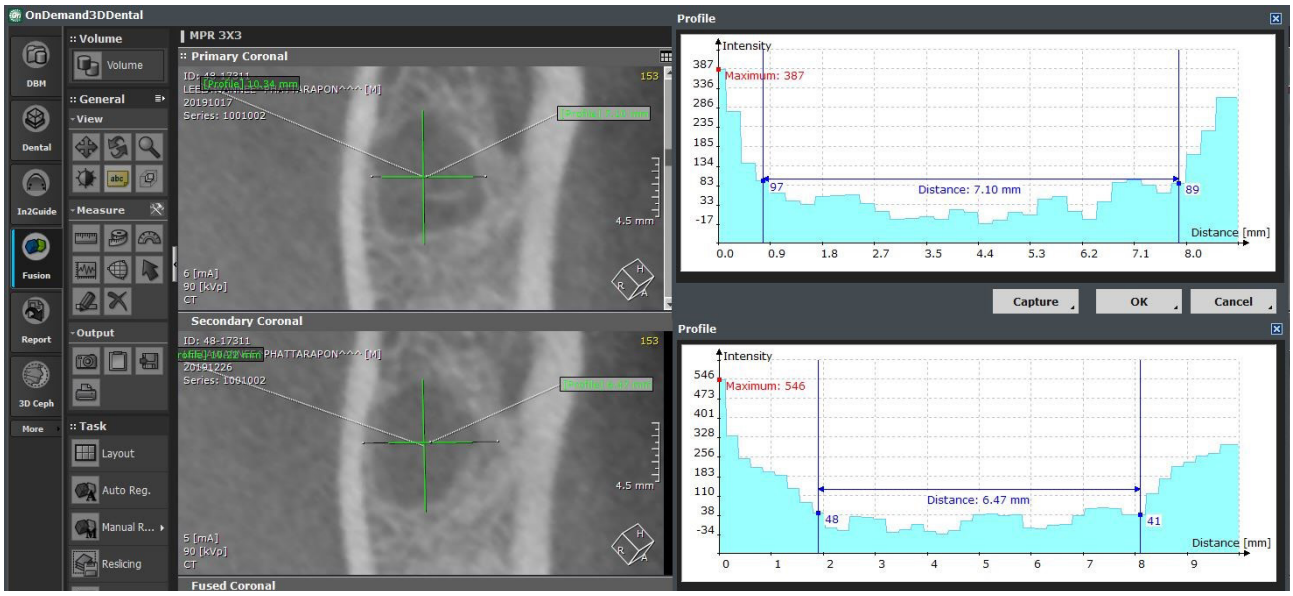

Figure 3 *Showed how profile linear measurements tools in the OnDemand3D® software were used to measure socket dimensions (DL-PCL side). The upper row showed CBCT image at T1 with profile linear measurements tools to measure socket width (7.10 mm). The lower row showed CBCT image at T2 with profile linear measurements tools to measure socket cavity (6.47 mm). Difference between the values in T1 and T2 was recorded as bone gain (7.10 – 6.47 = 0.63 mm)*

Statistical analysis

The data were analyzed by SPSS software version 22.0, IBM, NY, USA. All quantitative data variables were calculated with the Kolmogorov-Smirnov test for evaluation of data distribution. Wilcoxon signed ranks test was used for two samples comparison. Intra-observer reliability was evaluated using Pearson correlation test. The significant level was set at $P<0.05$.

Results

Twenty-three patients, 5 males and 18 females, with mean age of 20.68 years ranging from 16-28 years, underwent surgical removal of bilateral impacted mandibular third molars (Table 2).

No surgical complications were observed during the operation in all cases. At post-operative day 7, none of the subjects had major post-operative complications for instance facial hematoma, paresthesia, severe infection, or alveolar osteitis.

Due to minor late infection of the surgical sites, 4 cases were excluded from the study. The subjects experienced mild dull pain with gingival inflammation in the fifth and sixth post-operative week. The infection occurred at the DL-PCL side in three cases and on both sides in one case. In each infected case, the affected area was curetted, copiously irrigated, and allowed the wound to heal by secondary intention. Amoxicillin 500 mg was prescribed for 7 days. The symptoms were subsided within a week and the wounds healed uneventfully in all cases.

Post-operative pain scores

The pain evaluation with visual analogue scale (VAS) was presented on Table 3.

Significant differences between the control and the experimental group were found on the 1st, 2nd, and the 3rd days after the operation. However, no significant difference was found on day 7 (P =0.196). The patients' pain symptom could be relieved by paracetamol (500 mg) and ibuprofen (400 mg) only.

The mean facial swelling score in the control group was 3.55 ± 1.62 mm which was lower than that of the DL-PCL group at 3.70 ± 1.36 mm. The difference was not statistically significant (P = 0.497).

CBCT evaluation revealed statistically significant difference of the socket bone fill between the the control group (6.55 ± 2.46 mm) and the DL-PCL group (3.57 ± 1.77mm) (P = 0.001).

Table 4 showed the bucco-lingual and mesio-distal socket bone gain for both groups. Statistically significant differences were observed at all three levels on bucco-lingual (P = 0.044, 0.002 and 0.023) and mesio-distal direction (P = 0.001, 0.004, 0.012). The intra-observer reliability was excellent with r = 0.972 (P < 0.01).

Table 2 *Patient demographic data and characteristics of the impacted teeth in this study*

	Number (n=19)	%
Gender		
Male	5	26.3
Female	14	73.7
Age		
16 – 20	11	57.9
21 – 25	6	31.6
26 – 30	2	10.5
Experiment side		
Right	8	42.1
Left	11	57.9
Impaction characteristics		
Class I	9	47.4
Class II	10	52.6
Position A	7	36.8
Position B	12	63.2
Vertical angulation	2	10.5
Mesio angulation	11	57.9
Horizontal angulation	6	31.6

Table 3 *Mean post-operative pain scores with standard deviation (SD) on day 1,2,3 and 7 after the operation*

Post-operative evaluation time	Control side Mean (SD)	DL-PCL side Mean (SD)	*P* - value
Day 1	4.68(2.29)	3.90(2.16)	0.024*
Day 2	2.95(2.32)	2.21(1.93)	0.041*
Day 3	2.37(2.50)	1.74(2.23)	0.017*
Day 7	0.37(0.76)	0.13(0.33)	0.196

**Significant difference*

Table 4 *Results of socket bone gain in millimeter at three levels (8 mm, 10 mm and 12 mm) from the deepest point of the tooth socket in bucco-lingual and mesio-distal direction at 2 months after surgical operation (T2)*

Socket bone gain	Control side		DL-PCL side		*P* – value
	Mean	SD	Mean	SD	
Bucco-lingual					
8 mm	3.70	2.06	1.90	1.11	0.044*
10 mm	4.43	1.92	1.95	1.41	0.002*
12 mm	3.07	2.65	1.28	0.89	0.023*
Mesio-distal					
8 mm	4.17	1.55	1.51	0.83	0.001*
10 mm	4.44	1.80	1.79	1.69	0.004*
12 mm	3.61	1.99	1.41	0.74	0.012*

**Significant difference*

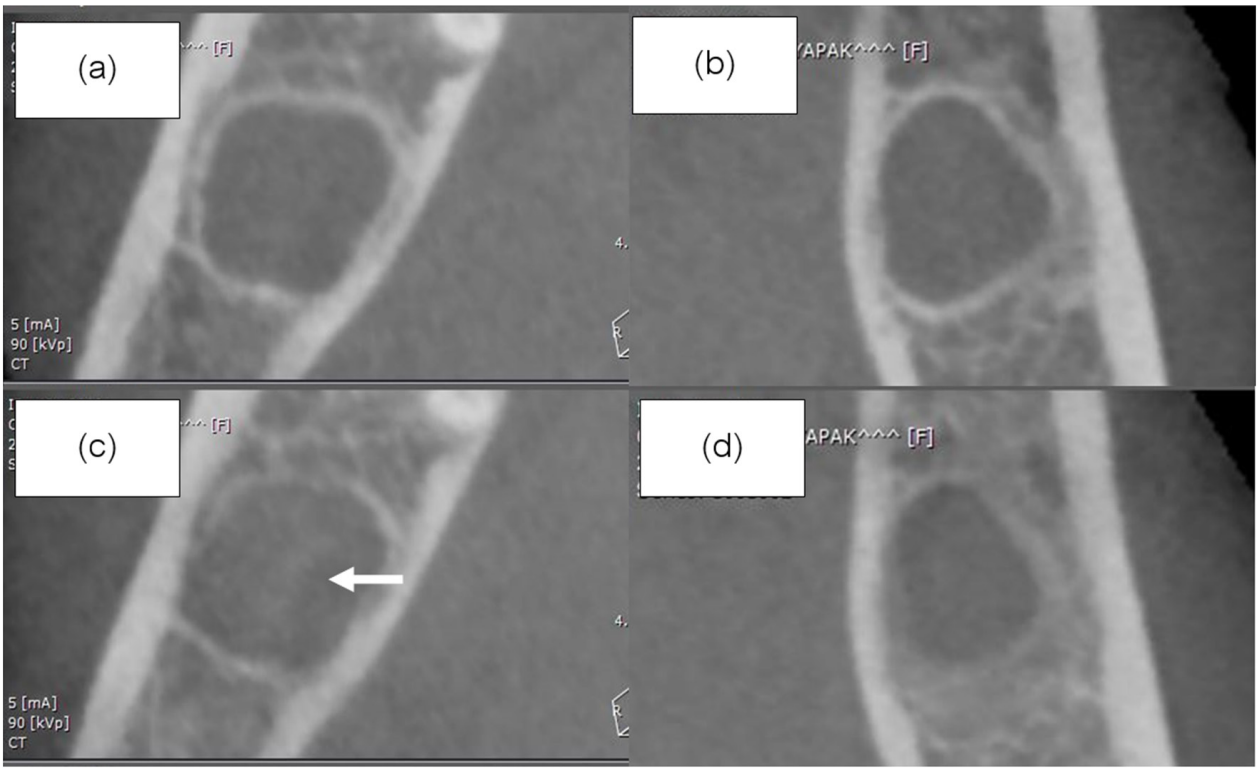

Figure 4 *The upper row (a) and (b) showed radiographs at T1, left (a) was the DL-PCL side, right (b) was the control side. The lower row (c) and (d) showed radiographs at T2, left (c) showed relatively radiopaque area in the center of the socket (arrow), right (d) was the control side.*

Discussion

The purpose of this study was to evaluate the ability of the DL-PCL scaffold for promoting bone healing in the tooth socket by using CBCT analysis with OnDemand3D® software to quantify the new bone formation.

The DL-PCL scaffold was validated *in vitro* by SEM analysis and the MTT assay demonstrated favourable porous interconnectivity, but no cytotoxicity[5]. Previously, the study was performed to assess *in vitro* biocompatibility and osteogenic conduction potential of the DL-PCL scaffold *in vivo*[6]. With respect to biocompatibility, it had the ability to support bone cell adherence and differentiation. Concurrently, bone regeneration was detected at the centre and the edge of the cavity, resulting in a significant increase in bone volume above the control group. It has been noted that the fibrous structure and highly interconnected network of pores on the scaffold facilitate increased bone volume.

Surprisingly, the results of our study revealed considerably less bone formation in the DL-PCL group compared to the control group, as opposed to the previous *in vivo* study[6]. However, despite the efficacy of DL-PCL scaffold for bone formation was questionable, the biocompatibility of the DL-PCL scaffold in humans was evident in this study. All subjects show no tissue reactions and were free from any adverse symptoms for 4-10 weeks. We suggested that the degradation time of the DL-PCL scaffold and the physical characteristics of an extraction socket were the reason for the negative results.

An extraction socket is a clean-contaminated wound and healed by secondary intention. After filled with granulation tissue, the socket is occupied by woven bone islands formed around the periphery of the socket by the 3rd week, and eventually undergoes remodelling by deposition and resorption processes. Radiographic indication of new bone formation becomes apparent as early as the 6th-8th weeks after the tooth extraction. Placing the DL-PCL scaffold in an extraction socket should promote a more rapid healing of the socket, since it has been proven to have the ability to sustain adhesion and differentiation of bone cells.

The results of this study concurred with the experiment done by Bee Tin Go *et al.* in 2015.[16] Their experiment in human found that from histological sections, the PCL scaffold could remain in the socket as late as 6 months.[16] Nonetheless, a prolonged period of degradation may adversely affect and delay the bone healing process.[16] According to the animal study[6], in which the thickness of the DL-PCL scaffold used was only 1 mm and it took about 8 weeks for the scaffold to break down. The DL-PCL scaffold used in our study, on the other hand, had a much greater volume than that of an animal study, hence a more extensive period of degradation would be expected. This can be compatible with the experiment carried out in human by Bee Tin[16]. It was found that based on histological sections, the PCL scaffold could remain in the socket for up to 6 months. Consequently, the prolonged degradation of the DL-PCL scaffold led to a foreign body reaction that interfered with the wound healing process.

Evaluation of the physical characteristics of the impacted mandibular third molar socket after tooth removal revealed loss of alveolar bone in the distal and parts of buccal aspects of the mandibular second molar. These created a pathway of food debris and microorganisms intrusion into the bony cavity through the buccal and distal gingival crevice of the mandibular second molar through the pumping action of saliva. It should last up to 2-3 weeks after the operation before the periodontal tissue remodelling.[18] As a result, the foreign body, along with the accumulation of microorganisms and food debris, further interferes with the natural wound healing process by triggering the inflammatory response and increasing the risk of infection.

There were 5 surgical sites, 4 in the DL-PCL group and 1 in the control group, showing evidence of minor infection, which accounted for 10.9 % of the infection rate. Besides, the consequence of the aforementioned, the primary closure of the surgical wound following removal of impacted mandibular third molar compared to the secondary closure, demonstrated a relatively increased incidence of post-operative infection.[19]

Nevertheless, the hyperdensity sign in the middle of the socket was only detected in 2 out of 19 in the DL-PCL group, accounting for 10.5%, but it was absent from the control group. It may represent the formation of new bones.

This pattern was also observed in the histological sections of the preceding animal study.[6] A new bone formation in the middle of the socket did not occur at the beginning of healing process, but instead, it took place on the surface of the socket wall. It could be assumed that new bone formation in the middle of the extraction socket was attributed to the osteoconductive property of the scaffold. Interestingly, despite less bone formation, the DL-PCL group had lower pain scores compared to the control group. Although there was no scientific explanation for this incidence, it could be implied that the DL-PCL scaffold did not induce tissue reaction.

The assessment of bone gain in the study used CBCT with high spatial resolution. Nevertheless, it cannot display the Hounsfield Unit (HU) as the multi-slice CT.[20] Consequently, the quantitative measurement of immature bone formation was difficult to obtain. With the two-month period after the surgery, CBCT might not be able to show slightly ossified new bone; however, due to the limitation of recalling the subjects, longer follow-up period was not possible. The gold standard for assessing the effect of scaffold on bone formation is the histological section, which could bot be achieved by our research design.

In the future study, to evaluate the efficacy of the scaffold, one should include fabrication of rapid degradation- DL-PCL scaffold and the histological section which could be a useful method to accurately assess the new bone formation. Even though it was proven that DL-PCL scaffold was biocompatible and degradable in the human body, the current study design did not represent the osteoconductivity of the scaffold in a bony, critical-size defect. Therefore, in further clinical trials, the use of a composite scaffold comprising an autologous material and a DL-PCL scaffold, to reduce the volume of the harvested bone, could be investigated for its capability of osteoconduction for bony, critical-size defect.

Conclusion

It can be concluded that the use of DL-PCL scaffold as a socket filling material is still questionable within the two-month follow-up period. Although the findings did not show benefits for new bone formation, the DL-PCL scaffold is undoubtedly compatible with the human body within the two-month observation period.

Acknowledgement

This study was supported by the 2012 Research Chair Grant from the National Science and Technology Development Agency (NSTDA).

References

1. Murphy CM, O'Brien FJ, Little DG, Schindeler A. Cell-scaffold interactions in the bone tissue engineering triad. ***Eur Cell Mater*** 2013;26:120-32.

2. O'brien FJ. Biomaterials & scaffolds for tissue engineering. ***Materialstoday***. 2011;14(3):88-95.

3. Wan DC, Nacamuli RP, Longaker MT. Craniofacial bone tissue engineering. ***Dent Clin North Am*** 2006;50(2):175-90.

4. Hutmacher DW. Scaffolds in tissue engineering bone and cartilage. ***Biomaterials*** 2000;21(24):2529-43.

5. Thadavirul N, Pavasant P, Supaphol P. Development of polycaprolactone porous scaffolds by combining solvent casting, particulate leaching, and polymer leaching techniques for bone tissue engineering. ***J Biomed Mater Res A*** 2014;102(10):3379-92.

6. Aksorn P, Chaikiawkeaw D, Sastravaha P, Supaphol P, Pavasant P. Osteoconductivity evaluation of 3-dimensional dual-leached polycaprolactone scaffold. ***J Dent Assoc Thai*** 2021;71(4):283-91.

7. Pillai C, Sharma C. Review Paper: Absorbable Polymeric Surgical Sutures: Chemistry, Production, Properties, Biodegradability, and Performance. ***J Biomater Appl***. 2010;25(4):291-366.

8. Azimi B, Nourpanah P, Rabiee M, Arbab S. Poly (Є-caprolactone) Fiber: An Overview. ***J Eng Fibers Fabr***. 2014;9(3):155892501400900.

9. Yang X, Wang Y, Zhou Y, Chen J, Wan Q. The Application of Polycaprolactone in Three-Dimensional Printing Scaffolds for Bone Tissue Engineering. ***Polymers***. 2021;13(16):2754.

10. Teoh S, Goh B, Lim J. Three-Dimensional Printed Polycaprolactone Scaffolds for Bone Regeneration Success and Future Perspective. ***Tissue Eng Part A***. 2019;25(13-14):931-935.

11. Williamson M, Chang H, Coombes A. Gravity spun polycaprolactone fibres: controlling release of a hydrophilic macromolecule (ovalbumin) and a lipophilic drug (progesterone). ***Biomaterials***. 2004;25(20):5053-5060.

12. Cui X, Abdullah A, Lee J, Kang H, Lee D. Controlled Release of Antibiotics from Air Jet Spun Polycaprolactone Scaffolds. ***Sci Adv Mater***. 2017;9(9):1533-1539.
13. Chang H, Lau Y, Yan C, Coombes A. Controlled release of an antibiotic, gentamicin sulphate, from gravity spun polycaprolactone fibers. ***J Biomed Mater Res A***. 2008;84A(1):230-237.
14. Miner MR, Berzins DW, Bahcall JK. A comparison of thermal properties between gutta-percha and a synthetic polymer based root canal filling material (Resilon). ***J Endod*** 2006;32(7):683-6.
15. Kim JJ, Bae WJ, Kim JM, Kim JJ, Lee EJ, Kim HW, *et al.* Mineralized polycaprolactone nanofibrous matrix for odontogenesis of human dental pulp cells. ***J Biomater Appl*** 2014;28(7):1069-78.
16. Goh BT, Teh LY, Tan DB, Zhang Z, Teoh SH. Novel 3D polycaprolactone scaffold for ridge preservation--a pilot randomised controlled clinical trial. ***Clin Oral Implants Res*** 2015;26(3):271-7.
17. Mantovani E, Arduino PG, Schierano G, Ferrero L, Gallesio G, Mozzati M, *et al*. A split-mouth randomized clinical trial to evaluate the performance of piezosurgery compared with traditional technique in lower wisdom tooth removal. ***J Oral Maxillofac Surg*** 2014;72(10):1890-7.
18. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. ***Nature*** 2008;453(7193):314-21.
19. Carrasco-Labra A, Brignardello-Petersen R, Yanine N, Araya I, Guyatt G. Secondary versus primary closure techniques for the prevention of postoperative complications following removal of impacted mandibular third molars: a systematic review and meta-analysis of randomized controlled trials. ***J Oral Maxillofac*** Surg 2012;70(8):e441-57.
20. Cassetta M, Stefanelli LV, Pacifici A, Pacifici L, Barbato E. How Accurate Is CBCT in Measuring Bone Density? A Comparative CBCT-CT *In Vitro* Study. ***Clin Implant Dent Relat Res*** 2014;16(4):471-8.