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Original Article

Pure type-1 collagen application to third molar extraction socket reduces postoperative pain score and duration and promotes socket bone healing

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KEYWORDS
Pure type-1 collagen;
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Socket bone healing

Background/Purpose: Extraction of the third molar may cause post-operative complications. This study assessed whether application of pure type-1 collagen to the third molar extraction socket can reduce post-operative pain score and duration and promote socket bone healing.
Methods: Fourteen patients who underwent 20 bilateral and symmetric third molar extractions were included in this study. After two tooth extractions at two different occasions in the same patient, one socket was filled with pure type-1 collagen (experimental group, n = 20) and the other socket received nothing but the blood clot (control group, n = 20). The post-operative pain score and duration, mouth-opening limitation, and the bone density at the socket site were assessed at weeks 1, 2, 4, and 8 after tooth extraction.
Results: Patients in the experimental group had a significantly lower mean post-operative pain score (2.6 ± 1.2) than patients in the control group (4.7 ± 2.0), and had a significantly shorter post-operative pain duration (2.7 ± 1.4 days) than patients in the control group (3.7 ± 1.8 days). We also observed a significantly lower frequency of mouth-opening limitation in 20 experimental-group patients (45%) than in 20 control-group patients (90%, $P = 0.007$). Moreover, a significantly higher mineralization ratio (10.2%) was found in the experimental socket site than in the control socket site.
Conclusion: Application of pure type-1 collagen to the third molar extraction socket can reduce post-operative pain score and duration, decrease the frequency of mouth-opening limitation, and increase mineralization ratio at the extraction socket site.

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Introduction

Extraction of the third molar is a regular practice for oral and maxillofacial surgeons. The patient's comfort during surgery and post-operative complications are perennial concerns. Complications such as pain, swelling, and trismus influence the patient's quality of life. Therefore, it is crucial for us to decrease the post-extraction complications and improve the third molar extraction socket healing by using a simple method. Many treatment modalities have been proposed for the reduction of post-operative pain, one of which is pre-medication before surgery.[1,2]

Some researchers have mentioned that application of antimicrobials, antifibrinolytics, and anti-inflammatory medications to the tooth extraction sockets can reduce post-operative complication rates.[1,2] The materials such as hydroxyapatite, beta-tricalcium phosphate, polylactide sponge, and Bio-Oss provide different outcomes for the alveolar ridge preservation. However, none of the materials have been identified to be consistently beneficial for the alveolar ridge preservation.[3–7] Studies have been conducted on intra-socket management with different materials, and the results have shown that inserting proper materials is more effective than allowing natural healing of the sockets.[8–11] Notably, systemic studies of ridge preservation following tooth extraction have reported a 59% and 109% reductions of the horizontal and vertical ridge loss, respectively, after management of the tooth extraction sockets.[7]

Because histological results suggest a delay in bone regeneration at the grafting sites without inflammation, the appropriateness of inserting materials into the extraction sockets has been considered questionable. It has been shown that the amount of new bone formation at the grafted sites with bovine bone mineral particles is equal to that at the ungrafted sites.[10] Grafting with bovine bone mineral particles has been shown to delay bone degeneration and even to result in a complete absence of resorption of the grafted materials. This implies that the bone formation rate is slower at the grafted sites than at the ungrafted sites.[12–14] This was the main reason why we further investigated whether insertion of pure type-1 collagen into tooth extraction socket is necessary or not.

Filling of the type-1 collagens in the post-extraction socket helps reduce complications via the new granulation tissue formation, blood clot stabilization, and wound protection. Blood clots act as scaffolds for angiogenesis and fibrous tissue growth in the extraction sockets.[15] The stabilization and maintenance of blood clots during the healing period can prevent complications caused by infection and inflammation. Many systemic and local administration methods for preventing blood clot dislodgement have been proposed. However, local administration in the socket wound provides a higher local concentration of drug or material and fewer systemic side effects on the entire human body.[1,2] Consequently, inserting the pure type-1 collagen into the post-extraction socket can reduce the possibility of infection and inflammation.

Ridge preservation is technique-sensitive and is not always successful, with the outcome depending on the surgical skills involved in the management of wounds using different materials.[16,17] The type-1 collagen plug is the least complex filling material that can be used for management of alveolar ridge preservation. The pure type-1 collagen plug, SurgiAid (Maxigen Biotec Inc., Taoyuan, Taiwan), has sufficient porosity for post-operative blood penetration and promotes socket wound healing by stabilizing the blood clot in the extraction socket, covering the extraction socket, and forming new granulation tissue. Therefore, there is an increased trend to put the pure type-1 collagen into the socket after tooth extraction. The purpose of this study was to assess whether application of pure type-1 collagen to the third molar extraction socket can reduce post-operative pain score and duration and promote socket bone healing.

Material and methods

This study was approved by Research Ethics Committee B of National Taiwan University Hospital (approval number: 20101100IRB). This retrospective study enrolled 14 patients (5 males and 9 females; mean age, 22.5 years; age range, 18—30 years) who received mandibular and/or maxillary third molar extraction surgeries for orthodontic reasons from December 21, 2010 to December 20, 2011 at the Department of Oral and Maxillofacial Surgery, National Taiwan University Hospital. Patients were excluded from the study if they were pregnant or had diabetes mellitus, hypertension, compromised immune system or other systemic diseases. Each patient signed the informed consent form before entering the study. The clinical parameters and pocket depths were recorded.[18–20] Of these 14 patients, 8 underwent bilateral and symmetrical mandibular third molar extractions and 6 underwent bilateral and symmetrical mandibular and maxillary third molar extractions. Only one patient suffered from cellulitis due to poor oral hygiene, but he recovered after appropriate antibiotic treatment. The bilateral and symmetrical third molar extractions were performed at two different occasions with one tooth extraction at each occasion. Radiographic data were also recorded; 9 patients with post-operative follow-up radiographs of the bilateral and symmetrical third molar extraction sites were analyzed using a generalized estimating equation model.

Presurgical treatment

At the first visit, periapical radiographies of the third molars were taken, probing depths at the disto-buccal line-

angle of the second molars were recorded, and questionnaire responses were assessed for all patients receiving third molar extractions. Panoramic radiographs were also taken to record the bilateral third molar impaction sites at the same level according to Pell and Gregory A, B and C classification of third molar impactions.[19]

Extraction surgery

Disinfection and draping were performed as usual. Surgical procedure was done under block anesthesia with the 2% lidocaine. Full thickness flaps were reflected from the distal marginal gingiva of the second molar to the distal side of the impacted third molar. Buccal cortical bone plate and third molar crown were removed by the hand piece bur technique. The third molar tooth roots were extracted with an elevator. Irregular buccal cortical plate was ground by a bone file. Pure type-1 collagen was inserted into the extraction tooth socket and a blood clot was formed around the inserted type 1 collagen fibers. The extraction wound was then sutured with silks. The bilateral and symmetrical third molar extractions were carried out at two different occasions with one tooth extraction at each occasion. A randomized clinical trial was conducted, with one extraction socket being filled with pure type-1 collagen (experimental group) and the other extraction socket being filled with nothing but the natural blood clot (control group) in the same patient. The selection of extraction socket site for filling with pure type-1 collagen or not was blind to each patient.

Wound observation

A follow-up clinical and radiographic examination of the extraction socket sites was performed at 1, 2, 4, and 8 weeks after the third molar extractions.

Measurement of bone deposition

Standardized periapical digital radiographs were taken with the periapical film placed parallel to the second molar using an Instrumentarium Focus periapical X-ray machine (Palodex Group Oy, Tuusula, Finland) to evaluate the changes in the bone density of the extraction socket site. The x-ray beam was directed perpendicularly to the second molar. The entire socket image should be visible on each radiograph. All radiographs were taken by the same experienced radiologist.

Image analysis

First, the ImageJ image analytics program was used to measure the bone density. The extraction socket area was divided into 3 parts: the cervical region of newly formed bone (RNFB-C), the middle region of newly formed bone (RNFB-M), and the apical region of newly formed bone (RNFB-A). Second, healthy bone was determined as the natural bone area (NBA), and air was determined as the background (BA). Third, a 2500-pixel square image was selected from each position. ImageJ was used to produce 3 sets of image information for each position to determine the mean value of the target position (i.e., RNFB-C, RNFB-M, RNFB-A, NBA, and BA) (Fig. 1).

The equation for the region of newly formed bone density was RNFB (%) = (RNFB − BA) × 100%/(NBA − BA). This equation not only eliminated contrast interference in the data for each image but also enabled quantization of the measurement area.[21] Cone beam computed tomography (CBCT) provided inconsistent Hounsfield unit values, necessitating an additional equation for re-adjusting the pixel number. Even with an applicable equation, retrospective investigation with both multiple-row detector computed tomography (MDCT) and CBCT results must be compared and converted for each patient. However, the radiation dose for both MDCT and CBCT for a single follow-up examination for each patient may contravene regulations for avoiding acute late-onset encephalopathy after radiation.[22] Therefore, an easier and safer method for the follow-up of alveolar bone healing at the extraction socket site by using periapical radiographic evaluation, developed by Celio-Mariano et al., was adopted in the present study.[21] Digital periapical radiographic examination, using the paralleling technique, was performed by an experienced radiologist for all patients. The Instrumentarium Focus periapical X-ray machine (Palodex Group Oy) was employed, with a cone length of 12 inches, exposure time of 0.32 s, voltage of 70 kV, and amplitude of 7 mA. Size 2 digital X-ray film was scanned using the Air Techniques ScanX digital imaging system with an in-line eraser (Air Techniques, New York City, NY, USA).

Statistical analysis

The generalized estimating equation (GEE) model was used to estimate the effect of interaction between type-1 collagen insertion and the post-operation period on the region of newly formed bone density. Paired *t*-tests, Wilcoxon

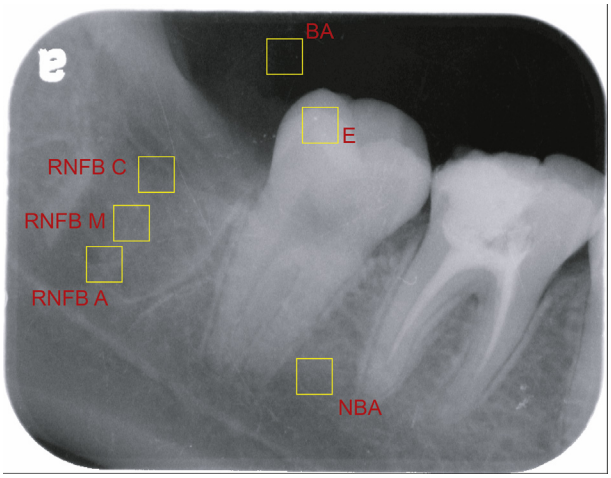

Figure 1 Choosing an adequate periapical radiograph and determining the measurement target areas: the cervical region of newly formed bone (RNFB-C), the middle region of newly formed bone (RNFB-M), the apical region of newly formed bone (RNFB-A), healthy bone as the natural bone area (NBA), and air as the background (BA). Enamel and other restoration material as the (E) were not set in the target area due to the different conditions of filling of tooth structure.

signed-rank tests, McNemar's tests, and generalized McNemar's tests (Stuart–Maxwell tests) were used to estimate each post-operative parameter. Statistical analysis was performed using SAS Version 9.2 (SAS Institute, Cary, NC, USA).

Results

In this study, the clinical and radiographic data of 14 patients including 8 patients who underwent bilateral and symmetrical mandibular third molar extractions and 6 patients who had bilateral and symmetrical mandibular and maxillary third molar extractions were analyzed and presented.

Analysis of bone density

In the GEE model, consideration was given to the effect of interaction between type-1 collagen insertion and the post-operation period on the region of newly formed bone density. After controlling the effect of the post-operation period on the region of newly formed bone density, we found that the experimental socket site with type-1 collagen insertion had significantly higher bone mineralization ratio than the control socket site without type-1 collagen insertion (parameter estimation, PE = 10.2%; standard error, SE = 2.7, $P = 0.0001$, Table 1, Figs. 2 and 3).

After controlling the impact factor of type-1 collagen insertion, we discovered a significantly larger region of newly formed bone density at the post-operation time point of week 4 than week 1 (PE = 9.6%, SE = 1.1, $P < 0.0001$, Table 1) as well as at the post-operation time point of week 8 than week 1 (PE = 9.2%, SE = 2.2, $P < 0.0001$, Table 1).

Analyses of post-operation parameter

Regarding the post-operative pain score and duration at the post-operation time point of week 1, we found that patients in the experimental group (with type-1 collagen insertion into the extraction socket) had a significantly lower mean pain score (2.6 ± 1.2) than patients in the control group (without type-1 collagen insertion into the extraction socket, 4.7 ± 2.0), and had a significantly shorter post-operative pain duration (2.7 ± 1.4 days) than patients in the control group (3.7 ± 1.8 days) (Table 2).[18–20] Regarding the frequency of occurrence of post-operative mouth-opening limitation at the follow-up week 1, we observed a significantly lower frequency of mouth-opening limitation in patients in the experimental group (45%) than in patients in the control group (90%, $P = 0.007$, McNemar's test, Table 2). Regarding the operation-induced pain and extraction force during surgery, we also showed a significantly greater frequency of no pain or no pressure at the

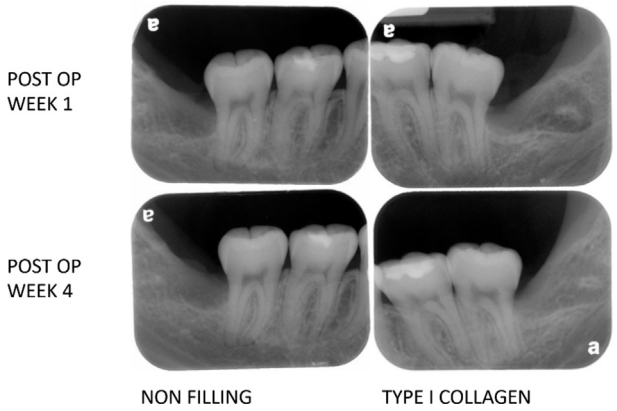

Figure 2 The third molar extraction sockets with insertion of pure type-1 collagen showed a higher bone mineralization ratio than the control third molar extraction sockets without insertion of pure type-1 collagen. In addition, the bone mineralization ratio was higher at the post-operation week 4 than at the post-operation week 1.

Table 1 Generalized estimating equation model results for dressing (pure type 1 collagen) insertion according to different post-operation time points.

Independent variable	Parameter estimation[a]	Standard error	95% confidence interval	*P*-value
Intercept[b]	81.5	3.6	(74.5, 88.5)	<0.0001
Dressing insertion				
Exp: Type-1 collagen	10.2	2.7	(5.0, 15.4)	0.0001
Con: without dressing	Reference	–	–	
Post-operation time point				
Week 1	Reference	–	–	
Week 2	1.5	1.9	(−2.2, 5.2)	0.416
Week 4	9.6	1.1	(7.6, 11.7)	<0.0001
Week 8	9.2	2.2	(4.9, 13.6)	<0.0001
Dressing insertion × post-operation time point				
Exp vs. Con, week 1	Reference	–	–	
Exp vs. Con, week 2	1.0	2.0	(−2.9, 4.9)	0.615
Exp vs. Con, week 4	−3.3	2.1	(−7.4, 0.7)	0.109
Exp vs. Con, week 8	−1.9	2.8	(−7.5, 3.7)	0.507

Exp: Experimental group had pure type-1 collagen insertion in the extraction socket.
Con: Control group had nothing but the natural blood clot in the extraction socket.
[a] Parameter estimation after adjusting for other factors, mean deviation of nominal to reference on region of newly formed bone (RNFB) (%).
[b] Intercept represents control, week 1 average of RNFB (%).

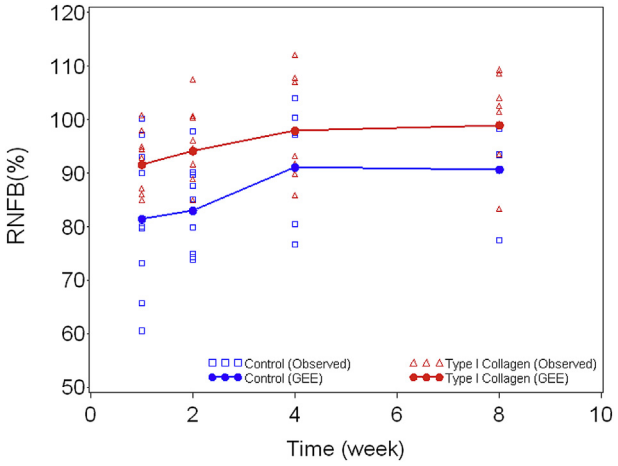

Figure 3 A scatter diagram combined with a trend chart of regions of newly formed bone (RNFB) (%) at the different time points. The RNFB (%) exhibits better results at the experimental sites than the control sites.

experimental site (65% or 60%, respectively) than the control site (15.0% or 25.0%, respectively; $P = 0.004$ or $P = 0.035$, respectively, generalized McNemar's test, Table 2). The results of operation-induced pain and extraction force were in agreement with those of the post-operative pain score, pain duration, and mouth-opening limitation, indicating an intimate association between superior wound dressing with pure type-1 collagen and better operation experience. Operation-induced pain and extraction force during surgery might correlate with post-operative pain score, pain duration, and mouth-opening limitation. Because the first follow-up time point was one week after surgery and questionnaire responses were assessed. Patient's questionnaire choice might have correlation between post-operative parameters (pain score, pain duration, and mouth-opening limitation) and operation experience (operation-induced pain and extraction force).

Analysis of pocket depth

Pocket depth was recorded at the disto-buccal line-angle of the second molar at the pre-operation time point and weeks 1, 2, 4, and 8 after third molar extraction.[18–20] We found that the mean pocket depth was shallower at the experimental site (7.1 ± 3.1 mm, 5.7 ± 3.7 mm, and 3.2 ± 1.6 mm, respectively) than the control site (7.6 ± 2.8 mm, 6.6 ± 2.7 mm, and 3.6 ± 1.7 mm, respectively) at week 1, week 2, and week 8 (all P-values > 0.05, paired t-test, Table 3), the differences were not significant.

Discussion

Many types of graft materials have been used to fill the extraction sockets or bone defects to promote the bone healing and reduce the post-operative complications. It has been proven over the course of innumerable studies starting in the 1990s that the hyaluronic acid and fibronectin within collagen can influence the collagen morphology and inter-channel connection and it is better to use the collagen fibers rather than collagen fibrils for filling the extraction socket to obtain a better socket bone healing.[23] Although collagens with hyaluronic acid or fibronectin generally can achieve a favorable fibroblast in-growth rate within 6, 9 and 12 days of observation, collagen fibers alone also have an equal fibroblast in-growth rate.[23] This study showed that application of pure type-1 collagen to the third molar extraction socket can also provide a superior biocompatible environment for the socket bone healing.

Type-1 collagen may diminish inflammation of extraction sockets and thus reduce the post-extraction complications, especially the post-operative socket site infection, alveolar

Table 2 Summary of each post-operative parameter.

		Experimental group	Control group	Exp - Con	P-value
		n = 20	n = 20		
Post-operative	Mean ± SD	2.6 ± 1.2	4.7 ± 2.0	−2.1 ± 1.8	<0.0001[a]
pain score	Median	2	5	−3	<0.0001[b]
Post-operative	Mean ± SD	2.7 ± 1.4	3.7 ± 1.8	−1.0 ± 2.0	0.035[a]
Pain duration	Median	2	3	−1	0.056[b]
Limitation of mouth-opening	Yes	9 (45.0%)	18 (90.0%)		0.007[c]
	No	11 (55.0%)	2 (10.0%)		
Operation-induced pain	No pain	13 (65.0%)	3 (15.0%)		0.004[d]
	Mild pain	7 (35.0%)	14 (70.0%)		
	Severe pain	0 (100.0%)	3 (15.0%)		
Extraction force	No pressure	12 (60.0%)	5 (25.0%)		0.035[d]
	Mild pressure	8 (40.0%)	13 (65.0%)		
	Severe pressure	0 (100.0%)	2 (10.0%)		

Exp: Experimental group had pure type-1 collagen insertion in the extraction socket.
Con: Control group had nothing but the natural blood clot in the extraction socket.
[a] Paired t-test.
[b] Wilcoxon signed-rank test.
[c] McNemar's test.
[d] Generalized McNemar's test (Stuart-Maxwell test).

Table 3 Pocket depth of disto-buccal line-angle of the second molar.

Time	Experimental group	Control group	Exp−Con	*P*-Value
Pre OP	N = 20	N = 20		
Average ± SD	3.6 ± 1.5	4.1 ± 1.6	−0.5 ± 2.4	0.321
Week 1				
Average ± SD	7.1 ± 3.1	7.6 ± 2.8	−0.5 ± 3.3	0.547
Week 2				
Average ± SD	5.7 ± 3.7	6.6 ± 2.6	−0.9 ± 2.9	0.390
Week 4				
Average ± SD	4.4 ± 2.1	3.4 ± 1.5	1.0 ± 2.3	0.264
Week 8				
Average ± SD	3.2 ± 1.6	3.6 ± 1.7	−0.4 ± 1.1	0.477

Paired *t*-test.
SD: Standard deviation.

osteitis, and hematoma.[15] In this study, detailed parameters such as post-operative pain score and duration, mouth-opening limitation, operation-induced pain, and extraction force during surgery were measured and compared between the patients in the experimental and control groups and between two different post-operation time points. We found that insertion of pure type-1 collagen to the third molar extraction socket could reduce post-operative pain score and duration, decrease the frequency of mouth-opening limitation, and increase mineralization ratio at the extraction socket site. Our findings indicate that insertion of pure type-1 collagen to the tooth extraction socket has the advantage of promoting socket bone healing and is better than leaving the extraction socket filled with nothing but the natural blood clot. Other studies also used the radiographic scoring system and criteria as tools for evaluating the grade of bone regeneration in the bone defects.[24,25] Moreover, using the ImageJ analytic program as a bone density detector provides additional objective information on evaluation of bone regeneration in the third molar extraction sockets.[21]

Bio-Oss collagen provides favorable results of bone regeneration in the Le Fort-I osteotomy model.[26] In fact, one previous study has shown that enamel matrix derivatives and Bio-Oss collagen provide an equal bone regeneration effect.[27] However, Heberer et al. claimed that insertion of Bio-Oss collagens into the extraction socket retards bone formation but does not increase any risk of inflammation at the extraction socket site. Bone regeneration occurs within all extraction sockets regardless of whether grafting materials are added to the socket or not.[10,28] However, in this study, pure type-1 collagen alone reduced inflammation during the bone healing process, and improved mineralization of bone was also observed at the extraction socket site grafted with pure type-1 collagen. Therefore, the notion that addition of bone substitute to the collagen composition may retard bone formation remains controversial. One of our major concerns during the study was ensuring the least amount of discomfort for each patient. Thus, in this study only pure type-1 collagen was inserted into the extraction socket to promote bone regeneration and increase bone density at the extraction socket site, reduce post-operative pain score and pain duration, and decrease the frequency of mouth-opening limitation in patients in the experimental group.

However, only the bilateral mandible third molar extraction model can provide favorable bone regeneration results without the need of a reentry for obtaining socket bone specimens for histological confirmation. Our study revealed that pure type-1 collagen had a good biocompatibility and can be used to fill an extraction socket without the necessity of reentry concerns.

Due to symmetrical mandibular and maxillary third molar extraction model were conducted. Position level of third molars within experimental group and control group possessed the same difficulty and time-consuming of surgery for the experienced surgeon. Therefore, extraction time factor was not considered within this study.

The findings of this study indicate that implantation of pure type-1 collagen into the extraction sockets can ensure a high quality of life following surgery by relieving post-operative pain, shortening post-operative pain duration, reducing the frequency of mouth-opening limitations, and promoting socket bone healing. The results of this investigation should inspire clinical dentists' efforts in ensuring the post-extraction quality of life in patients receiving tooth extraction. Insertion of pure type-1 collagen into the extraction sockets has the advantages of reducing the unfavorable complications and promoting socket bone healing. Thus, the pure type-1 collagen has a high potential to be used as a routine material for insertion into the socket after tooth extraction. In addition, insertion of pure type-1 collagen into the extraction socket may act as a routine procedure for pre-implantation alveolar bone preparation and post-extraction socket care.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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