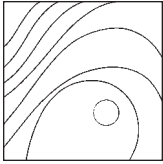


A Prospective, Randomized, Controlled, Multicenter Evaluation of Extraction Socket Management Comparing a Wound Dressing and a Soft Tissue Substitute



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Postextraction bone grafting and implant placement help preserve alveolar bone volume. Collagen wound dressings and soft tissue graft substitutes may help protect extraction socket bone grafts and provide better gingival contours. This randomized, controlled, multicenter, and double-blinded study was conducted to compare a control (wound dressing) and a test (soft tissue graft) substitute in nearly intact extraction sockets. Both test and control sockets were grafted with a xenogeneic bone graft. Graft containment, extraction socket soft tissue gap closure, gingival contour, and gingival thickness were examined over 16 weeks, at which time implants were placed. Healing was uneventful for both groups, and there was no significant difference ($P < .05$) between the times required to close the extraction socket soft tissue gap (~80% of sites closed by 8 weeks). Bone grafts were covered and contained longer in the test group (~4 weeks vs ~2 weeks), with less contour disruption out to 4 weeks; however, at implant placement, soft tissue contours in both groups were comparable, and soft tissue thicknesses were not significantly different. *Int J Periodontics Restorative Dent* 2022;42:e161–e174. doi: 10.11607/prd.6124

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Table 1 Study Visits and Duration

Screening/surgery	Posttreatment follow-ups						
Visits 0/1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (final)
Screening measures (visit 0) were made within 30 days before extraction, including immediately before extraction (visit 1).	3 d ± 1 d	1 wk ± 1 d	2 wk ± 2 d	3 wk ± 2 d	4 wk ± 2 d	8 wk ± 5 d	16 wk ± 5 d (implant placement)

Baseline measurements occurred at either visit 0 or visit 1.

Sufficient oral bony ridge volume is essential for implant support. Following tooth extraction, remodeling and loss of the bony ridge volume are common.^{1,2} Although bone grafting and implant placement can help preserve bone volume, soft tissue volume loss and associated gingival contour changes can present esthetic challenges at restoration, particularly for anterior teeth.³⁻⁵

Bone grafting has been shown to be a predictable method for forming and preserving bone volume in and around extraction sockets prior to implant placement (ie, ridge preservation).⁶⁻⁸ If soft tissue augmentation is desired, harvest grafts (free gingival or connective tissue grafts) may be employed, but these grafts are time-consuming to harvest, are in limited supply, and are associated with patient morbidity. Hemostatic collagen sponges are promoted as coagulum stabilizers to protect extraction socket healing; recently, harvest graft substitutes have become available and are promoted as protective, hemostatic agents, and they provide longer-term containment and protection of bone grafts, promote soft tissue closure over bone grafts,

and maintain soft tissue thickness and dimension.⁹⁻¹¹

For ridge augmentation following extraction, the BioCol technique as described by Sclar⁹ utilizes a xenogeneic, particulate bone graft material (Bio-Oss Collagen [BOC], Geistlich) covered with a hemostatic collagen plug or collagen tape (Helistat [CPlug], Integra Miltex). In order to preserve soft tissue volume and contour, Jung et al¹⁰ and Thoma et al¹¹ have shown that a xenogeneic collagen matrix (a harvest graft substitute; Mucograft Seal [XCM], Geistlich) performs as well as a free gingival graft.

Accordingly, the present study was designed to compare extraction socket management using the BOC bone graft covered with either CPlug (control) or XCM (test) in order to compare graft containment and soft tissue management for the two biomaterials. The null hypothesis was that the hazard rate (assumed to be constant across all study intervals) was identical in the two groups.

Materials and Methods

A study protocol was established and approved by an internal re-

view board (Advarra, Columbia, Maryland). Using in-person visits and/or group teleconferences, all investigators, geographic location coordinators, blinded office examiners, and blinded evaluators were trained in study protocol and assessments. All investigators and clinical staff were trained in Human Research Participant Protection and Good Clinical Practices. The study was registered under clinicaltrials.gov (NCT03003819). Patients who met inclusion and exclusion criteria signed informed consent forms and were enrolled, treated with tooth extraction and biomaterial placement, and exited from the study after 4 months, immediately before implant placement.

Study Endpoints and Measures

The primary study outcome evaluated was soft tissue wound healing as measured by (1) extraction socket soft tissue gap closure in the buccolingual and mesiodistal dimensions, and (2) graft containment of loose granules, as observed by blinded examiners and reported by patients at each office

Table 2 Study Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Aged 18 to 75 y	Known allergy or sensitivity to collagen
Indicated for anterior (premolar to premolar) tooth extraction intended for implant placement	Taking intramuscular or intravenous bisphosphonates
Nearly intact extraction sockets (bony dehiscences less than one-third the depth and mesiodistal width of the socket)	Women who are pregnant or lactating, or who intend to become pregnant during the study period
Read, understood, and signed an informed consent form approved by the institutional review board	Acute, suppurative lesions with pain and swelling, and apical lesions > 5 mm are excluded (but antibiotic prophylaxis may be employed to reduce infection, possibly enabling the patient to be reconsidered for inclusion)
Able and willing to follow study procedures and instructions	Heavy smoking/tobacco habit (≥ 10 cigarettes or ≥ 4 cigars or ≥ 4 pipes per day)
	Participating in other clinical studies involving therapeutic intervention (either medical or dental)
	If the respective investigator determines the patient will be unable to complete the study per protocol
	Healing disorders (ie, diabetes mellitus, cancer, HIV, bone metabolic diseases) that could compromise wound healing and/or preclude implant surgery
	Those currently receiving (or within 2 months before study entry) systemic corticosteroids, immunosuppressive agents, radiation therapy, and/or chemotherapy, which could compromise wound healing and preclude periodontal surgery

visit (Table 1). Additionally, blinded evaluators (D.V. and C.R.) analyzed standardized photos taken at each visit to assess biomaterial integrity and socket healing tissue topography.

Secondary study outcome included: (1) soft tissue inflammation scores at all time points and (2) change in soft tissue thickness, measured by transparency (show-through of probes) before extraction and biopsy sample harvesting, prior to implant placement. Other/exploratory outcomes included: (1) time to complete the procedures, beginning immediately after BOC graft placement and ending when the last suture was tied, and

(2) keratinized tissue width (KTW), measured from the gingival margin to its apical extent (midline) prior to surgery, and from the lingual to buccal extent immediately before implant placement.

Control and Test Biomaterials

The particulate bone graft (BOC) is a combination of purified spongia (cancellous) natural bovine bone mineral granules and 10% collagen fibers in a block form. It is indicated for the filling of extraction sockets to enhance alveolar ridge preservation. CPlug (control) is a bovine collagen sponge used to

control bleeding and protect dental wounds. It is a cylindrical plug (3/8 inches wide by 3/4 inches long [9.7 × 19 mm]) designed to resorb within 10 to 14 days. XCM (test) is a porcine, bilayer collagen matrix for soft tissue regeneration used as a socket seal in extraction socket grafting. The outer layer is intended to provide a firm structure for anchoring sutures and limit exposure to the oral cavity. The inner layer is a spongy collagen mesh engineered to resemble the connective tissue structure of mucosa. The collagen structure is fragmented, providing a pathway for vascular ingrowth and the migration of fibroblasts and other soft tissue cell types critical to

regeneration of keratinized mucosa. It also serves as a clot stabilizer. The XCM (8-mm diameter and 2.5- to 5-mm thickness) is indicated for "localized ridge augmentation for later implantation."

Patient Participation

Two to four patients were treated per investigator. Table 2 lists the inclusion and exclusion criteria for this study. Eligible patients were enrolled, and medical and dental histories were collected, along with demographic and current medication information. An oral exam and dental cleaning or debridement were performed; duplicate, standardized photographs were taken; and oral hygiene procedures reviewed. Following resolution of any periodontal issues in the region of study, pre-surgical antibiotics (1 g amoxicillin) were administered 1 hour before surgery (allergy alternative: 300 mg clindamycin or azithromycin/Z-Pak). After administration of local anesthetic, baseline (screening; visit 0/1) soft tissue thickness was measured (Colorvue Biotype Probe System, Hu-Friedy), and minimally traumatic extractions were performed using periotomes, without raising flaps. Extraction socket dehiscence dimensions were recorded and compared with overall extraction socket dimensions to ensure that the sockets were essentially intact (ie, bony dehiscences were less than one-third of overall extraction socket dimensions). Patients with dehiscence dimensions of one-third or more of the bony wall were removed from

the study. All measures were performed by blinded evaluators using UNC-15 probes.

Surgical Procedures and Postoperative Maintenance

After extraction socket degranulation and BOC graft placement, control or test biomaterials were placed according to the manufacturers' surgical instructions. Biomaterials were pre-assigned according to a randomization scheme, with assignments (test or control) revealed immediately prior to biomaterial placement. Surrounding soft tissue margins were deepithelialized with a no. 8 round, coarse diamond bur, encouraging soft tissue cells to migrate from the soft tissue border into the biomaterials. Both test and control biomaterials were applied in a dry state. The control CPlug cylinder was cut to an appropriate length for soft tissue adaptation (ie, so that the top of the cylinder, when placed over the graft, was level with surrounding soft tissue). Both test and control biomaterials were adapted to surrounding soft tissue margins using 6-0 polypropylene sutures (Prolene Blue 18" P-3 Cutting, 13-mm 3/8 circle reverse cutting, Ethicon). XCM was adapted with a minimum of six single interrupted sutures at the midbuccal, midpalatal/midlingual, and distal and mesial aspects on the buccal and palatal/lingual surfaces. Because CPlug is more friable than XCM, optional cross-stitch suturing was employed at the discretion of the investigators. Suturing under the free gingival

margin helped keep the margin elevated and "sharp." Care was taken to not compress the biomaterials and to avoid impingements, such as flippers that might contact or crush the biomaterials.

Postsurgical instructions included the following: (1) chlorhexidine oral rinse (0.12%; bid) for the first 4 weeks ("bathing" the area only, not swishing); (2) no aggressive movements, disruptive foods, or trauma to the treated areas for the first 4 weeks; (3) not brushing the area for the first 2 weeks and then avoiding apically directed trauma; and (4) resuming normal tooth brushing after 4 weeks, and gradual resuming of normal chewing. Following surgery, amoxicillin (500 mg; bid) was prescribed for 5 to 7 days, ibuprofen (800 mg; tid) for 5 to 7 days, and chlorhexidine rinse (1/2 oz; bid) for 2 weeks. Alternatives for penicillin allergy were clindamycin (300 mg; qid) for 5 to 7 days or continuation of azithromycin/Z-Pak, if initiated before surgery.

Clinical Measurements

Soft tissue extraction socket dimensions (evaluated using UNC-15 probes), biomaterial integrity, and inflammation were recorded (Table 3). Standardized photos were taken before, during, and after the surgical procedure. The first follow-up visit occurred 3 days postsurgery, and inflammation, socket soft tissue gap, graft containment, and biomaterial integrity were clinically measured. Oral hygiene instructions were reviewed. Further follow-up

Table 3 Blinded-Examiner Biomaterial Integrity, Graft Containment, and Inflammation Assessments

	Score
Biomaterial integrity	
Biomaterial completely present, without any sign of fragmentation or degradation	0
Biomaterial somewhat degraded and/or fragmented	1
Some evidence of new tissue, but portions of biomaterial are still evident	2
New tissue and/or clot, but no biomaterial is evident	3
No evidence of biomaterial, complete granulation, or other tissues	4
Graft containment	
No graft particles observed and no report of graft particles by patient since previous visit	0
No graft particles observed, but patient reports graft particles since previous visit	1
Graft particles observed, and patient reports graft particles since previous visit	2
Inflammation	
Normal (absence of inflammation)	0
Mild inflammation of any portion of the gingival unit (slight changes in color)	1
Mild inflammation of entire gingival unit (but no edema)	2
Moderate inflammation (moderate glazing, redness, edema, and/or hypertrophy)	3
Severe inflammation (marked redness, edema/hypertrophy, spontaneous bleeding, and/or ulceration)	4

Table 4 Blinded-Examiner Biomaterial Integrity Assessments

	Score
Biomaterial completely absent/gone/lost, with immature tissue at an early time frame (fibrin or granulations tissue may be present with or without bone graft particles)	1
Biomaterial completely present	2
Biomaterial partially present with visible graft particles	3
Biomaterial partially present without visible graft particles	4
Biomaterial completely absent with mature tissues present (epithelialization complete), and the area is completely healed without visible graft particles	5

evaluations occurred at 1, 2, 3, 4, and 8 weeks postsurgery. Sutures were removed at 2 weeks. Changes in medications and adverse events were documented at each visit. Photos were taken of the extraction site, and the remaining socket soft tissue gap, graft containment, biomaterial integrity, and socket healing

were measured (Tables 3 to 5; Figs 1 and 2). At 4 and 8 weeks, teeth adjacent to the extraction treatment site were lightly debrided. KTW was measured at 8 weeks. Biomaterial integrity, graft containment, and inflammation were assessed at each follow-up visit (Table 3). Socket soft tissue gaps (in both mesiodistal

and buccolingual dimensions) were measured using a UNC-15 probe, rounding down to the nearest 0.5 mm. Any changes in medications or adverse events were noted, and oral hygiene procedures were reviewed at each visit.

At 16 weeks postsurgery, prior to implant placement, soft tissue

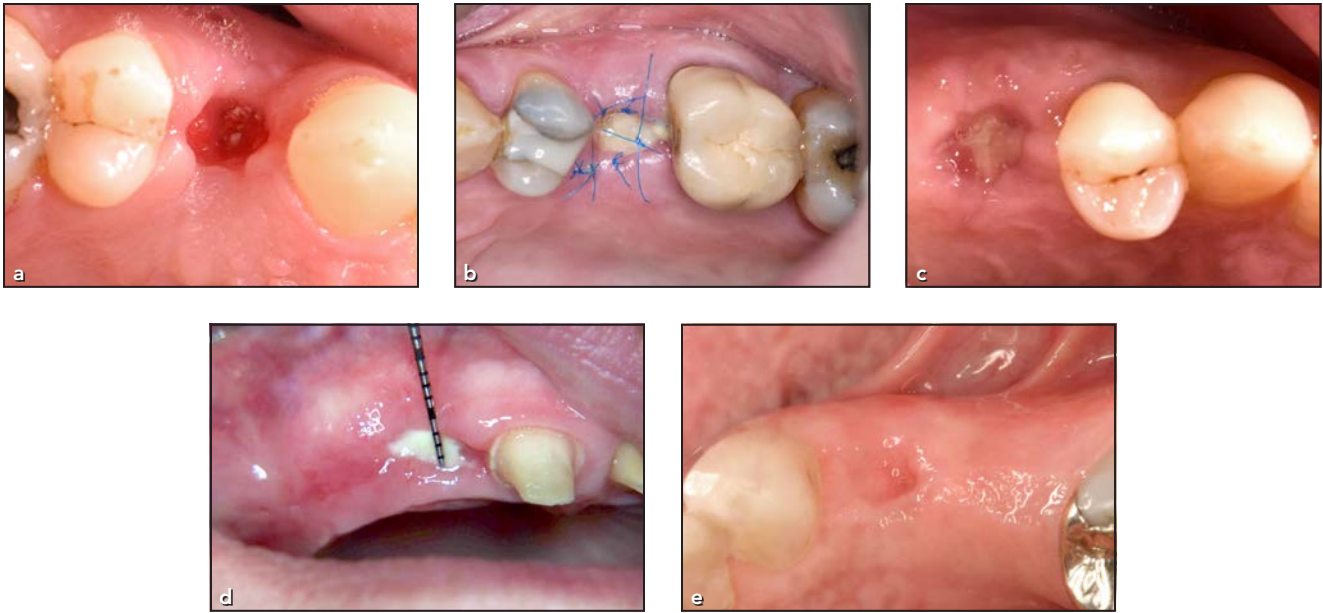


Fig 1 Biomaterial integrity assessment examples. (a) The biomaterial is absent, with only early clot/granulation present. (b) The biomaterial is completely present, with little to no sign of tissue integration or biomaterial degradation. (c) The biomaterial is partially present and there are particles of graft material visible. (d) The biomaterial is partially present, and there are no particles of graft material visible. (e) The biomaterial is completely absent, and mature tissue can be seen (epithelialization complete). The area is completely healed without visible graft particles.

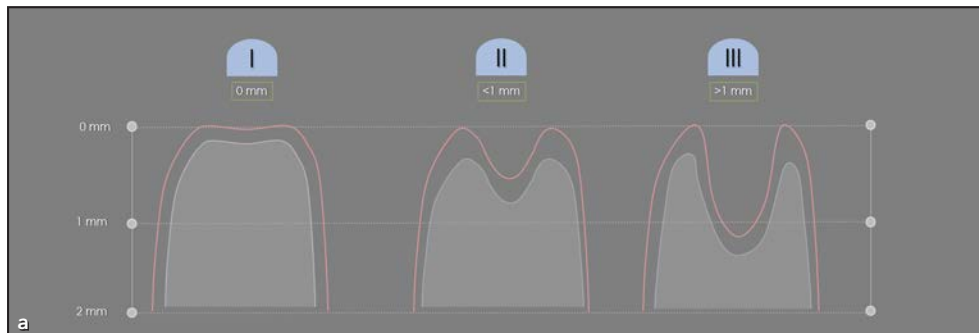


Fig 2 (a) Soft tissue topography designations showing clinical and schematic examples of (b) slight (I), (c) moderate (II), and (d) severe (III) tissue outline disruptions.

Table 5 Blinded Evaluators Socket Healing Assessment

	Score
Slight disruption of tissue outline. Disruption appears close to a 0-mm vertical discrepancy between the native gingival margin ridge and the newly formed soft tissue.	1
Moderate disruption of tissue outline. The healing outline is not completely seamless to adjacent native gingival tissue, and there is a vertical drop not extending further than 1 mm.	2
Severe disruption of tissue outlines associated with early loss of healing barrier material and loss of graft material concomitant with its frank exposure.	3

esthetics were evaluated in relation to the surrounding tissue. Texture was assessed using a gloved finger “feel” and rated as more, equal, or less firm; and color was rated as more, equal, or less red.^{12,13} Ease of soft tissue elevation for implant placement was also rated in comparison to nontreated gingival tissues. Standardized photos, periapical radiographs of the extraction site, and clinical measurements of the remaining socket soft tissue gap were obtained. Biomaterial integrity and inflammation were measured, and KTW was measured from the lingual to the buccal extent, over the middle of the healed extraction socket. Following local anesthetic, soft tissue thickness at the center of the extraction site was measured using a 3-mm biopsy punch. The biopsy punch was inserted and seated firmly against the underlying crestal bone. Using a 0.5-mm bur, the punch was scored at the coronal extent of the soft tissue at four aspects: mesial, distal, lingual, and buccal. After removing the punch, the soft tissue thickness dimensions were measured outside of the subject’s mouth using a boley gauge, rounding down to the nearest 0.5 mm.

Histologic Assessments

Four of the present authors who had experience with bone/soft tissue biopsy procedures (D.V., M.M., T.S., and C.R.) harvested core tissue samples from 10 consenting patients for histologic analysis. Soft tissue and bone core biopsy samples were harvested by first inserting the 3-mm biopsy punch, marking and recording the extent of the four soft tissue measures (as described above), then leaving soft tissue in place/attached; then, a 3-mm trephine was used for combined bone and soft tissue harvest. Biopsy samples were kept intact within trephines, wrapped with surgical gauze, stored in formalin, and then labeled and shipped for histologic analysis at the Center for Dental Research (Loma Linda University School of Dentistry). For further analysis, histologic slides were sent to the histology laboratory of Universidade Estadual de Maringá, Department of Dentistry. Morphometric dimensions were measured as follows:

- Supracrestal tissue width (w-SCT), measured from the outer surface of the gingival epithelium to a line parallel to

the epithelium that crossed the most coronal portion of the newly formed bone (bone crest level)

- Epithelium width (w-EP), measured from the outer surface of the gingival epithelium to the interface between the epithelium and the connective tissue
- Supracrestal connective tissue width (w-CNT), measured from the interface between the epithelium and the connective tissue and the bone crest level

All measurements were assessed in millimeters at three equidistant points on the histologic section ($\times 25$ magnification), perpendicular to the horizontal border between supra- and infracrestal compartments. Morphometric measurements were assessed using a point counting procedure, according to a method originally described by Schroeder and Münzel-Pedrazzoli.¹⁴ A lattice comprising 100 light points was superimposed over the supra- and infracrestal tissues presented in the biopsy sample to describe the percentages of the various newly formed tissues. Mean values and

standard deviations were calculated for each variable, patient, and experimental group.

Statistical Methods

Patients were block-randomized in a 1:1 ratio to establish a balanced number of test and control sites. Baseline analysis was used to determine whether the randomized groups were balanced. Continuous variables were evaluated with *t* tests, categorical variables with chi-squared analyses, and dichotomous variables with Fisher exact test.

The primary outcome (extraction socket soft tissue gap closure) was analyzed using survival analysis, which tested the null hypothesis that the hazard rate, which is assumed to be constant across all study intervals, was identical in the two groups. Power computation was based on a hazard ratio of 2.20. Specifically, it assumed instantaneous hazard rates of 0.05 for the control group and 0.11 for the test group. Because the hazard rate was constant across intervals, this was equivalent to median closure times of 13.86 days for the control group and 6.30 days for the test group. This was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantial importance. The power analysis was based on 30 subjects in each group, using alpha of .05 and power of 83%. The effect size was considered reasonable based on a previous extraction socket study

conducted by Scheyer et al.¹⁵ Note that the extraction sockets in the present study were not dehiscenced, as in the referenced study¹⁵; thus, extraction socket gap closure was expected to occur sooner.

Soft tissue gap size measured as a continuous outcome supposes that the mean gap size is different over time for the two groups. Therefore, repeated-measures analysis of variance was used with treatment group and time (after baseline) as main effects, examining interactions between the two effects. If the treatment group effects were significant ($P < .05$), it would indicate that the groups were different over time.

The intent-to-treat (ITT) population and safety population consisted of all subjects randomized into the trial. The per-protocol (PP) population consisted of all ITT subjects followed over 4 months. Efficacy analyses were conducted using the PP population. Baseline, procedure, and safety analyses were conducted using the ITT population.

Results

Between October 2016 and June 2017, all patients were entered into the study, treated, and exited from the study at 16 weeks (implant placement). In total, 49 patients (the ITT population) were randomized and treated at 14 different clinical practices: nine clinical practices treated 4 patients, four clinical practices treated 3 patients, and one clinical practice treated 1 patients. One patient planned for the control group was exited from the study after extrac-

tion and upon measuring extraction dehiscences, and this resulted in 48 patients treated, grouped as follows: 25 CPlug (control) and 23 XCM (test) sites. Three additional patients were not included in the PP population at the end of the study because their extraction socket bony dehiscences were larger than the study inclusion criteria (PP population of 45 patients/sites).

Baseline patient characteristics (Tables 6a and 6b) were balanced between test and control groups, including the following factors: age, gender, oral hygiene, body mass index, tobacco use, KTW, tissue phenotype, and initial extraction socket soft tissue gaps. However, body mass index was significantly higher for test patients (30.06 ± 5.79 vs 25.83 ± 4.13 ; $P < .005$). The suture technique chosen by the investigators was primarily single-interrupted for XCM but was split between cross-stitch and single-interrupted for CPlug (2 and 21 for XCM, and 13 and 12 for CPlug, respectively). Time to complete the procedures (starting after BOC graft placement and finishing when the last suture was tied) was borderline significant: 6.65 ± 2.37 minutes for the test group vs 8.05 ± 2.97 minutes for the control group ($P = .077$).

As observed by blinded examiners, healing was uneventful. The time to soft tissue gap closure of the extraction socket (Fig 3) indicated no significant difference between therapies. By 4 weeks, approximately 60% of sites were closed for both therapies, 80% were closed by 8 weeks, and all remaining sites were closed at 16 weeks.

Table 6a Baseline Values by Number of Sites

	Gender, n		Tobacco use, n			Tissue phenotype, n				Sutures, n	
	Female	Male	Never	Former	Current	Thin	Medium	Thick	Very thick	Single interrupted	Cross-stitch
Control (CPlug)	19	7	15	9	2	6	11	4	5	12	13
Test (XCM)	13	10	14	8	1	5	6	5	7	21	2
<i>P</i>	NS		NS			NS				.0016	

CPlug = Helistat (Integra Miltex) collagen plug; XCM = Mucrograft Seal (Geistlich) xenogeneic collagen matrix; NS = not significant. Tissue phenotype was determined by transparency (show-through of colored probes). Baseline is visit 0/1 (screening).

As patients were removed throughout the study (as detailed in the Results), the number of evaluated patients and sites decreased, as seen in the Sutures section of this table (ie, 1 patient was removed from the study at surgery, and therefore 48 patients were evaluated for suture technique instead of 49 patients).

Table 6b Baseline Measurements

	Extraction socket dimensions, mm						Age, y	BMI	Oral habits, no. times/day			Socket tissue gap, mm		Suture time, min
	A	B	C	D	B/A	D/C			Brushing	Flossing	KTW, mm	Bucco-lingual	Mesio-distal	
Control (CPlug)	12.1 ± 2.9	0.9 ± 1.1	5.1 ± 1.2	0.6 ± 0.8	0.08 ± 0.10	0.11 ± 0.16	59.5 ± 9.8	25.8 ± 4.1	2.2 ± 9.8	1.3 ± 1.0	3.6 ± 1.5	7.5 ± 1.9	5.4 ± 1.3	6.6 ± 2.4
Test (XCM)	11.6 ± 2.6	1.7 ± 2.4	6.0 ± 2.2	0.9 ± 2.11	0.14 ± 0.18	0.11 ± 0.19	59.9 ± 12.8	30.1 ± 5.8	2.8 ± 4.4	1.0 ± 0.6	3.9 ± 1.6	7.8 ± 0.8	5.5 ± 1.0	8.0 ± 3.0
<i>P</i>	NS	NS	NS	NS	NS	NS	NS	< .005	NS	NS	NS	NS	NS	.077

CPlug = Helistat (Integra Miltex) collagen plug; XCM = Mucrograft Seal (Geistlich) xenogeneic collagen matrix; BMI = body mass index; KTW = keratinized tissue width; NS = not significant.

Extraction socket dimensions were categorized as follows: A = bony crest to apex; B = bony crest to dehiscence; C = mesiodistal socket at crest; D = Coronal mesiodistal.

Data are presented as mean ± SD. Measuring the suture time began after graft placement and ended when the last suture was placed. Baseline is visit 0/1 (screening).

Clinical Evaluations

Soft tissue thickness, as measured clinically using biopsy samples, histologically using microcomputed tomography (micro-CT), and histomorphometrically, was approximately 0.4 to 0.9 mm greater for XCM sites. The changes in soft tissue thickness for XCM and CPlug sites, respectively, averaged 2.0 ± 1.5 mm and 1.6 ± 1.0 mm clinically;

2.72 ± 1.85 mm and 1.82 ± 0.55 mm via micro-CT; and 2.0 ± 0.46 mm and 1.6 ± 0.39 mm histomorphometrically. These differences were not statistically significant.

At 2 weeks, when evaluating the ITT population, a blinded evaluator (C.R.) observed more CPlug biomaterial completely absent (73% to 85%) than XCM (35% to 56%). At 3 weeks, another blinded evaluator (D.V.) observed 92% of CPlug ab-

sence (24 of 26 sites), while XCM was still present in 22% of sites (5 of 23 sites). Blinded examiners at each clinical practice saw no significant differences, except at 4 weeks, when tissue containing bone graft particles was observed at 27% of CPlug sites (7 of 26) but 65% of XCM sites (15 of 23) ($P = .042$, Bonferroni adjustment). At 4 weeks, the blinded evaluators observed socket healing disruption (presence of bone

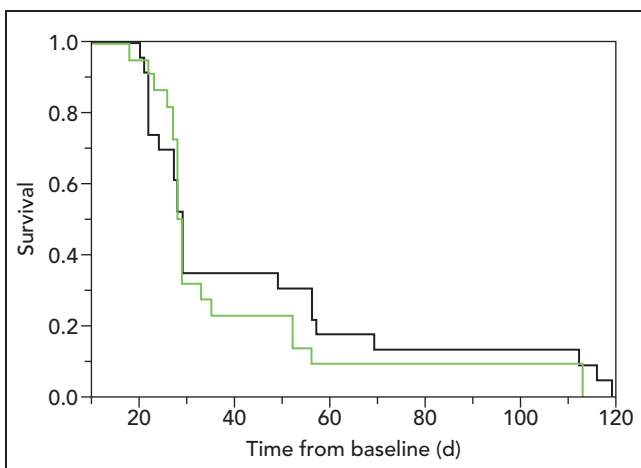


Fig 3 Survival analysis: Time to extraction socket soft tissue gap closure (days). Control/CPlug group = red; test/XCM group = blue.

Table 7 Secondary Clinical Outcomes

	Change in tissue thickness, mm	KTW, mm	Inflammation, no. of sites		Soft tissue esthetics			Ease of soft tissue elevation, no. of sites		
			Normal	Mild	Firmness	Redness, no. of sites		Normal	Slight	Scarred
						Equal	More			
Control (CPlug)	1.6 ± 1.0	7.8 ± 5.4	25	1	All equally firm	24	2	16	8	1
Test (XCM)	2.0 ± 1.5	9.5 ± 4.6	21	2	All equally firm	21	2	16	5	1
<i>P</i>	NS	NS	NS		NS	NS		NS		

CPlug = Helistat (Integra Miltex) collagen plug; XCM = Mucrograft Seal (Geistlich) xenogeneic collagen matrix; KTW = keratinized tissue width; NS = not significant.

Change in tissue thickness was measured buccally from baseline to 16 weeks. KTW and inflammation were measured at 16 weeks. As patients were removed throughout the study (as detailed in the Results), the number of evaluated patients and sites decreased.

graft particles) for 31% to 46% of CPlug sites and 9% to 21% of XCM sites. At 8 and 16 weeks, the evaluators observed no differences in socket healing profiles between the two groups.

The remaining outcomes, including inflammation and KTW, were similar for both therapies, and no statistically significant differences were seen (Table 7). At implant placement, five XCM and two CPlug sites were re-grafted, but it is unclear whether the need for re-grafting was due to treatment type

or defect morphology. Soft tissue esthetics were all judged to be equally firm and equally red to surrounding tissues for all patients, except for two test sites and two control sites, which were deemed more red than surrounding tissues.

Histology

All evaluated biopsy samples were occupied by soft and hard tissues and graft particles. The composition of the supracrestal soft tis-

sue was similar for both test and control sites: primarily comprising epithelium and connective tissue, with minute amounts of granulation tissue and scattered biomaterial particles (Fig 4). The connective tissue at both test and control sites was covered with parakeratinized, stratified, squamous epithelium. The interface between the epithelium and the connective tissue exhibited typical epithelium rete pegs and connective tissue papillae. The connective tissue in both groups was rich in collagen fibers

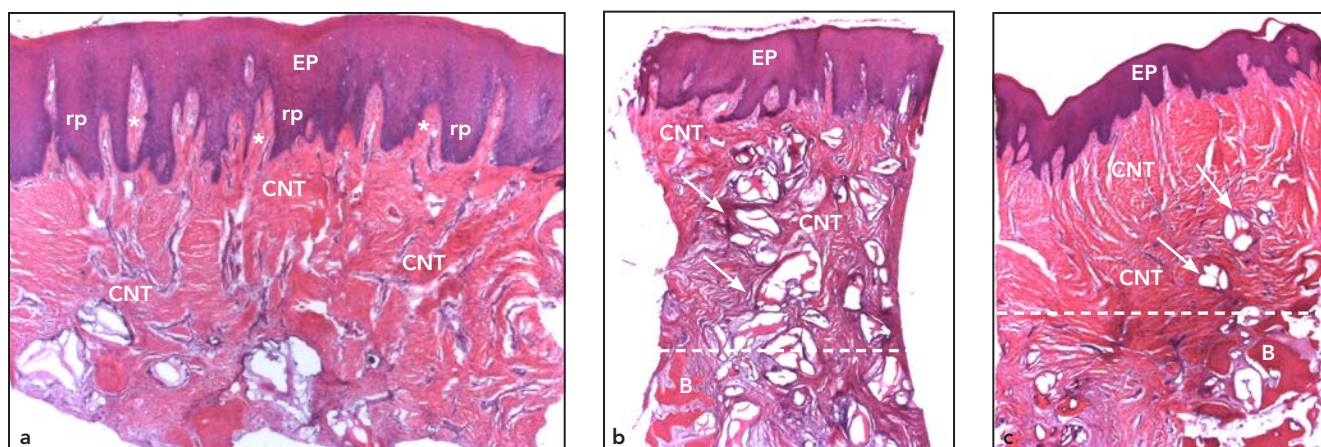


Fig 4 Histologic observations on an example biopsy sample from the test group (XCM). (a) Parakeratinized, stratified, squamous epithelium that covered the connective tissue in both test and control groups (h&e staining; x25 magnification). Asterisks indicate connective tissue papillae. CNT = connective tissue; EP = epithelium; rp = rete pegs. (b) Overview of the supracrestal compartments in example XCM and (c) CPlug samples (h&e staining; x25 magnification). Arrows point to biomaterial granules. The dotted lines indicate the border between supra- and infracrestal compartments. B = bone; CNT = connective tissue; EP = epithelium.

and cells but poor in vessels. Biomaterial particles were found in the supracrestal connective tissue and were occasionally surrounded by multinucleated cells. The newly formed tissues at the infracrestal compartment of the biopsy samples were similar for both test and control groups, composed of provisional connective tissue, newly formed bone, biomaterial particles, and some granulation tissue. The provisional connective tissue was located mainly at the center and coronal portions of the infracrestal compartment, and its collagen fibers were organized in a woven arrangement. The newly formed bone was composed of woven, parallel-fibered and some lamellar bone. Most graft particles were located in the connective tissue and were in direct contact with collagen fibers or with multinucleated cells, while the biomaterial particles were occasionally surrounded by newly formed, mineralized bone.

Results of the linear and morphometric measurements were similar for both test and control groups. The amount of graft biomaterial that occupied the soft tissues was, however, greater for test (12%; range: 5% to 20.1%) than control (5%; range: 0.0% to 9.2%) specimens. After 4 months, the healing process for the ridge mucosa was not complete for either test or control specimens.

Micro-CT Results

Micro-CT scans (Fig 5) revealed a mix of connective tissue and hard tissue in both the crestal bone compartments and supracrestal soft tissue. Soft tissue thickness was measured along the midline plane of the biopsy samples. On average, XCM sites were 0.9 mm thicker than CPlug sites, though this difference was not statistically significant ($P = .3904$). Blood vessels found throughout the biopsy samples (Fig 6) indicate that

the biomaterials were incorporated and vascularized.

Discussion

Bone graft placement and the cohesive, collagen composite bone grafts used in the present study (BOC) appear to aid in socket preservation.^{6,16} Puisys and Linkevičius found that mucosal thickness had a positive effect on crestal bone stability around bone-level implants.¹⁷ Likewise, others have proposed that a gingival phenotype comprised of thicker and more keratinized tissues may relate to bone level stability over time.^{18–20} Also, sites with significant soft tissue cratering may require more apical placement of implants in order to compensate for the loss of vertical height.

In the present study, the observations and measures of particular interest were: (1) time to socket soft tissue closure, (2) duration of graft

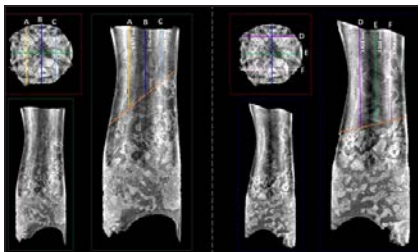


Fig 5 Cross-sample scans of a test group (XCM) sample, taken at a 90-degree angle. Micro-CT was utilized to measure soft tissue thickness on the samples.

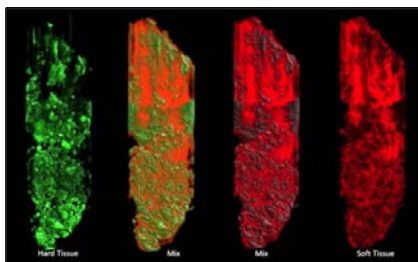


Fig 6 Micro-CT Imaging: Mineral (green) and vascular components (red) indicate well-vascularized biomaterials, with evidence of graft particles within the soft tissue component of the biopsy samples (test group; XCM).

containment, (3) end-of-study soft tissue thickness, and (4) contour. Blinded evaluators and examiners at the clinical practices reported that both extraction socket therapies appeared to follow a similar healing trajectory of gap closure, with survival analysis (time to extraction socket soft tissue gap closure) similar between the two therapies; therefore, the null hypothesis was accepted. XCM appeared to cover graft particles longer, and CPlug was observed to have more severe (Grade III) disruption/cratering of the socket soft tissue profile during the first 3 weeks of healing. However, after 4 weeks, the profiles for

both control and test sites evened out between the groups (ie, sites appeared healed in/closed), and the tissue declivities “flattened,” either from apical fill, coronal resorption, or both. At 16 weeks (end of study), soft tissue thicknesses (measured clinically, histologically, and via micro-CT) were greater for XCM than CPlug, but these differences were not statistically significant; further, there were no clinically significant differences in tissue texture, tissue color, or the investigators’ ability to raise flaps and place implants.

Surgery time for XCM was an average of ~1.5 minutes longer than the CPlug surgery. The investigators’ surgical approaches reflected their experience using cross-stitching to secure CPlug but interrupted sutures for XCM, as featured in the product’s instructions for use.

Histologically, collagen maturity was delayed by both test and control treatments compared to using no socket covering (ie, open healing). This is because all grafts delay healing, even connective tissue and free gingival grafts, as found by Araújo et al.²¹ In the present study, a histologist (M.A.) determined the healing to be approximately halfway complete at the end of the study (a mature healing site has 4 to 5 times more collagen than cells). There tended to be more bone granules in the soft tissue component of the XCM biopsy samples, which may indicate longer covering/protection of the sites. Also, XCM sites were approximately 25% thicker on average, but this difference was not statistically significant.

Morelli et al performed a study very similar to the present one but used a more precise, intraoral-scanning measurement technique.²² They found that, at 3 months postextraction, significantly more volume (average: ~20 mm³) was preserved by XCM, though the clinical significance of this volume difference is not clear. Linear differences in the present study were not significantly different, nor was the amount of bone preserved by the two treatment types. Similarly, 4 months after ridge preservation, Natto et al found no significant differences in ridge preservation or soft tissue thickness between XCM and a collagen sponge placed over freeze-dried bone allograft.²³

Covering/protecting extraction socket graft sites for a longer amount of time may provide better outcomes, but these benefits were not observed in the present study. Such protection might be more critical with dehisced, non-intact sockets,²³ as seen in a previous work by Scheyer et al.¹⁵ However, considering the biomaterial costs and surgery times required for the therapies in our study of essentially intact extraction sockets, the finding of no significant differences may still be “significant” to both practice and patient.

The present study was conducted by a practice-based network of 17 investigators and 14 clinical practices and benefits from the inherent range of approaches (despite calibration) and real-life patient variables encountered by the dental community, and thus the study may be more indicative of outcomes that can be expected by the dental

community at large. Private-practice research also benefits from patient retention, and the patients studied herein are now being followed out to 5 years, with particular attention paid to implant survival and esthetics.

Rather than utilizing individual examiners at each clinical practice, healing assessments were performed by blinded and calibrated evaluators (D.V. and C.R.) to decrease variability, and this method should be used in future studies. To confirm the presence of biomaterial and better understand the composition and sequence of tissue healing in extraction sockets, earlier and sequential soft tissue biopsies could be performed of the “scab-like stratum” tissue, which appeared to protect sockets in some patients up to the third week postsurgery. In future studies, buccal bone plate thickness should also be measured, as it may influence ridge preservation success.²⁴ Standardized radiographs (for crestal bone level and, consequently, the level of implant placement) and more accurate intraoral-scanning gingival contour measures should also be employed. Intraoral scans could also be used to evaluate more objective esthetic values, like tissue color. Finally, extraction sockets that are dehiscenced and difficult to manage should be studied and compared with the nearly intact extraction sockets studied herein.

Conclusions

In this multicenter (14 clinical practices and 17 investigators), practice-based study of ridge preservation

for essentially intact (loss of less than one-third of the buccal bone plate) extraction sockets, there were no clinically relevant differences at the time of implant placement (16 weeks postoperative) observed between using a hemostatic sponge or a collagen matrix soft tissue substitute to cover a bovine, collagen/bone block graft. Bone grafts were covered and contained longer by XCM (approximately 4 weeks vs 2 weeks), with less contour disruption out to 4 weeks; however, at implant placement, soft tissue contours were comparable for both groups, and soft tissue thicknesses were not significantly different.

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