Title
Comparing Two Ridge Preservation Techniques: With And Without Soft Tissue Primary Closure

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Publication Date
2018

Comparing Two Ridge Preservation Techniques:
With And Without Soft Tissue Primary Closure

by

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THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Oral and Craniofacial Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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ACKNOWLEDGMENTS

Division of Periodontology and Department of Orofacial Sciences

at University of California, San Francisco

BioHorizons Company

Second Center of The Study - Dr. Bach Le

Hard Tissue Research Laboratory at University of Minnesota - Hari Prasad

C-Dental Company - Jerry Peck and Julia Peck

Statistician - Dr. Robert Rubin

Committee in Charge: Dr. Xenoudi, Dr. Kapila, and Dr. Ryder

Great appreciations to my beloved family, co-residents, faculty, staff for all of your unconditional love and supports

~ Life is about the people you are with ~ Pham 2018

Tuesday June 12, 2018

San Francisco, CA

ABSTRACT

Comparing Two Ridge Preservation Techniques:
With And Without Soft Tissue Primary Closure

by

Anh Nguyen Quynh Pham, D.D.S

Objective: The goal was to compare two surgical approaches for extraction and ridge preservation: primary soft tissue closure and secondary healing intention. Data from one center is presented.

Materials and methods: UCSF IRB approved. Prospective split mouth study design was used. Each patient (n=7) obtained CBCTs before and 3.5 months after extractions. Two teeth with intact sockets (premolars/anteriors) in each patient were randomized to one of the two techniques for extractions and ridge preservation using allograft and collagen membrane. Control group had buccal mucoperiosteal flap to obtain primary soft tissue closure and test group had secondary healing intention. Patients reported post-operative discomfort at 1,3,5,7 days using visual analog scale. At 4.5 months after extractions, during implant placement or ridge augmentation, soft tissue thickness in the grafted area was measured and bone cores were harvested. Cores were sent to University of Minnesota for histologic and histomorphormetric analyses using a non-decalcified technique. A superimposition of CBCTs were performed to compare the changes in alveolar bone.

Outcome variables were the level of post-operative discomfort, percentage of vital bone, residual allograft and marrow spaces/fibrous tissue, changes in vertical and horizontal dimensions of alveolar process, and resultant differences in soft tissue thickness.

Results: pain scale analyses showed no significant differences between two groups at any time point (1,3,5,7 days). Analyses of the resultant soft tissue thickness revealed no significant differences between two techniques. CBCTs revealed no significant differences between two groups for the buccal plate thickness. In addition, there were no differences in alveolar bone changes between two techniques. There were significant differences in changes in width and height of alveolar bone within each group pre-operatively and post-operatively ($p<=0.05$). Histomorphometric analyses revealed no significant differences between two groups. Mean percentage of newly formed bone was 38.55% versus 39.62%; residual graft was 10.17% versus 9.24%; and marrow spaces/fibrous tissue was 51.28% versus 51.14% for primary soft tissue closure versus secondary healing intention, respectively.

Conclusion: No significant differences were observed in post-operative discomfort, soft tissue thickness, and alveolar bone changes when comparing between two surgical approaches.

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ABBREVIATIONS

CBCT - Cone Beam Computed Tomography

IRB - Institutional Review Board

Micro-CT - Micro Computed Tomography

SAP - Statistical Analysis Plan

SD - Standard Deviation

UCSF - University of California, San Francisco

UMN - University of Minnesota

VAS - Visual Analog Scale

I. BACKGROUND

I. BACKGROUND

The dental alveolar socket is a tooth-dependent tissue, and dimensional changes of the dental alveolar socket following tooth extraction has been documented in previous studies (Johnson 1963 , Johnson 1969, Pietrokovski 1967, Pietrokovski 2007, Scropp 2003, Trombelli 2008). Tooth loss can result in resorption of up-to 60% of the alveolar ridge within the first 1 to 2 years after extraction. Ridge preservation has been advocated to decrease the amount of bone loss following tooth extraction (Lekovic et al. 1997, Araujo & Lindhe 2005, Fickl et al. 2008). Comparative research has shown that patients who underwent a ridge preservation procedure sustained significantly less resorption than patients who were not treated (Iasella et al. 2003, Barone et al. 2008). The concept of alveolar ridge preservation has been investigated over the last 2 decades, yet many questions remain unanswered. Various surgical protocols have been described for different socket morphologies with varying residual osseous walls. However, there is insufficient data regarding which surgical technique for ridge preservation is superior with regards to primary soft tissue closure or healing by secondary intention (Horowitz et al. 2012, Cochrane Review 2015).

In a recent animal study, Park et al. evaluated the efficacy of alveolar ridge preservation with and without primary wound closure. Porcine hydroxyapatite with a polytetrafluoroethylene membrane were used in a canine socket preservation model. The density of the total mineralized tissue, remaining hydroxyapatite, and new bone were analyzed by histometry and micro-CT. This study showed that the group which underwent ridge preservation without primary wound closure had significantly higher new bone density than the group with primary wound closure. The authors suggested that alveolar ridge preservation without primary closure may enhance new bone formation more effectively than that with primary closure. (Imaging Science in Dentistry 2014; 44: 143-8)

In human studies with a parallel-group design, Barone et al. reported that a flapless technique preserved the horizontal hard tissue dimension and increased the keratinized gingiva more successfully than an open flap technique. However, the authors found no histological or histomorphometrical differences when comparing an open flap versus a flapless approach in alveolar ridge preservation (J Periodontol 2014, 85:14-23, Clinical Oral Implant Research 26, 2015, 806-813). In these parallel group studies, inter-individual differences, such as local and systemic factors, can introduce confounders, which may significantly affect results.

A coronally advanced flap to obtain primary wound closure has been considered necessary for the successful integration of biomaterials (Lekovic et al. 1997, Darby et al. 2009). However, animal studies have shown that the buccal plate resorbs approximately 0.7mm due to detachment of the periosteum from the plate (Fickl et al., 2008). It is hypothesized that separation of the periosteum from its underlying bone causes vascular damage and acute inflammation leading to increased bone loss (Wilderman 1963; Wood et al. 1972). In a recent animal study, Park et al. suggested that alveolar ridge preservation without primary closure may enhance new bone formation more effectively than that with primary closure (Imaging Science in Dentistry 2014; 44: 143-8).

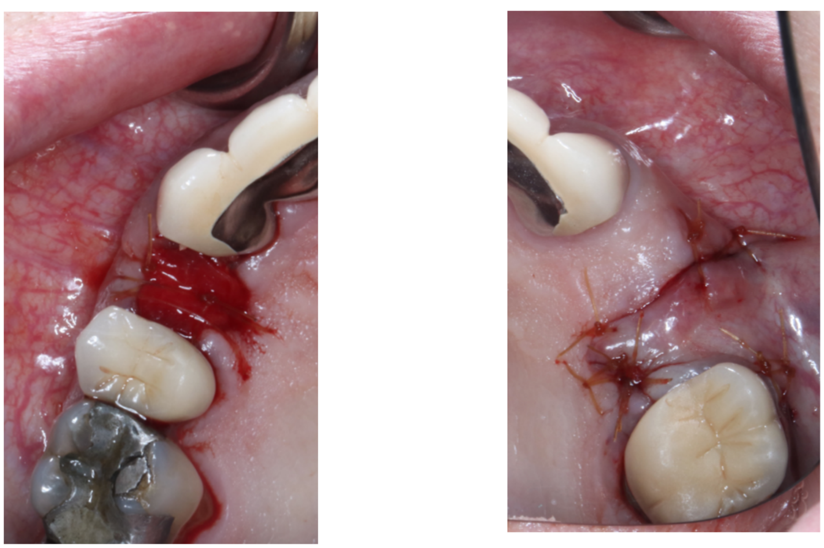
Prior studies have evaluated the three dimensional changes of the alveolar ridge after extractions. They compared the use of different biomaterials and unassisted healing in sockets (UHS). The comparisons also included utilizing different biomaterials, including but not limited to, autogenous grafts, allografts, xenografts, and alloplasts. (Vignoletti et al. 2012, Avila-Ortiz et al. 2014, Jambhekar et al. 2015, Cochran Review 2015).

In this present study, an allograft was used to graft all sockets after extractions. An allograft, with its slow resorbing nature provides a physical matrix and space maintenance to reduce the loss of tissue volume while supporting new bone formation. Then a resorbable collagen membrane (Bio-Horizon Mem-Lok Pliable®) was used to cover the grafted sockets of both groups, primary soft tissue closure and secondary healing intention. The collagen membrane consists of porcine collagen and is designed for soft tissue regeneration. It also helps to stable and support open wound healing.

The allograft used in this study is a mixture of cortical and cancellous chips. It forms an osteoconductive scaffold providing volume enhancement and site development. Allografts promote the initial biologic processes of cell adhesion and proliferation. The human body recognizes and accepts its crystaline structure, and the particles become integrated into living bone. Therefore, its crystaline structure helps to preserve natural bony structures and assist the remodeling process.

The goal of this proposed study is to evaluate and compare two surgical approaches for alveolar ridge preservation after extractions; primary soft tissue closure with coronally advanced mucoperiosteal flap and healing by secondary intention.

Currently, there are few studies addressing the need for primary closure with alveolar ridge preservation. There are no standard guidelines and there is limited data indicating which surgical approach is superior. Hence, we conducted a multi-center controlled clinical trial on human subjects to address this gap in knowledge. To minimize inter-individual variability, a split-mouth design was used. The results of this study will provide needed scientific data to help form surgical guidelines for hard and soft tissue regeneration, specifically in the area of alveolar ridge preservation. Furthermore, this study is to help addressing the primary question: Is there a need to obtain primary soft tissue closure in alveolar ridge preservation?



Secondary Healing Intention **Primary Soft Tissue Closure**

Figure 1: Two surgical approaches

We hypothesized that the lack of primary soft tissue closure and collagen membrane exposure during ridge preservation did not adversely affect the subsequent soft and hard tissue remodeling and regeneration, and therefore, did not affect the effectiveness of alveolar ridge preservation. We further hypothesized that there was no difference in dimensional changes of the resultant alveolar process, in terms of quantity and quality of newly formed bone between the two approaches. There was less post-operative complications in the group without primary soft tissue closure.

II. MATERIALS AND METHODS

II. MATERIALS AND METHODS

1. STUDY DESIGN:

This was a multi-center controlled clinical trial on 10 human subjects. The study employed a split-mouth design. Patients needed at least two extractions consisting of a pair of non-molar teeth (anteriors and premolars) with intact sockets. Two teeth from a pair were randomly assigned into experimental and control groups. In both study groups, an allograft (Biohorizons-MinerOss® Cortical & Cancellous) was mixed with autogenous blood and condensed into the extraction socket to the level of the alveolar crest, then test sites received a resorbable collagen membrane (Biohorizons-Mem-lok Pliable®) over the sockets. For the control group, a coronally advanced facial flap was raised to obtain primary soft tissue closure, and it was secured with 4.0 Chromic Gut. For the experimental group, flapless extraction was performed; the resorbable collagen membrane (Biohorizons-Mem-lok Pliable®) was secured with horizontal mattress sutures using 4.0 Chromic Gut, and left exposed to heal by secondary intention.

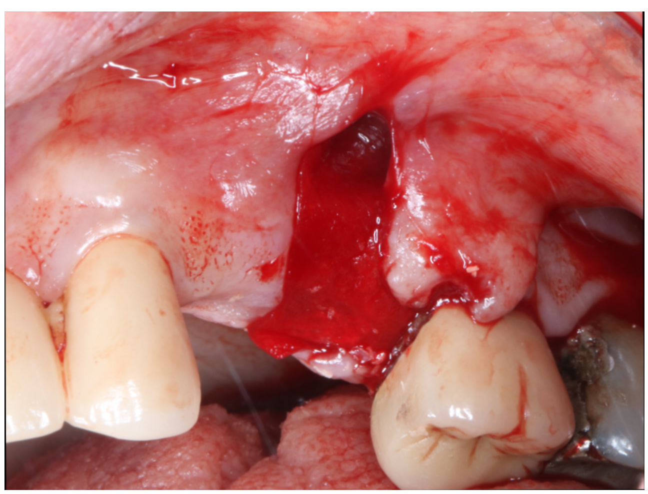


Figure 2: Primary soft tissue approach with two vertical release incisions and coronally advanced mucoperiosteal buccal flap to obtain primary closure

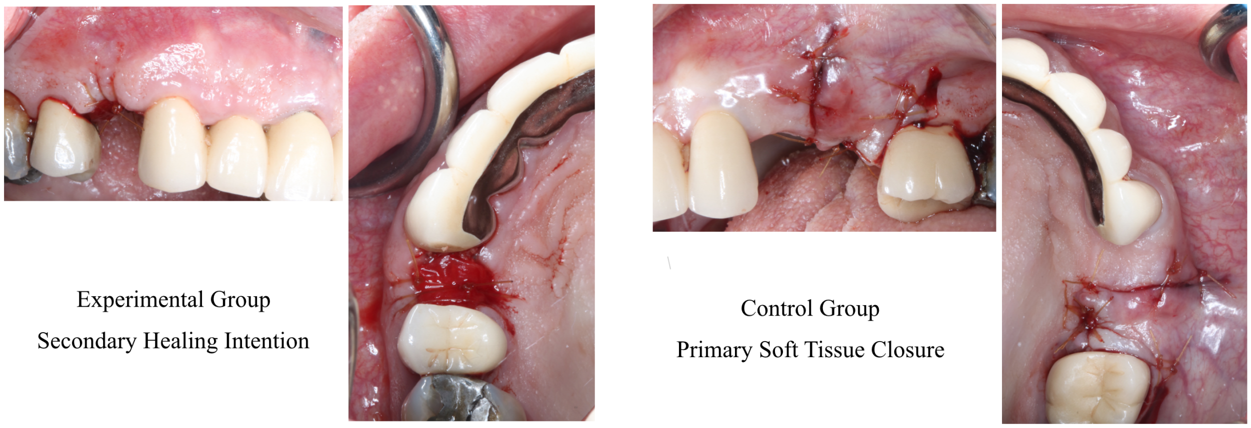


Figure 3: Primary soft tissue closure versus secondary healing intention groups

Cone beam computed tomography (CBCT) scans were taken at baseline and 3.5 months after extractions. The thickness of buccal plates of studied teeth were measured on pre-operative CBCT scan. Then the two CBCT scans were superimposed for analyses of hard tissue changes. Vacuum matrix was customized for each patient prior to extractions. It was used to reproduce the

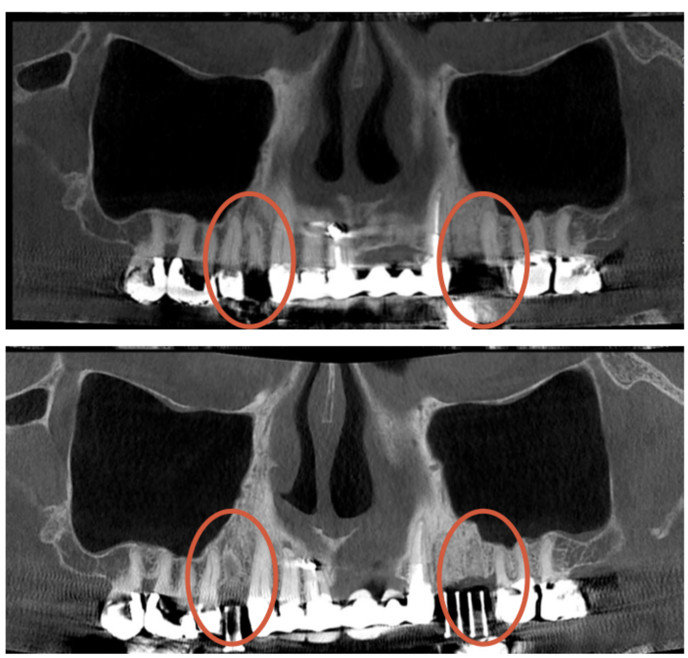


Figure 4: Pre-operative and post-operative scans from each patient

landmark for clinical measurements of the soft and hard tissues, including the thickness of soft tissue at crest, and position of grafted sockets to assist refine burs in harvesting bone cores at the time of implant placement or ridge augmentation.

After 4.5 months of healing, a re-entry surgery was performed for implant placement, at which time a 2/2.8mm (inner and outer diameters) trephine burs were used to harvest bone cores from both studied extraction grafted sockets. The implant osteotomies were subsequently prepared for implant placements. If grafted areas needed further ridge augmentation before implant placement, a bone core was harvested simultaneously during the augmentation procedure. Trephined cores were sent for processing and histological and histomorphometric analyses at the University of Minnesota Hard Tissue Research Laboratory. Histologic and histomorphometric analyses were performed to analyze the percentage of newly formed bone, residual allograft material, fibrous tissue and marrow space in trephined cores. All statistical analyses were performed by private statistician service.

2. SUBJECT SELECTION:

a. Study Population:

This is the data from one center, University of California, San Francisco. A total of 7 patients completed the study. Patients who met the inclusion and exclusion criteria, needed at least two extractions, consisting of a pair of non-molar teeth (anteriors and premolars) with intact sockets, and subsequent implant-supported dental restorations were included in this study.

b. Inclusion Criteria:

1. 18 years of age or older and able to sign informed consent - Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

2. In good general health

3. Requiring a pair of non-molar teeth extractions (anteriors and premolars) with intact sockets, followed by implant-supported restorations. Although the original criteria for inclusion was a pair molar-molar or a pair of non-molar-non-molar teeth, the final result only included non-molar pairs (anteriors and premolars only).

c. Exclusion Criteria:

1. Uncontrolled systemic diseases - contraindications for surgery and/or affect wound healing

2. Heavy smoker (more than 10 cigarettes per day)

3. Use of bisphosphonates

4. Unwillingness to return for follow-ups

5. Pregnancy (Pregnancy test performed onsite)

3. STUDY TREATMENTS

a. Blinding:

Due to the nature of the surgical procedures, it was not possible to conduct the surgical aspects in a blinded manner. The histologic and histomorphometric analyses of the bone cores and superimposition and analyses of CBCT scans were conducted in a blinded manner.

b. Method of Assigning Subjects to Treatment Groups:

Up to 9 eligible patients with two teeth needing extractions were included. Two teeth of a pair were randomly assigned to control and experimental group in a 1:1 ratio. The study team completed a series of visits, as detailed below.

c. Surgical Products:

i. Grafting Materials:

All extraction sockets of both experimental and control groups were grafted using an allograft (Biohorizons MinerOss® Cortical & Cancellous) and a resorbable collagen membrane (Biohorizons Mem-lok Pliable®).

The Biohorizons Company provided the study materials. The initial study drug shipment was shipped after site activation. Subsequent study material shipments were made after site request for resupply.

ii. Dosage:

The average amount of allograft (Biohorizons MinerOss® Cortical & Cancellous) used for each extraction socket was 0.5cc. Each treated area received one resorbable collagen membrane (Biohorizons Mem-lok Pliable®). A 4.0 chromic gut suture was used to secure the flaps over the grafts

iii. Storage:

Study materials were stored at room temperature according to the manufacturer's instructions.

iv. Study Drug Accountability:

An accurate and current accounting of the study materials was maintained for each subject by the study staff.

d. Evaluation by visits:

Each patient will have an initial screening visit prior to surgical extractions to review the study objectives with the patient (or patient's legal representative) and obtained written study informed consent, periodontology clinic informed consent for the procedures, and HIPAA authorization. Then each patient was assigned a unique screening number. Medical and dental history were recorded and pregnancy test was performed for female patients. Peri-apical x-rays was obtained to confirm the need for tooth extractions if needed.

Alginate impressions of upper and lower teeth was obtained for study purposes. Then patient was scheduled for, visit 2, referring for study standardized CBCT scan. Once the first set of CBCT scan obtained and patient fully qualified as a study subject, studied teeth were randomized to control and experimental groups. Prior to extractions, clinical measurements of study areas were recorded. Tooth extractions and ridge preservation were performed according to assigned groups following our standardized protocol as also described previously in study design: Two teeth from a pair were randomly assigned into experimental and control groups. In both study groups, an allograft (Biohorizons-

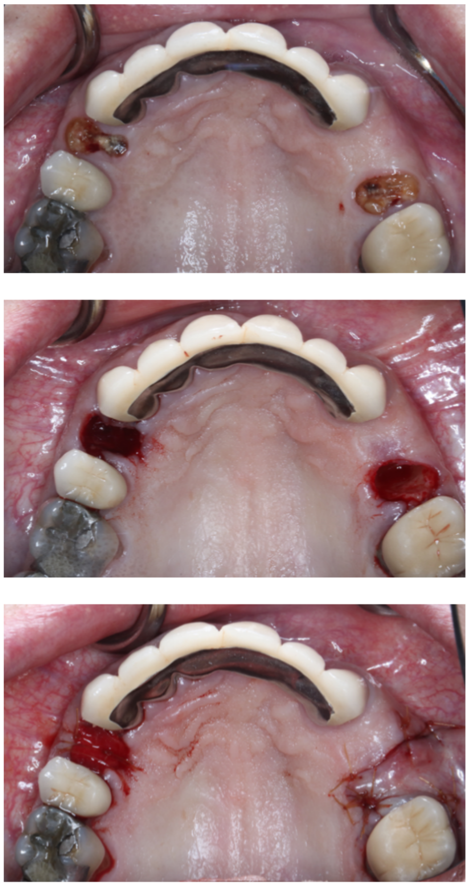
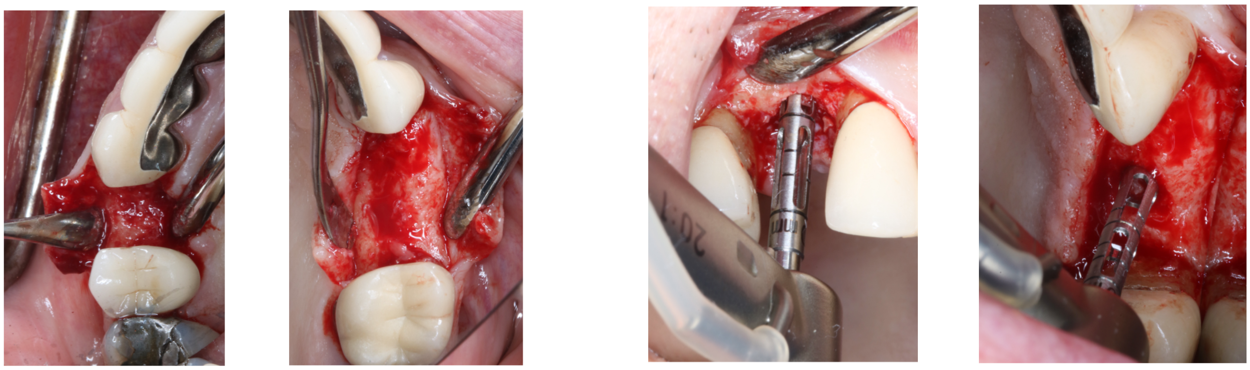


Figure 5: Split mouth design of primary soft tissue closure and secondary healing group; a. #5 and #13 studied teeth prior to extractions b. minimal traumatic extractions c. primary soft tissue closure (patient's left side) versus secondary healing intention groups (patient's right side)

MinerOss® Cortical & Cancellous) was mixed with autogenous blood and condensed into the extraction socket to the level of the alveolar crest, then test sites received a resorbable collagen membrane (Biohorizons-Mem-lok Pliable®) over the sockets. For the control group, a coronally advanced facial flap was raised to obtain primary soft tissue closure, and it was secured with 4.0 Chromic Gut. For the experimental group, flapless extraction was performed; the resorbable collagen membrane (Biohorizons-Mem-lok Pliable®) was secured with horizontal mattress sutures using 4.0 Chromic Gut, and left exposed to heal by secondary intention. Surgical outcomes of the extraction sockets were assessed at the time of surgery after extractions. Teeth with broken buccal or lingual plate, or fenestrations, dehiscences on the socket walls were eliminated from the study. Patient were also informed of the exclusion from the study due to surgical outcomes that made the teeth no longer qualified for the study. In these scenarios, patient continued with the treatment as a regular patient of periodontology clinic. Post-operative instruction was given. Antibiotics were prescribed case by case basis. For qualified patient, Visual Analog Scale (VAS) (under the form of Numerical Pain Rating Scale from 0-10 with 0 is no pain and 10 is very severe pain) was given for each tooth for patient's self-report level of discomfort.

Patient came for post-operative visit at 7 days after the extractions and ridge Preservation (1 day window). During this visit, standard post-operative procedure was performed, and VAS data was collected. Then, patient came back at 1 month after extractions and ridge preservation (1 week window). At each post-operative visit, all adverse events and post-operative complications were recorded. Patient was recalled at 3.5 months after extractions and ridge preservation (2 week window) for abbreviated dental examination to evaluate the readiness for implant placement of the grafted areas. Then patient was referred for the second CBCT scan, which for planning the implant placement and superimposition with the first CBCT scan for study purposes. At 4.5 months after extractions and ridge preservation (2 week window), patient either received dental implant placement or ridge augmentation based on bony condition. At this surgical visit, bone cores were harvested simultaneously from the grafted sockets using the vacuum matrix as a reproducible landmark. Clinical measures of soft and hard tissue of study areas were recorded.

Patient continued and completed standard post-operative visits at the USCF Postgraduate Periodontology Clinic.



Secondary Healing Intention | Primary Soft Tissue Closure | Secondary Healing Intention | Primary Soft Tissue Closure

Figure 6: Harvesting bone cores at re-entry surgery 4.5 months after extractions

4. MEASUREMENTS

a. Clinical and radiographic measurements:

At initial visit, research protocol was explained and informed consent was discussed.

Cone beam computed tomography (CBCT) scans were taken at baseline and 3.5 months after extractions radiographic measurements of hard tissues and for superimposition.

Clinical photographs will be taken at each visit. For each extraction site, study cast was used to fabricate vacuum matrix to obtain a standard index and reproducible reference for all hard and soft tissue clinical measures. Vacuum matrix was also used to identify position of grafted areas. Then the bone cores were taken within the grafted socket. Based on the pre-operative CBCT scan, buccal plate thickness was measured in advancements of 2mm starting at crest unto the root apex. Based on the superimposition of first and second CBCT scans taken before extraction and at 3.5 months, horizontal changes of alveolar ridge was measured at 0, 2, 4, 6, 8mm from alveolar crest, and vertical changes of alveolar ridge were measured at buccal plate, crest, and lingual plate.

Figure 7: Customized vacuum matrix

Superimposition of CBCT scans:

Software generated fusion of pre-op and post-op CBCT scans delivers unparalleled accuracy in analyzing the planning, and integration of bone grafts for the placement of dental implants. Precise imaging diagnostics start with using the proper CBCT settings to deliver high image quality and low exposure. Accurate studies further require high performance computers and proficient configuration and use of 3D planning software. Below is an overview of the CBCT imaging settings, computer specifications, software and planning sequence used in this study:

CBCT Settings - NewTom VGi Mark III

- Focal spot 0.3
- Scan Time 18-32 Seconds

- Voxel Size 0.125
- inter slice Distance 0.3
- Image detector Amorphous Silicon Flat Panel
- Gray scale 14bit scanning 16bit reconstruction
- Field of View 12 x 8cm
- Dose 211 micro sieverts

  *+/- 20 micro sieverts depending positions of head in primary beam

Planning Software

Cybermed Ondemand 3D - Version 1.0 (Build 1.0.10.7510) x64 edition

Modules: Database Management, DICOM Export/Import, XReport, Fusion

Planning Sequence - Superimposition of Pre-Op and Post-Op DICOMS

- Select DICOM files
- Select Fusion Module
- Select all files to merge both series
- Indicate Primary and Secondary volumes by date
- Select *Manual Sync* to superimpose data
- Move secondary image on Axial, Sagittal, and Coronal views to optimal manual merge in fused view
- Select auto registration for an ideal superimposition of Pre-Op and Post Op images
- Set crosshairs to point of interest

- Set thickness of crosshairs from 0.0 to 10 or user defined (set at 4.0mm in this study)

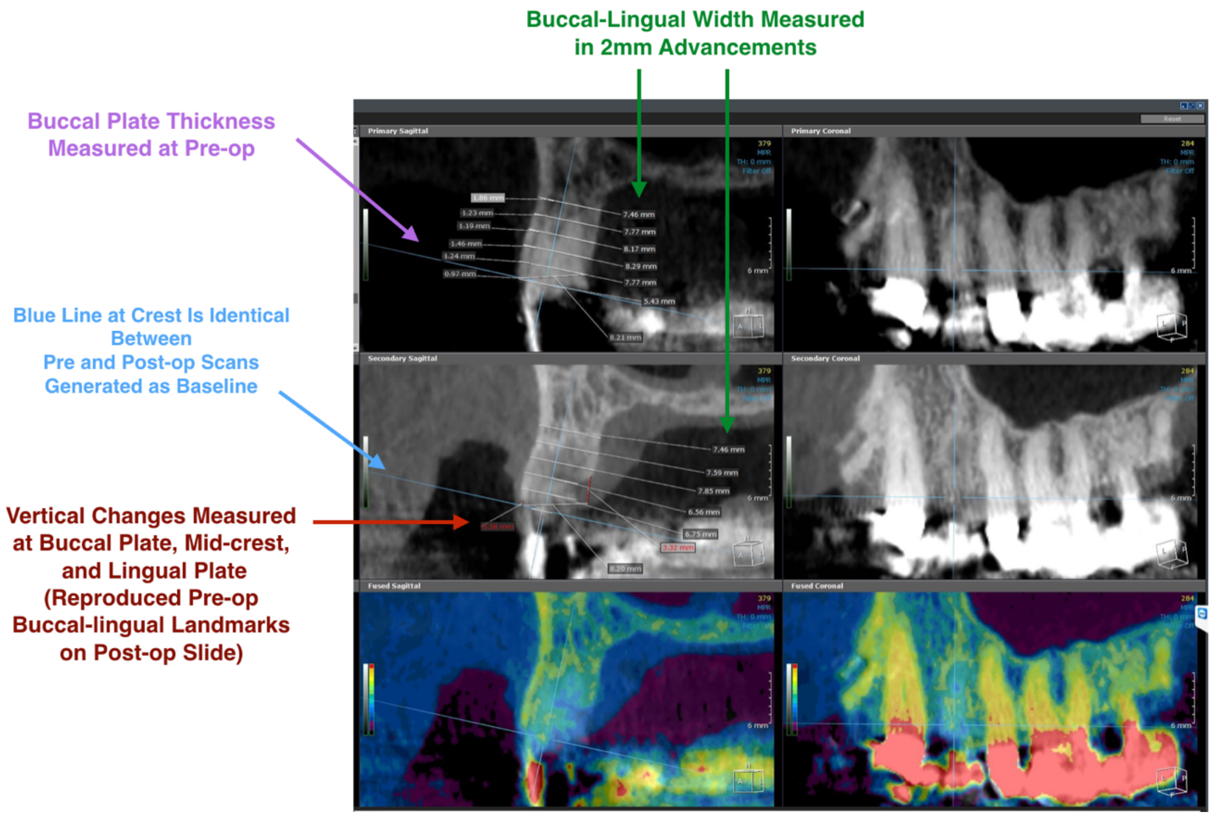


Figure 8: Superimposition of pre-operative and post-operative CBCT Scans

b. Research Laboratory Measurements:

Hard tissue healing via percentage of newly formed bone, residual allograft material, fibrous tissue and marrow space in trephined cores with histologic and histomorphometric analyses:

i. Histology:

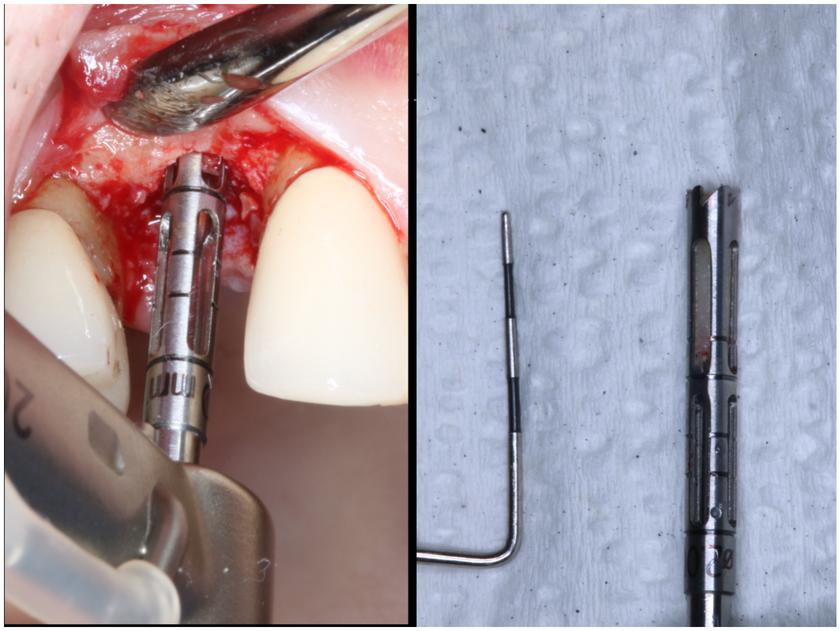


Figure 9: Bone core harvested using trephine bur

After being harvested, the bone cores were placed in 10% formalin and sent for processing at the University of Minnesota Hard Tissue Research Laboratory. Specimens were

dehydrated with a graded series of alcohols for nine (9) days. Following dehydration, the specimens were infiltrated with a light-curing embedding resin (Technovit 7200 VLC, Kulzer, Wehrheim, Germany). Following twenty (20) days of infiltration with constant shaking at normal atmospheric pressure, the specimens were embedded and polymerized by 450 nm light with the temperature of the specimens never exceeding 40°C. The specimens were then prepared to by the cutting/grinding method of Donath (Rohrer Schubert)1,(Donate & Breuner) 2. The specimens in the middle of the bone cores will be cut to a thickness of 150µm on an EXAKT cutting/grinding system (EXAKT Technologies, Oklahoma City, USA). Following this, cores were polished to a thickness of 45-65µm using a series of polishing sandpaper discs from 800 to 2400 grit using an EXAKT micro-grinding system followed by a final polish with 0.3 micron alumina polishing paste. The slides were stained with Stevenel's blue and Van Gieson's picro fuchsin and coversliped for histologic analysis by means of bright field and polarized microscopic evaluation.

ii. Histomorphometry:

Following histologic preparation, the specimens were evaluated histomorphometrically. All the specimens were digitized at the same magnification using a NIKON ECLIPSE 50i microscope (Nikon corporation, JAPAN) and a SPOT INSIGHT 2 mega sample digital camera (Diagnostic instruments inc, USA). Histomorphometric measurements were completed using a combination of spot insight program and Adobe PhotoShop (Adobe Systems, Inc.) One slide of each specimen was evaluated. Histomorphometric analysis were performed and the following parameters were measured in terms of the percentage of the total core area: Total bone area, vital bone and new bone formation, residual graft material and fibrous or marrow space.

5. STUDY AIMS

The aims of clinical, radiographic, and laboratory measurements are to assess:

1. Level of discomfort (VAS from 1-10), and complications (infections)
2. Soft tissue thickness center of grafted sockets
3. Buccal plate thickness

4. Changes in width and height of alveolar processes at the time of pre-extraction and post-extraction
4. Percentage of tissue changes: newly formed bone, residual allograft, fibrous tissue and marrow space
5. Need of further ridge augmentations

6. CRITERIA FOR EVALUATION:

a. Efficacy Endpoint:

After 4 months of healing, clinical measures of soft and hard tissue were obtained. Re-entry surgeries were performed and trephined bone cores were harvested.

b. Safety Evaluations:

Incidence of adverse events was monitored by a safety committee.

Chair of Safety committee:

Dr. Mark Ryder, DMD

Chair of Periodontology Divison, Orofacial Sciences Department, University of California, San Francisco

7. STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) was written describing all analyses that were performed. The SAP contained any modifications to the analysis plan described below:

A. Interim Analysis:

When approximately 50% of patients have completed the study through visit 2 – extractions and ridge presevations, an interim analysis for safety was conducted by an independent data monitoring committee. Serious adverse events was monitored by the committee on an ongoing basis throughout the study.

B. Sample Size and Randomization:

The table below gave estimates of the power for different sample sizes and estimated standard deviations assuming a difference of 1.0 mm comparing the extraction methods for each patient where the paired difference was comparing the randomized side of the mouth. All calculations assume a paired analysis with the level of the test (alpha) = 0.05. All calculations for sample size and power were done with Stata 14.1, Statacorp, College Station, TX. Histological, micro-CT, intergroup comparisons of changes, pre-operative and 4 month post-operative clinical datas was analyzed primarily by paired t-test.

Table A: Estimates of the study power

Assume difference = 1.0 mm
level of the test (alpha) = 0.05

	Power for different sample sizes and standard deviations				
	Sample size				
Estimated Standard Deviation	10	11	12	13	14
0.07	0.89	0.91	0.94	0.98	0.99
0.08	0.84	0.87	0.92	0.96	0.97
0.09	0.82	0.86	0.90	0.95	0.96

III. RESULTS

III. RESULTS

In this present prospective controlled clinical study, the data presented here was from one center, the Periodontology Division at University of California, San Francisco.

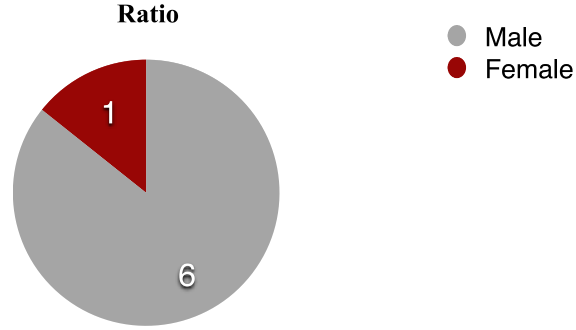
1. Demographic Data

Table 1 shows the demographic data of study population. A total of 9 patients were recruited into the study, 2 patients were excluded at the surgical phase due to unqualified surgical outcomes, which included non-intact and/or buccal bone dehiscences. The data of total of 7 patients qualified for the final analyses were included in this result.

Table 1: Demographic data	
Patients completed the study	7 (1 female 6 males)
Patients exluded due to surgical outcome	2
Age Range (years)	60-80
Mean	71.6
Maxilla Anteriors	2
Maxilla Premolars	5
Mandible Anteriors	6
Mandible Premolars	1
Additional Ridge Augmentation	1*
Infections	0

** Due to optimizing bony angulation for anterior implant*

Chart 1: Male : Female Ratio



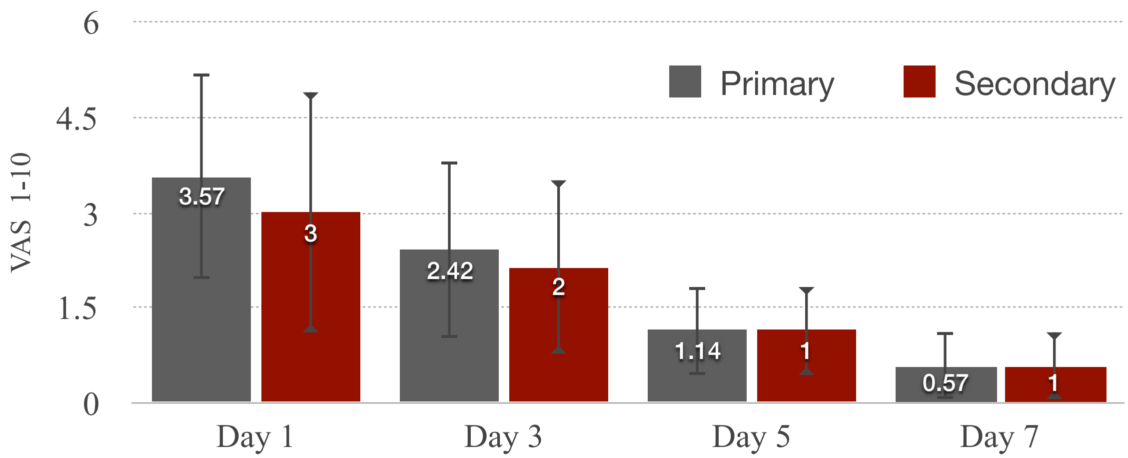
2. Level of discomfort based on visual analog scale (VAS 1-10)

Table 2 and Chart 2 are the level of discomfort of primary soft tissue closure and secondary healing intention groups based on visual analog scale from 1-10 (VAS). They show no statistically significant differences between two techniques (p>0.05 Welch Two Sample t-test).

Table 2: Level of discomfort

Level of Discomfort (Visual analog scale)	Primary Closure Mean	Secondary Healing Mean
Day 1 t = 0.60302, df = 11.676, p-value = 0.558 95 percent confidence interval: -1.499609 2.642466	**3.57** SD: +/-1.62	**3.00** SD: +/-1.91
Day 3 t = 0.38974, df = 11.983, p-value = 0.7036 95 percent confidence interval: -1.311798 1.883227	**2.43** SD: +/-1.40	**2.14** SD: +/-1.35
Day 5 t = 0, df = 12, p-value = 1 95 percent confidence interval: -0.8036672 0.8036672	**1.14** SD: +/-0.69	**1.14** SD: +/-0.69
Day 7 t = 0, df = 12, p-value = 1 95 percent confidence interval: -0.622518 0.622518	**0.57** SD: +/-0.53	**0.57** SD: +/-0.53

Chart 2: Level of Discomfort (VAS 1-10)



3. Soft tissue thickness measure at center crest of the grafted sockets

Table 3 and Chart 3 are the thickness of soft tissue measured at center crest of grafted sockets. They show no statistically significant differences between two techniques ($p>0.05$ Welch Two Sample t-test)

Table 3: Soft tissue thickness measure at center crest		
Soft Tissue Thickness	**Primary Soft Tissue Closure Mean (mm)**	**Secondary Healing Intention Mean (mm)**
t = -0.13525, df = 10.583 **p-value = 0.895** 95 percent confidence interval: -1.239421 1.096564	**2.93** SD: +/-0.79	**3.00** SD: +/-0.15

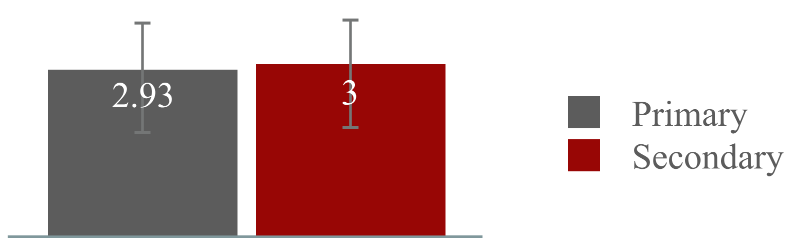


Chart 3 - Soft Tissue Thickness At Center Crest (mm)

4. Buccal plate thickness measured on CBCT

Table 4 and Chart 4a, 4b are the thickness of buccal plates measured on pre-operative CBCT. They show no statistically significant differences between two groups (p-value = 0.186 , Welch Two Sample t-test)

Table 4: Buccal plate thickness measured on CBCT

Buccal Plate Thickness measure on CBCT /Distance From The Crest (mm)	Primary Closure Mean (mm)	Secondary Healing Mean (mm)
0mm **t = -0.19673, df = 11.724** **p-value = 0.8474**	**0.87** SD: +/-0.56	**0.93** SD: +/-0.66
2mm **t = 0.67238, df = 10.72** **p-value = 0.5156**	**1.53** SD: +/-1.20	**1.15** SD: +/-0.84
4mm **t = 1.8601, df = 7.8611** **p-value = 0.1008**	**1.89** SD: +/-1.40	**0.83** SD: +/-0.56
6mm **t = 0.63787, df = 9.6832** **p-value = 0.5384**	**1.00** SD: +/-0.56	**0.82** SD: +/-0.46
8mm **t = 2.4043, df = 8.8704** **p-value = 0.04**	**1.46** SD: +/-0.64	**0.67** SD: +/-0.46
10mm **t = -2.2904, df =1.4455** **p-value = 0.1957**	**0.69** SD: +/-0.23	**1.53** SD: +/-0.47

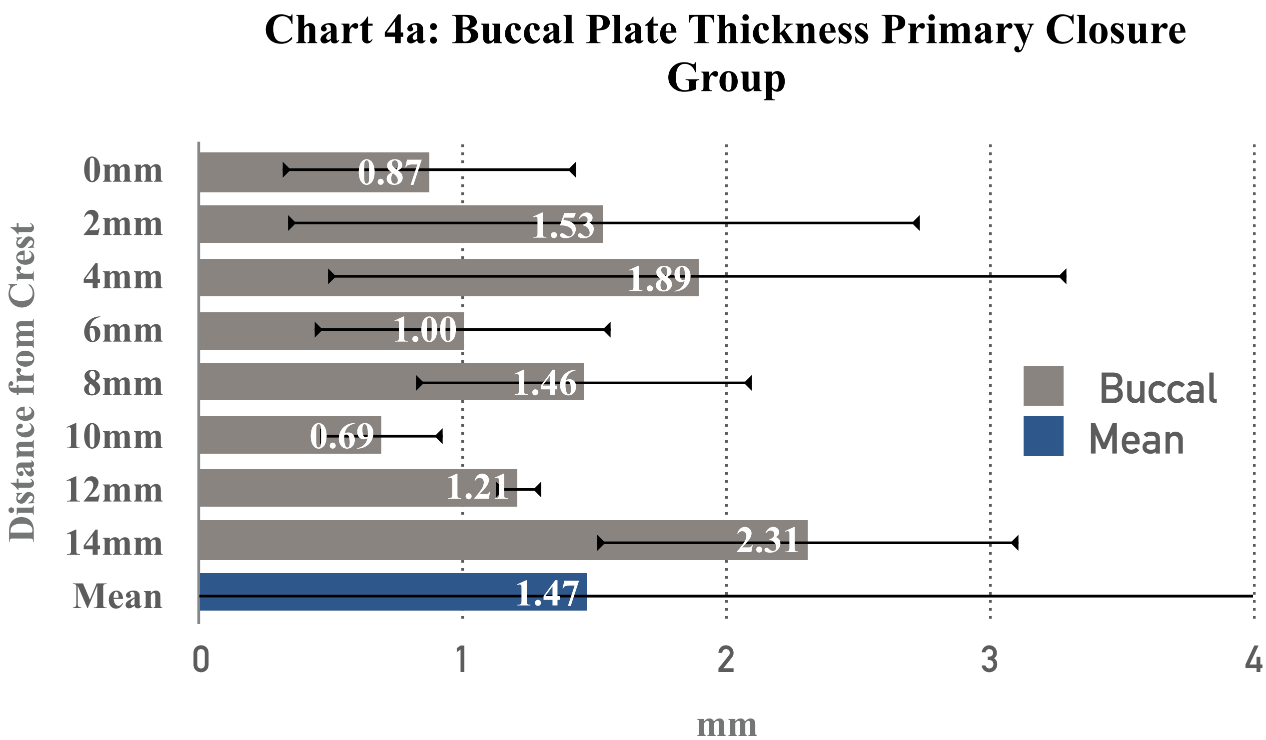


Chart 4a: Buccal Plate Thickness Primary Closure Group
Distance from Crest
0mm
2mm
4mm
6mm
8mm
10mm
12mm
14mm
Mean
0.87
1.53
1.89
1.00
1.46
0.69
1.21
2.31
1.47
Buccal
Mean
0
1
2
3
4
mm

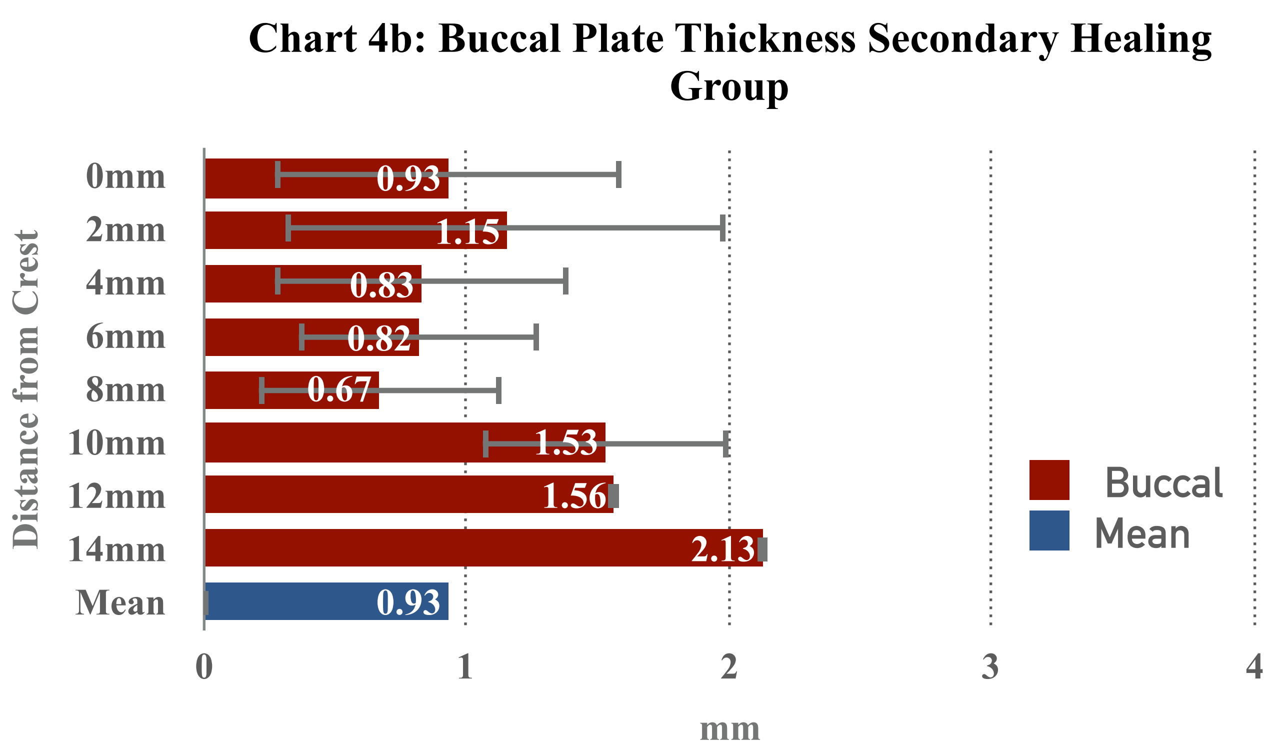


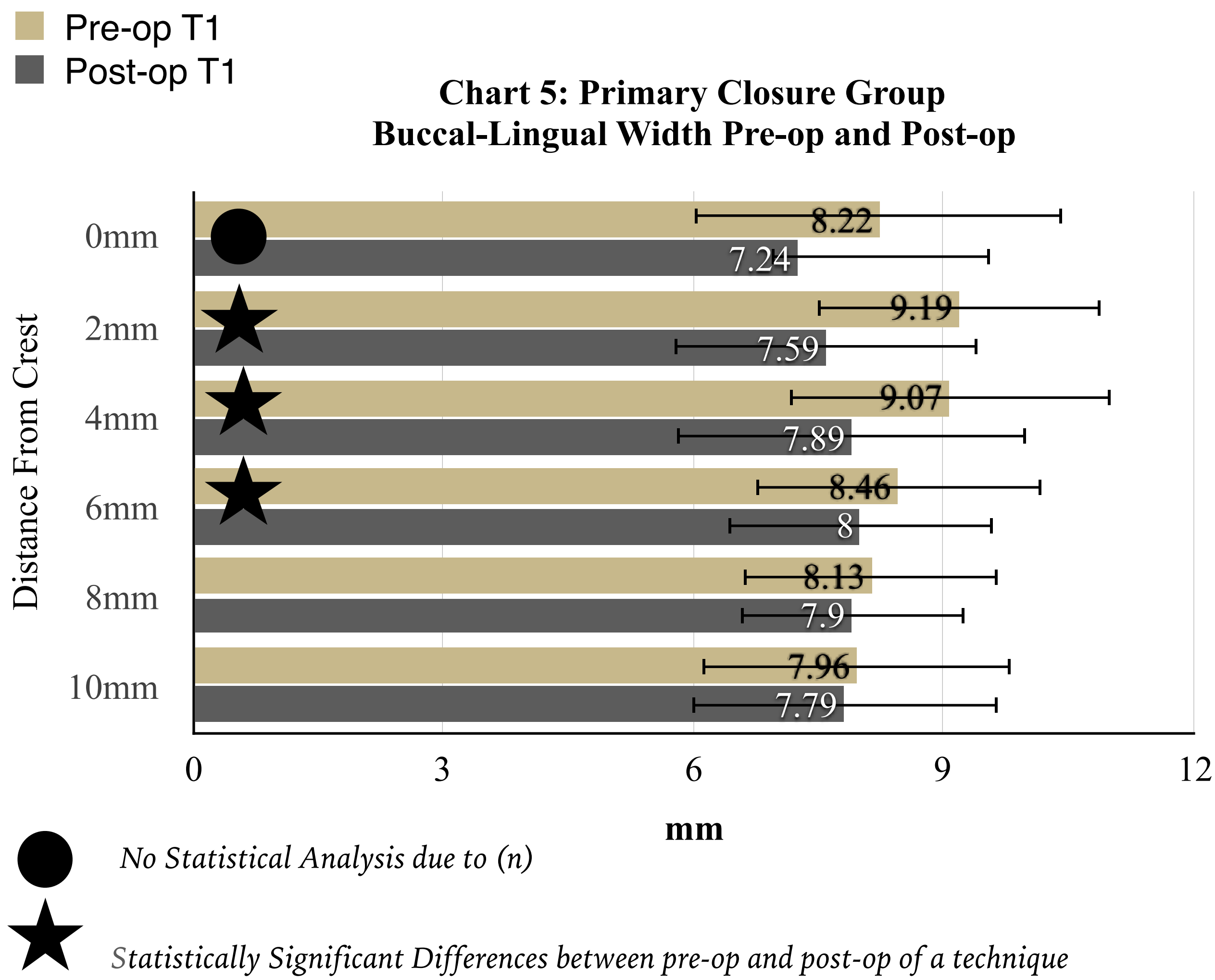
Chart 4b: Buccal Plate Thickness Secondary Healing Group
Distance from Crest
0mm
2mm
4mm
6mm
8mm
10mm
12mm
14mm
Mean
0.93
1.15
0.83
0.82
0.67
1.53
1.56
2.13
0.93
Buccal
Mean
0
1
2
3
4
mm

5. Buccal-lingual width of alveolar process of primary closure group

Table 5 and Chart 5 are the buccal-lingual width of alveolar process in 2mm advancements measured on pre-operative and post-operative CBCT scans of primary closure group. They show no statistically significant differences between two groups (p>0.05 Welch Two Sample t-test)

Table 5: Buccal-lingual changes of alveolar process of primary closure group

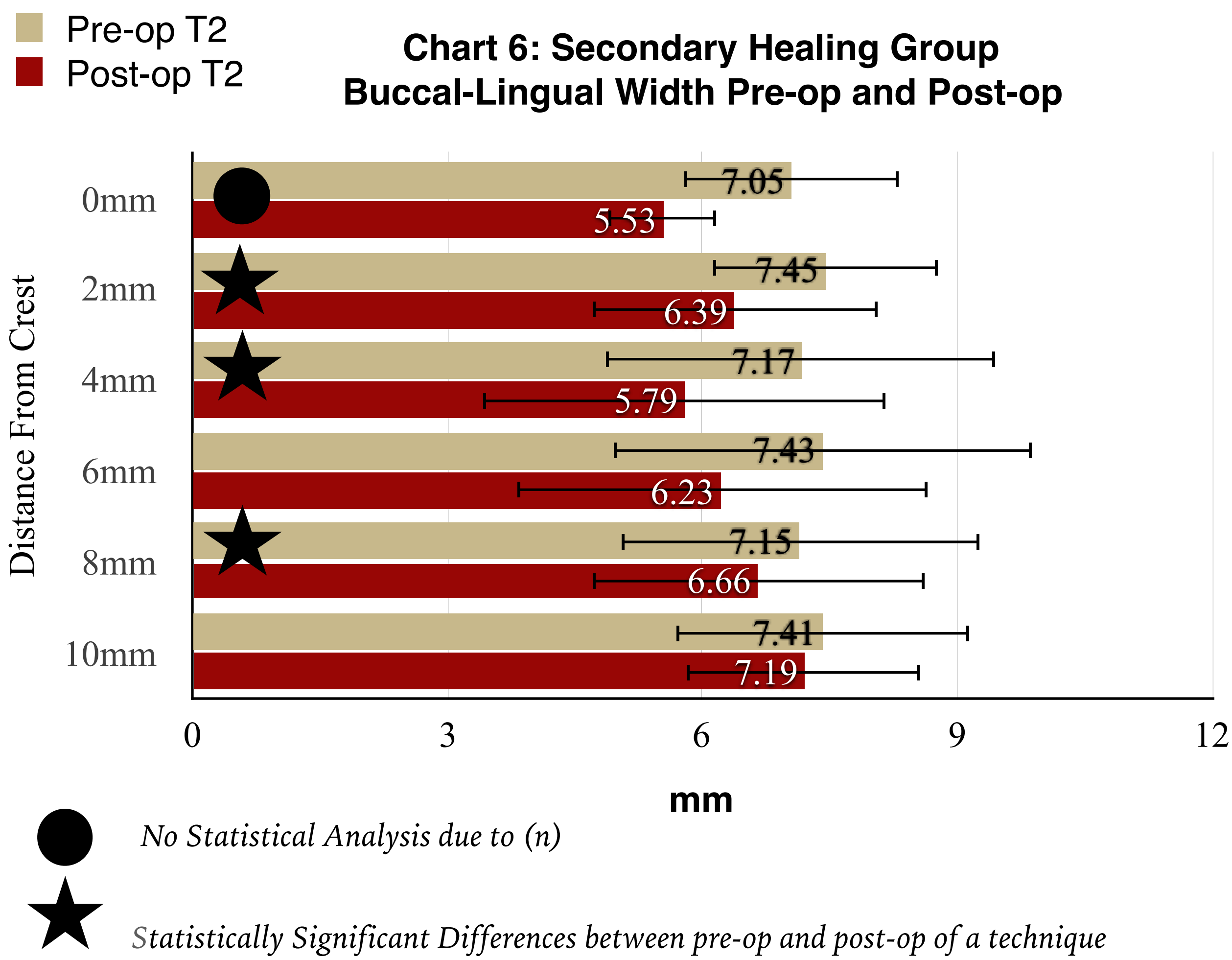
Buccal - Lingual Width Changes —————————————— Distance from the crest	Primary Closure Pre-operative Mean (mm)	Primary Closure Post-operative Mean (mm)
0mm	**8.22** SD: +/-2.21	**7.24** SD: +/-2.30
2mm **t = 7.0783, df = 4, p-value = 0.002103** 95 percent confidence interval: 1.475619 3.380381	**9.19** SD: +/-1.70	**7.59** SD: +/-1.81
4mm **t = 3.6405, df = 6, p-value = 0.01083** 95 percent confidence interval: 0.3864112 1.9709317	**9.07** SD: +/-1.92	**7.89** SD: +/-2.09
6mm **t = 2.6433, df = 6, p-value = 0.03837** 95 percent confidence interval: 0.03385697 0.87757161	**8.46** SD: +/-1.70	**8.00** SD: +/-1.57
8mm **t = 2.2171, df = 6, p-value = 0.06847** 95 percent confidence interval: -0.02384166 0.48384166	**8.13** SD: +/-1.53	**7.90** SD: +/-1.34
10mm	**7.96** SD: +/-1.85	**7.79** SD:+/-1.87



6. Buccal-lingual width of alveolar process of secondary healing group

Table 6 and Chart 6 are the buccal-lingual width of alveolar process in 2mm advancements measured on pre-operative and post-operative CBCT scans of secondary healing group. They show no statistically significant differences between two groups (p>0.05 Welch Two Sample t-test)

Table 6: Buccal-lingual changes of alveolar process of secondary healing group		
Buccal - Lingual Width Changes ——————————————— **Distance from the crest**	**Secondary Healing Mean Pre-operative (mm)**	**Secondary Healing Mean post-operative (mm)**
0mm	**7.05** SD: +/-1.27	**5.53** SD: +/-0.64
2mm **t = 3.0092, df = 4, p-value = 0.03958** 95 percent confidence interval: 0.1324394 3.2915606	**7.45** SD: +/-1.32	**6.39** SD: +/-1.69
4mm **t = 6.8082, df = 6, p-value = 0.0004922** 95 percent confidence interval: 0.8840205 1.8759795	**7.17** SD: +/-2.29	**5.79** SD: +/-2.38
6mm **t = 2.2432, df = 6, p-value = 0.06606** 95 percent confidence interval: -0.1088612 2.5060040	**7.43** SD: +/-2.46	**6.23** SD: +/-2.41
8mm **t = 2.9718, df = 6, p-value = 0.0249** 95 percent confidence interval: -0.08655095 0.89344905	**7.15** SD: +/-2.10	**6.66** SD: +/-1.96
10mm	**7.41** SD: +/-1.72	**7.19** SD:+/-1.36

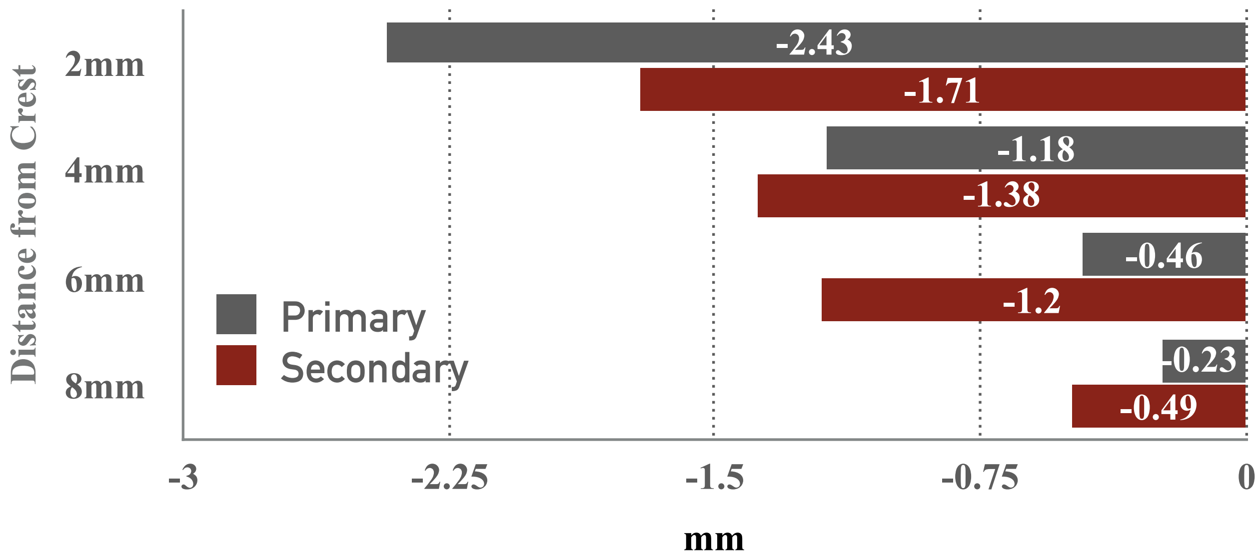


7. Comparing buccal-lingual width changes pre-operative and post-operative of primary closure and secondary healing groups

Table 7 and Chart 7 are the comparison of buccal-lingual width changes (pre-operative and post-operative) between primary closure and secondary healing groups. Buccal-lingual width changes of alveolar process were measured in 2mm advancements on pre-operative and post-operative CBCT scans of primary and secondary healing groups. They show no statistically significant differences between two groups (p>0.05 Welch Two Sample t-test)

Table 7: Comparing buccal-lingual changes pre-operative and post-operative of primary closure and secondary healing groups			
Buccal - Lingual Changes **Distance from the crest**	**Primary Closure** **Differences between Pre/post Mean (mm)**	**Secondary Healing** **Differences between Pre/post Mean (mm)**	**Primary Pre/post versus Secondary Pre/Post**
0mm	**N/a**	**N/a**	**N/a**
2mm	**-2.43** **t = 7.0783, df = 4** **p-value = 0.002103**	**-1.71** **t = 3.0092, df = 4** **p-value = 0.03958**	**t = -1.0778, df = 6.5688** **p-value = 0.3191** 95 percent confidence interval: -2.3080268 0.8760268
4mm	**-1.18** **t = 3.6405, df = 6** **p-value = 0.01083**	**-1.38** **t = 6.8082, df = 6** **p-value = 0.0004922**	**t = 0.52736, df = 10.078** **p-value = 0.6094** 95 percent confidence interval: -0.6487418 1.0515989
6mm	**-0.46** **t = 2.6433, df = 6** **p-value = 0.03837**	**-1.2** **t = 2.2432, df = 6** **p-value = 0.06606**	**t = 1.3231, df = 7.2359** **p-value = 0.2261** 95 percent confidence interval: -0.5760245 2.0617388
8mm	**-0.23** **t = 2.2171, df = 6** **p-value = 0.06847**	**-0.49** **t = 2.9718, df = 6** **p-value = 0.0249**	**t = 1.3347, df = 10.107** **p-value = 0.2113** 95 percent confidence interval: -0.1734238 0.6934238

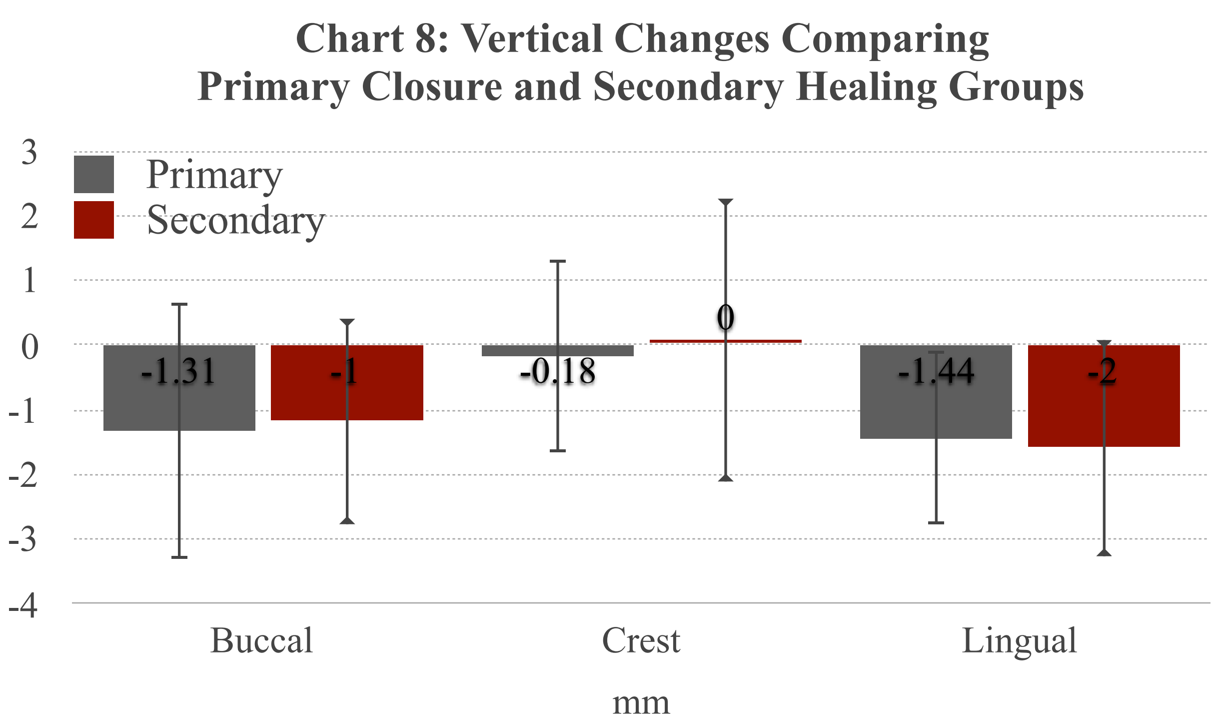
Chart 7: Comparing Buccal-Lingual Changes between primary closure and secondary healing groups



8. Vertical changes comparing between pre-operative and post-operative at buccal plate, crest, and lingual plate of primary closure and secondary healing groups

Table 8 and Chart 8 are the vertical changes comparing between pre-operative and post-operative at buccal plate, crest, and lingual plate of primary closure and secondary healing groups, measured on pre-operative and post-operative CBCT scans. They show no statistically significant differences between two groups ($p>0.05$ Welch Two Sample t-test)

Table 8: Vertical changes comparing pre-operative and post-operative of primary closure and secondary healing groups		
Vertical Changes (mm)	**Primary Closure Mean (mm)**	**Secondary Healing Mean (mm)**
Buccal t = -0.14602, df = 11.463, p-value = 0.8864	**-1.31** SD: +/-1.98	**-1.17** SD: +/-1.59
Crestal t = -0.27717, df = 10.579 p-value = 0.78	**-0.18** SD: +/-1.48	**-0.09** SD: +/-2.18
Lingual t = 0.18203, df = 11.471 p-value = 0.8587	**-1.44** SD: +/-1.34	**-1.59** SD: +/-1.67



9. Histologic and Histomorphometric Analyses

Figure 10: The bone core harvested from primary closure group. The lower magnification image shows a core that is intact in one piece. It consists of larger pieces of bone with dense vital bone. Trabeculae forms a good cancellous bone pattern. Particles of allograft incorporates with newly formed bone.
(X20 Stevenel's blue and Van Gieson's picro fuchsin)

Figure 10: Primary closure group low magnification

Figure 11: The bone core harvested from secondary healing group. The lower magnification image shows a core that is intact. It consists of smaller pieces of graft particles integrated with newly formed bone. Trabeculae forms a good cancellous bone pattern.
(X20 Stevenel's blue and Van Gieson's picro fuchsin)

Figure 11: Secondary healing group low magnification

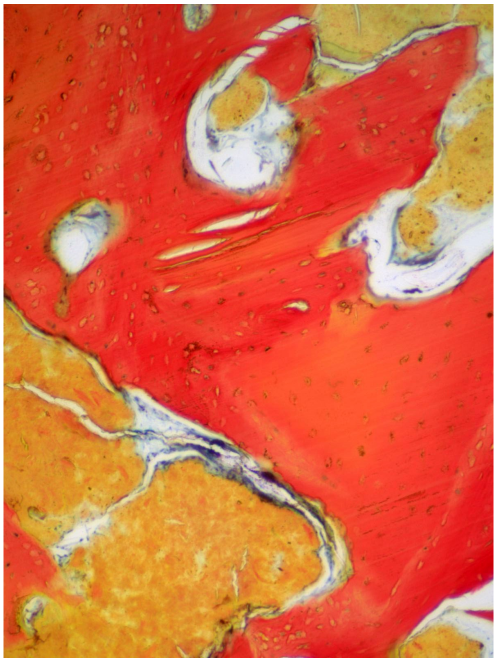


Figure 12: The high magnification image shows allograft particles embedded with newly formed bone. Different staining qualities reflect different areas of bone with the varying maturity levels. The lighter staining bone is more mature than the darker red staining bone.
(X100 Stevenel's blue and Van Gieson's picro fuchsin)

Figure 12: Primary closure group high magnification

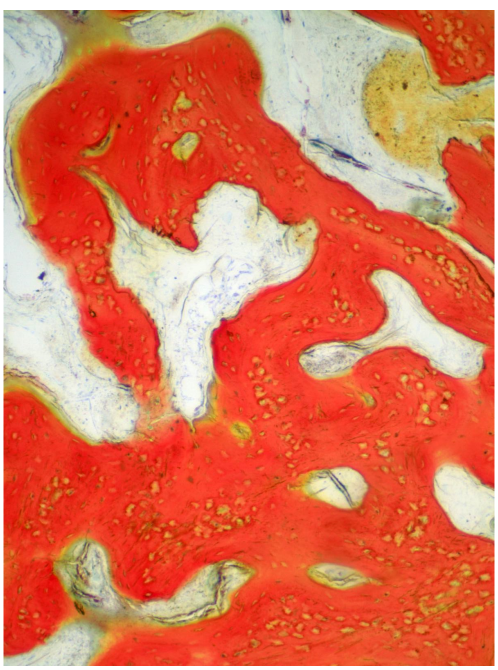


Figure 13: The high magnification image shows a large area of newly formed bone and a nice view of dense trabecular with good cancellous bone pattern. Allograft particles are well embedded in newly formed bone. Different staining qualities reflect different areas of bone with the varying maturity levels. The lighter staining bone is more mature than the darker red staining bone.

Figure 13: Secondary healing group high magnification

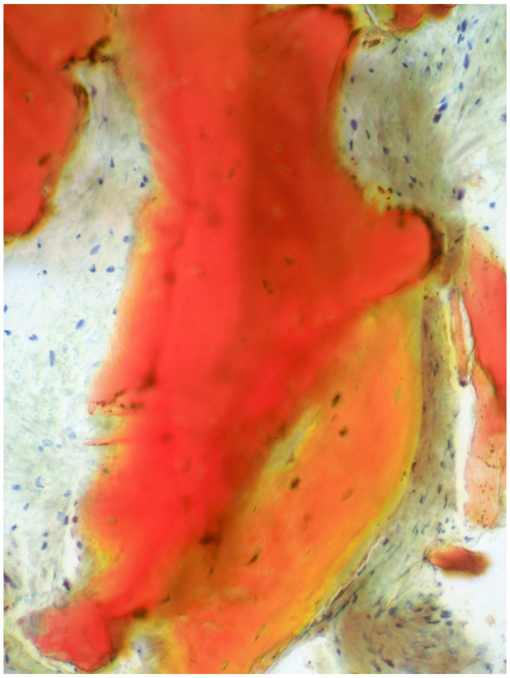


Figure 14: Primary closure group very high magnification

Figure 14: The very high magnification image shows an area of newly formed bone and mineralized allograft particles remodeling. with wide seam of green-staining osteoid lined with osteoblasts. Different staining qualities reflect different areas of bone with the varying maturity levels. The lighter staining bone is more mature than the darker red staining bone.
(X200 Stevenel's blue and Van Gieson's picro fuchsin)

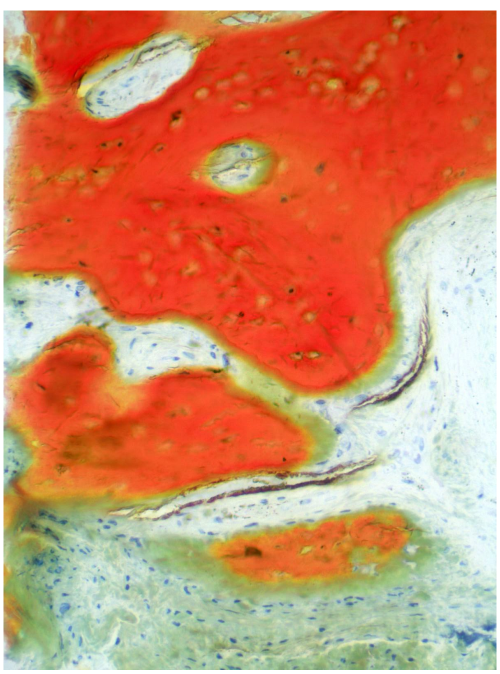


Figure 15: Secondary healing group very high magnification

Figure 15: The very high magnification image shows an area of newly formed bone and mineralized allograft particles remodeling with wide seam of green-staining osteoid lined with osteoblasts. Bridging of the allograft particles and newly formed bone is shown. Different staining qualities reflect different area of bone with the varying maturity levels. The lighter staining bone is more mature than the darker red staining bone.
(X200 Stevenel's blue and Van Gieson's picro fuchsin)

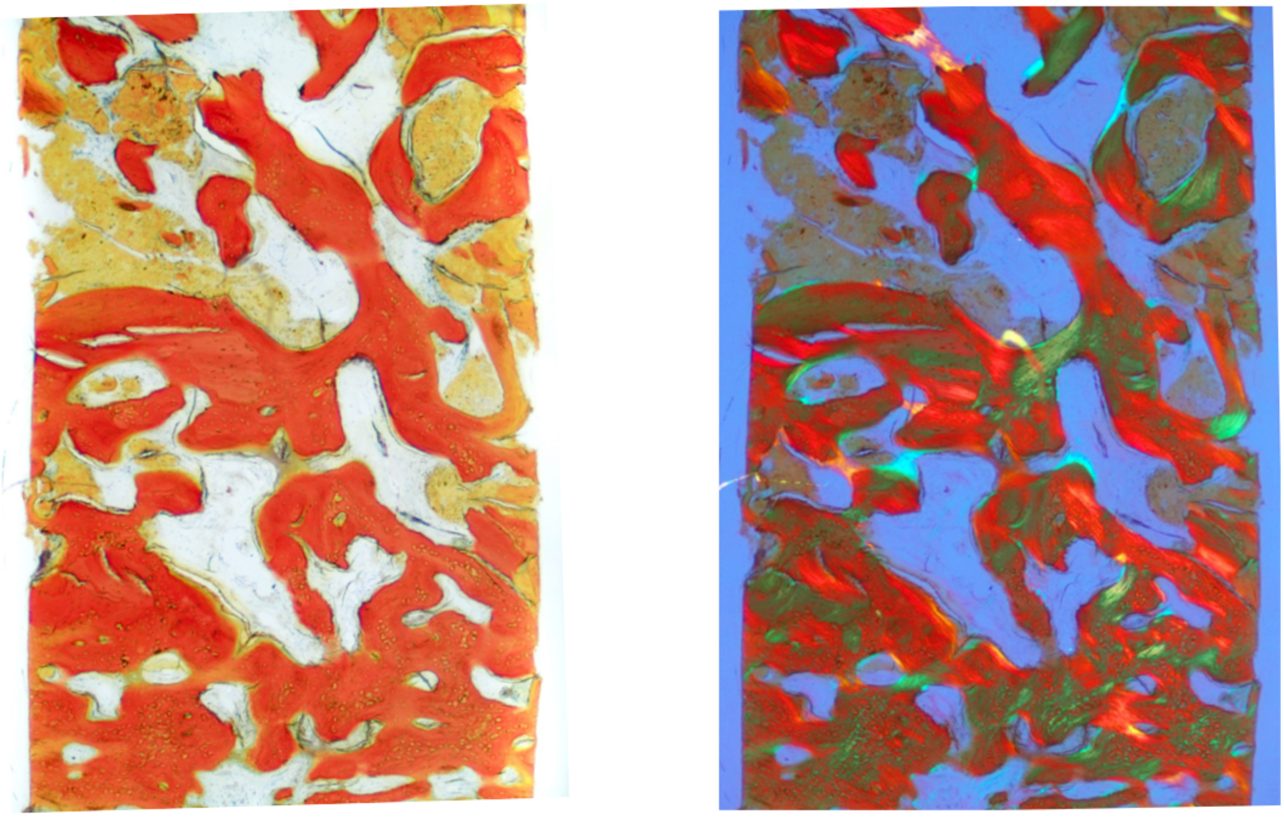


Figure 16: Core from secondary healing group
bright field vs polarized light

Figure 16: The two medium magnification images are the same view of a specimen. The left image is the view under bright light. The right image is the view under polarized light. They both assist each other in terms of determining the nature and the maturity of bone whether it is allograft particles or newly formed bone. Both images show newly formed bone along with bone remodeling with good cancellous bone pattern. (X40 Stevenel's blue and Van Gieson's picro fuchsin)

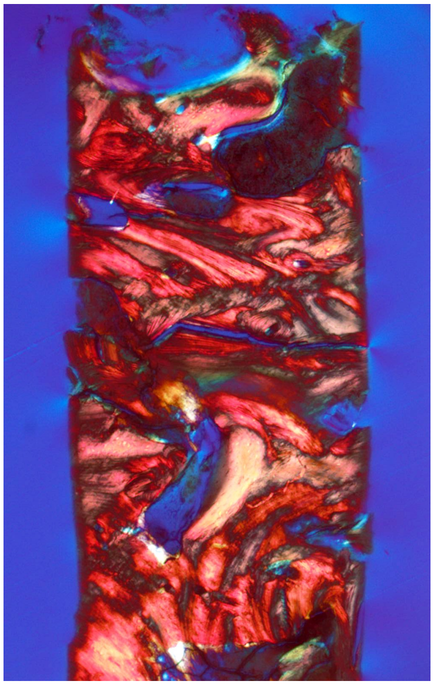


Figure 17: The lower magnification polarized image shows a core that is intact in one piece. It consists of particles of allograft incorporated and bridged with newly formed bone, along with bone remodeling.
(X20 Stevenel's blue and Van Gieson's picro fuchsin)

Figure 17: Primary closure group polarized view - low magnification

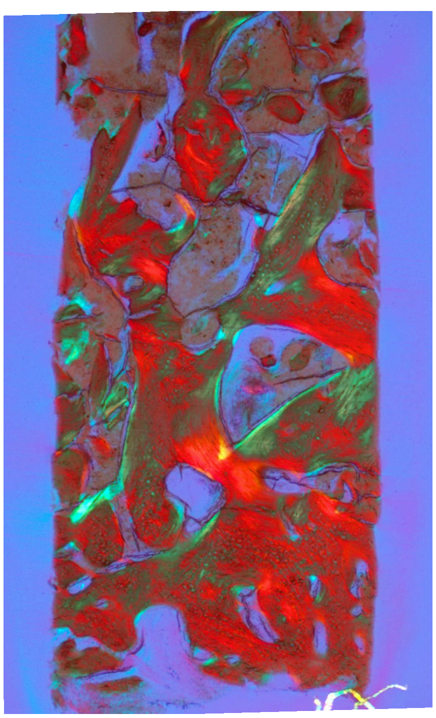


Figure 18: The lower magnification polarized image shows a core that is intact. It shows newly formed bone along with bone remodeling with good cancellous bone pattern.
(X20 Stevenel's blue and Van Gieson's picro fuchsin)

Figure 18: Secondary healing group polarized view- low magnification

TISSUE PERCENTAGE

Chart 9: Tissue Percentage Primary Closure Group

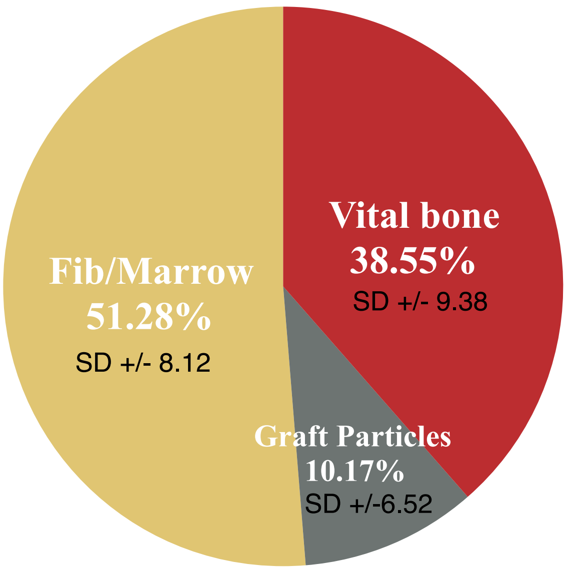


Chart 9: This pie chart shows the percentage of vital bone, residual graft particles, and fibrous tissue or marrow space along with standard deviations of the primary soft tissue closure group.

Chart 10: Tissue Percentage Secondary Healing Group

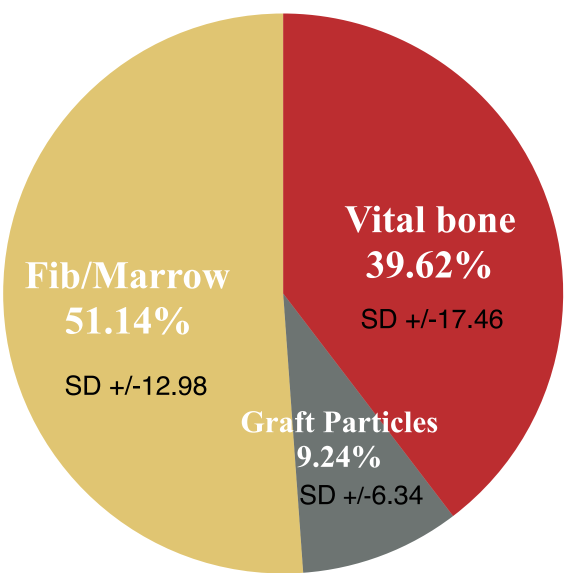


Chart 10: This pie chart shows the percentage of vital bone, residual graft particles, and fibrous tissue or marrow space along with standard deviations of the secondary healing group.

IV. DISCUSSION

IV. DISCUSSION

This present study found no statistically significant differences (p>0.05) between primary soft tissue closure and secondary healing intention groups regrading post-operative discomfort. Despite the presence of two vertical release incisions of the primary closure group, overall, patients generally healed rapidly after the procedures. In most cases, at day 1 post-operatively, the level of discomfort peaked to 4/10 on the VAS and then subsided gradually from day 3 to day 5. The level of discomfort returned close to baseline (0-1 on VAS) at 7 day post-operatively. To the best of our knowledge, there are no comparable studies that have examined the level of discomfort from primary soft tissue closure and secondary healing intention approaches.

We found no statistically significant differences (p>0.05) between primary soft tissue closure and secondary healing intention groups in term of soft tissue thickness at the center crest of the extraction grafted sockets. The mean soft tissue thickness at the center of the crest was 2.93mm in the primary closure group and 3mm in the secondary healing intention group. These measurements were comparable with those published by Iasella et al. 2003. We looked at the soft tissue thickness at the crest of the grafted sockets where the implants were placed, since published data shows a correlation between soft tissue thickness at the center of the crest and the amount of marginal bone loss around the dental implants. The soft tissue at the center of the crest forms a tissue cuff around the implant and establishes the biologic width around the implants. It has been documented that marginal bone around the implant undergoes remodeling until the biologic width has been created and stabilized. Hermann et al. concluded that biologic width did not change over the observation period in an animal model. These data indicate that the biologic width is a physiologically formed and stable structure over time. Berglundh et al. revealed that the biologic width was 2.05mm for teeth compared to 2.14mm for submerged implants. Furthermore, Linkevicius et al. showed that the gingival thickness at the crest effects marginal bone loss around implants. There was significantly more marginal bone loss around implants with thin mucosa (2mm or less) compared to those with thick mucosa(more than 2 mm).

We took into consideration the buccal plate thickness when analyzing the alveolar bone remodeling. Using DICOM data, we collected the measurements of buccal plate thickness of all studied teeth before the surgery. We understood that the measurements of buccal plate thickness on CBCTs would be an underestimation of the actual clinical measurements. However, our intent was to create a baseline to compare control and experimental groups, and we found no statistically significant differences between the two groups ($p>0.05$). Tavtigian showed that any periodontal surgery, which activates osteoclast activity, would contribute to alveolar bone loss especially at the facial aspect of the radicular alveolar crest. In an animal study, Araujo et al. 2005 revealed that full thickness flap elevation in areas with a thin buccal wall caused about 1 mm of vertical bone loss. In contrast, areas with a thick lingual wall exhibited only 0.1mm of bone loss. This suggested that a thin radicular bone is more prone to resorption than a thick radicular bone following a mucoperiosteal flapped procedure.

This present study revealed that both ridge preservation approaches, primary soft tissue closure and secondary healing intention, resulted in alveolar bone loss. This is consistent with published data on extraction sockets and flap elevation studies. An Oosteology consensus report from Hammerle et al. 2011 suggested that, within the first 6 months after tooth extraction, alveolar ridge undergoes a mean horizontal reduction of 3.8mm and a mean vertical reduction of 1.24mm. The alveolar ridge preservation technique aims to either maintain the profile of the alveolar ridge or enlarge the ridge width for predictability of future implant placement and esthetic outcomes. The results of this present study agree with those of Iasella et al. 2003. Both studies concluded that with ridge preservation and the use of freeze-dried allograft and collagen membrane, there was still statistically significant horizontal bone loss after the extraction ($p>0.05$). The most significant horizontal bone loss happened within 0-4mm from the alveolar crest based on our results.

Comparing primary soft tissue closure and secondary healing intention approaches, we found no statistically significant difference between the two groups. Our results contradicted those of Barone et al. 2014. Their results found that the primary closure group had more statistically significantly negative results, such as increased alveolar width resorption of the post extraction site. Their results also revealed that the flapped technique seemed to show less vertical bone resorption on the buccal plate than the flapless technique. Overall, the results related to the amount of vertical and horizontal bone loss of this present study are comparable to other published reports (Hammerle et al. 2011,Vignoletti et al. 2011, Horowitz et al. 2012, Avila-Ortiz et al. 2014, Jambhekar et al. 2015)

The tissue changes in this study at the histologic level were comparable with the other published studies (Iasella et al. 2003, Barone et al. 2015, Risi et al. 2015). In a systematic review, Risi et al. 2015 analyzed the histologic and histomorphometric data resulting fromvarious types of bone grafting materials in conjunction with various surgical approaches at different time points. At 3 months post-op, allograft had the highest percentage of newly formed bone. The findings relative to the percentage of tissue changes were comparable with the results of this present study. We found a mean of 38% newly formed bone and 9-10% particulate graft remaining. We also found no significant difference in terms of newly formed bone, graft particles, and soft tissue or marrow space between the two groups. Conducting a similar evaluation on two ridge preservation techniques, primary closure and secondary healing using xenograft, Barone et al. 2015 also revealed no statistically significant differences between the flapped and the flapless groups ($p>0.05$) in term of tissue changes.

V. SUMMARY

This present study found no statistically significant differences between primary and secondary healing approaches for ridge preservation after tooth extraction ($p>0.05$).

This present study agreed with previous systematic reviews, that ridge preservation provides a benefit in minimizing, but not completely preventing, horizontal and vertical tissue loss. (Ten Heggeler et al. 2010, Vignoletti et al., 2012; Avila-Ortiz 2014)

VI. FUTURE DIRECTION

Due to a small sample size (n=7) from one center of a multi center study, the data derived from this thesis provided preliminary results. A larger sample size and longer follow-up period would provide a more in-depth conclusion for comparing between primary closure and secondary healing intention approaches.

FUNDING

THIS STUDY WAS FUNDED BY

THE UCSF PERIODONTOLOGY DIVISION AND BIOHORIZONS COMPANY*

**This study was supported in part by a contract with BioHorizons; data from the study is independent of any oversight by BioHorizons.*

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