Study Title: **A Randomized Controlled Trial Comparing Esthetic Outcomes of Immediately Placed Implants Receiving Immediate Provisionalization and Delayed Restoration**

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A Randomized Controlled Trial Comparing Esthetic Outcomes of Immediately Placed Implants Receiving Immediate Provisionalization and Delayed Restoration

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Introductory Statement

Implant therapy is a highly predictable treatment option for replacing missing teeth; however, long waiting time for the conventional implant placement protocol (3-6 months) discourages many patients who are considering implant therapy. With improvement in technology, the immediate implant placement protocol (IIP) has become more popular, especially in the esthetic zone. The obvious advantage is to save the waiting time patients have to suffer through. Soft tissues might be preserved when the immediately placed implant is also restored immediately, following the immediately implant restoration protocol (IIR).[1,2] Limited evidence is present to demonstrate the esthetic advantages of the combination protocol (IIP + IIR).[3] Therefore, this study is aimed at investigating the esthetic outcome of single-tooth implants immediately placed and immediately restored, comparing to those immediately placed and restored after 4 months in the pre-maxilla. .

General Investigational Plan

A single center, randomized, controlled, parallel-arm study is planned to investigate esthetic outcomes after IIP + IIR in the esthetic zone. Forty adult patients who have a hopeless maxillary anterior or premolar tooth, with intact adjacent teeth will be enrolled. A signed written informed consent will be obtained after he or she has been given verbal and written information describing the nature and duration of the study. Subjects will not be screened or treated until an informed consent has been obtained. Patient information will be protected according to the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Enrolled patients will be randomly placed into one of two treatment groups, immediate implant placement and restoration group (IIR) or the IIP + delayed restoration group (DR). For all patients, the tooth will be extracted and an implant placed immediately. The subject will be randomly assigned before the surgery visit to either restoring the implant immediately (Test group) with a provisional crown or restoring the implant at 4 ± 1 month after implant placement (Control). Outcome analyses will be clinical and radiographic parameters to determine the esthetic outcomes of immediately restored IIP implants, in comparison to those immediately placed but restored in a delayed approach.

Study Protocol

I. Introduction

Immediate implant placement (IIP) is becoming a prevailing treatment modality because of improvement in implant surfaces and understanding of implant healing. The propelling force for the popularity of IIP is probably from patients' desire for faster dental rehabilitation. Numerous clinical trials[3-6] have proved predictability of this approach, with survival rate similar to the conventional approach, provided with prudent case selection and treatment planning. Without being satisfied by high success rate in terms of implant function, we are now striving to achieve esthetic success. IIP was supposed to preserve soft and hard tissues around the implant, but this statement failed to hold true, as suggested by preclinical[7] as well as clinical studies.[8] Bone and peri-implant mucosa continue to remodel after an implant is placed in a fresh socket. A recent long-term follow-up study[9] further pointed out there might be an increased risk of continued facial mucosa recession that is associated with IIP. On the other hand, some studies [1-3] suggested IIP might actually reduce the amount of facial mucosa recession, especially when the implants are also immediately restored. The effect of IIP on facial soft tissues remains unsolved.

Looking into this interesting and clinically relevant issue more closely, some factors might have contributed to the controversy that was observed in the literature. First and foremost is probably the implant position. Immediately placed implant has a tendency to shift to the buccal plate because it follows the pathway with the least resistance.[10] Buccally placed implants have three times the amount of mucosal recession.[11] Therefore, it is advisable to use a surgical guide and guide the implant in the cingulum position. Second, the tissue biotype might determine the amount of recession after implant placement. It has been long known that a thin tissue is more prone to recess.[12] Patients with a thin tissue biotype are at a higher risk for esthetic failures after receiving immediately placed implants.[9] Surgical modifications have been proposed to overcome potential recession, e.g. connective tissue graft and a flapless surgery. Placing a connective tissue graft has increased the buccal soft tissue by 1.1mm,[13] although its effect on recession has never been investigated.

Last but not the least, buccal plate thickness seems to be a determining factor for the stability of its overlying soft tissue. A thicker buccal plate might resist bone resorption more effectively.[14] Furthermore, it is suggested at least 2 mm

thick crestal bone might be necessary for a stable dimension of facial mucosa.[15] Unpredictable bone remodeling after immediate implant placement, especially in situations where there is a buccal wall defect, might be one of the reasons for seeing advanced soft tissue recession.[16]

Immediate implant restoration (IIR) is defined when an implant is restored within 48 hours after implant placement.[17] With adequate implant primary stability, an implant can be restored immediately, however, it might be wise to leave it out of occlusion during the healing phase to allow for proper formation of osseointegration. The greatest advantage of this approach is to restore esthetics immediately. The responses of soft and hard tissues to this approach have been studied to some extent. A recent systematic review[18] suggested that the timing of the restoration does not influence marginal bone level around implants. However, IIR might preserve the height of papilla[19] and the level of mucosal margin.[3] Therefore, IIR of immediately placed implants might improve the esthetic outcomes.

II. Objectives

The primary objective of this study is to evaluate the effect of IIR on clinical outcomes (mucosal recession and esthetics) of IIP implants, compared with the effect of DR on clinical outcomes of IIP implants. Essentially, we are testing whether a temporary crown placed right after the surgery will have better clinical outcomes than not placing one. Secondary outcomes will include radiographic marginal bone changes.

III. Treatment

A. Patient selection

Forty patients will be randomized into two experimental groups: 20 in the test group (IIR) and 20 in the control group (DR). In both groups, the hopeless tooth will be extracted atraumatically without raising a flap. The tooth is replaced by an immediately placed implant. The test implants will be restored with a provisional crown immediately, which will be replaced by a permanent crown at 4 ± 1 month (crown impression visit) after implant placement. The

control implants will be restored at 4 ± 1 month (crown impression visit) after the surgery.

Subjects can be considered a screen fail at any study visit prior to the surgery and up until the time that the implant is placed and deemed stable. All screen failed subjects will be replaced.

Inclusion and exclusion criteria

Inclusion Criteria
• Male or female, aged ≥ 21 • A minimum dentition of 20 permanent teeth (including natural rooted teeth or dental implants; pontic of a fixed bridge is not considered a tooth) • A maxillary premolar, canine, lateral incisor or central incisor with a hopeless prognosis • Presence of adjacent teeth and enough clearance for an implant crown • Presence of sufficient bone apical to the root apex of the hopeless tooth

Exclusion Criteria
Systemic criteria: • Current heavy smokers (>10 cigarettes per day) or heavy smoker who quit less than 1 year ago • Pregnant or plan to get pregnant or lactating mothers • Current alcoholism or drug abuse • Diseases of the immune system or any medical condition that may influence the outcome (uncontrolled diabetes (HbA1c >7), neurologic or psychiatric disorders, systemic infections, …) • Radiation therapy in the head and neck area within 3 years • Current use of oral bisphosphonates for >3 years • History of IV bisphosphonates use • Other medical conditions that may contradict an implant surgery **Intraoral criteria:** • Area of study is adjacent to an existing implant • Acute infection at/or adjacent to the extraction site (e.g., sinus tract, swelling) • Observable gingival changes due to use of medications known to affect the periodontal status (calcium antagonists, anticonvulsives, immunosuppressants, anti-inflammatory medications…)

- Untreated deep carious lesions or defective restorations that can potentially exacerbate during the course of the experiment
- Uncontrolled periodontal disease
- Poor oral hygiene (>20% FMPS)

CBCT criteria:

- More than 4mm of buccal plate dehiscence is present on the CBCT scans

Intraoperative criteria:

- More than 4 mm of buccal plate dehiscence is present once the tooth is extracted

The screening visit (V1)

All participants will receive an informed consent form that explains the aims, courses, and potential benefits/risks of this study. They will be given no limit of time to read through it. The research team members will answer any questions regarding this study. Any research related activity will not be initiated unless they sign the consent form.

Medical history will be reviewed by system, using the School of Dentistry Medical History Questionnaire. Relevant health history information will be highlighted. Eligibility screen will be performed, including systemic and intraoral criteria. Blood pressure and heart rate will be measured. A peri-apical (intraoral) film will be taken if the patient doesn't have one within 3 months available to the research team at the screening.

CBCT scans (V2 and V8)

Two CBCT scans will be taken by a trained technician under supervision of a board-certified oral radiologist at the University Of Michigan School Of Dentistry. The Dental School only does CBCT scans on certain days and at certain times. For subject convenience the first CBCT scan may be scheduled at the pre-implant visit and the second CBCT scan may be scheduled before the preparation and placement of crowns. However, one or both, may be done at separate visits due to dental school CBCT scan scheduling. Eligibility screening will be performed on the scan; subjects with more than 4 mm buccal bone dehiscence will be excluded.

Peri-apical radiographs

Peri-apical radiographs, including standardized radiographs, will be taken at the screening if unavailable, pre-implant placement, implant surgery, placement of restoration, and crown follow-up (final visit). At the

abovementioned visits, usually only one peri-apical film will be taken; however, if not of acceptable quality, it might be necessary to take another one. Likewise, if an x-ray was taken recently with good quality, a new x-ray might not be required at the screening visit. In the baseline surgery, 2 to 4 films may be taken to assure safety of the implant placement procedure. Custom-made stents will be fabricated from plastic film holders and blue mousse to ensure standardization of the radiographs.

Pre-implant placement visit (V3)

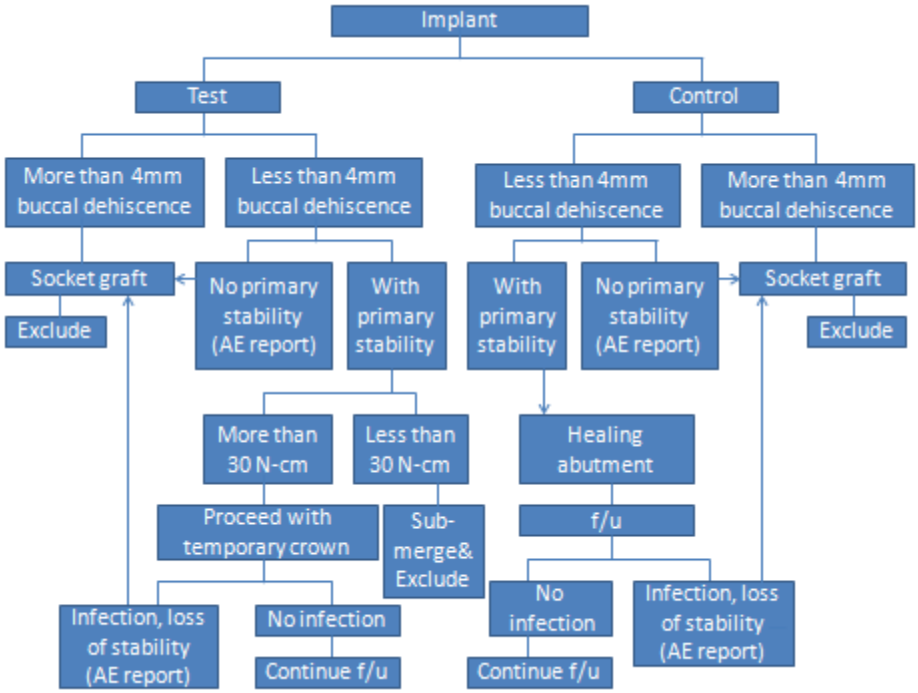
The informed consent will be checked (the purpose of checking the consent is to assure that the subject is still interested in the study and they are still eligible to be in the study which will also be another form of an AE screening) along with a review of the medical history. Impressions of the subject upper and lower jaws will be taken with alginate for preparation of study models and surgical guides. Bite registration will be taken with a silicone material. Clinical measurements will be taken, including probing depth, gingival recession, plaque index, gingival index, keratinized mucosa width, and the PES score. A standardized peri-apical film will be taken along with clinical photos. Eligible subjects will be randomly assigned to one of the two groups after V3.

Implant and bone surgery (V4)

The informed consent will be checked along with a review of the medical history. The blood pressure and heart rate will be checked before surgery. The area selected for surgery will be locally anesthetized and examined. The hopeless tooth will be extracted under local anesthesia, without raising a flap. If necessary, a small flap might be elevated to facilitate the extraction. For subjects with intact buccal plate (equal or less than 4 mm loss), an implant will be placed according to the manufacturer's protocol for both groups. The implant position follows the computerized surgical guides (Neoguide, Neobiotech, South Korea) that are designed based on the CBCT scans. The gap between the implant and socket wall will be filled with bone allografts (The tooth root dimension is most of the time larger than the implant). In cases with a small buccal wall defect, a collagen membrane will be used. The test implants will be restored immediately with a provisional crown, which will be replaced by a permanent crown. A healing abutment and collatape to contain bone grafts

will be placed for control implants but without immediate restoration during the healing period. A removable temporary denture may be provided at subject request. All surgical procedures will be performed by a periodontist. Implant stability will be assessed at the time of placement. Any adverse events such as no implant stability, etc. during the surgery will be reported. Clinical measurements will be taken including: socket-related and implant-related parameters. A standardized peri-apical radiograph will be taken, as well as clinical photos.

Subjects who lose more than 4mm of buccal plate after extraction will be excluded from the study at this time. They will receive bone allografts and collagen membrane as a socket grafting material. The test implant that does not achieve 30 N-cm will be treated as a control implant and excluded from the study.



Post-op visits after implant and bone surgery (V5, V6, V7 if necessary)

Post-op visits will be scheduled at 14 ± 3 days, 28 ± 3 days, and varied date upon subject oral condition, if needed. The informed consent along with a review of the medical history will be checked at each visit. Clinical measurements will be taken, including: mid-facial mucosal level, papilla height and labial ridge contour. Clinical photos will be taken during the visit. The

wound will be gently debrided and disinfected. Sutures, if any, will be removed.

Additional post-op visits (V7) may be necessary for conditions that require additional care for subject safety, such as premature wound exposure, minor infection, and slower healing. They are based on per subject needs for a visit, not for every subject and will be followed as adverse events. No clinical measurements will be taken at this visit.

Management of adverse events

If the dental implant does not achieve primary stability (10-20 % of prevalence rate) due to infection or other reasons, the implant will be removed in a brief surgery. The osteotomy site will be grafted with allograft bone and covered by a collagen membrane. The wound will be closed with sutures. The participants with the abovementioned conditions will be withdrawn from the study. Alternative treatments will be given. All adverse events will be reported.

Crown impression (V9)

The impression visit will be at 4 (+/- 1) months after the baseline surgery, depending on the healing of the bone graft and implant. The informed consent will be checked along with a review of the medical history. Any adverse events will be screened and reported. If the implant fails, it will be removed and the site will be grafted at no charge. The subjects with a failed implant will be excluded. Impressions will be taken for upper and lower jaws with alginate and silicone materials, along with a bite registration.

Crown placement (V10)

The final crown placement will be within several weeks from the impression. The informed consent will be checked along with a review of the medical history. Any adverse events will be screened and reported. If the implant is loose then the subject will be taken out of the study. The implant will be removed and bone placed where the implant was at no charge to the subject. Their participation in the study will be over at this time.

Clinical measurements, including PES/WES, mid-facial mucosal level, papilla height, and labial ridge contour will be taken. All components to be used will be commercially available from Neobiotech. A standardized radiograph and

intraoral photos will be taken. Multiple visits may be required to assure the quality of crowns.

Crown follow-up/Final visit (V11)

One crown follow-up visit will be scheduled at 10 (+/- 2) months after the baseline surgery. A standardized peri-apical film, clinical measurements, clinical photos and impressions/bite registration will be done. The clinical measurements include probing depth, plaque index, gingival index, keratinized mucosa width, PES/WES, mid-facial mucosal level, papilla height and labial ridge contour. The informed consent will be checked along with a review of the medical history. Any adverse events will be screened and reported.

Schedule of Events

Event	Screening	CBCT scan	Pre-implant placement	Implant and bone surgery	Post-Op visit 1	Post-Op visit 2	Additional post-Op visits (if necessary) (c)	CBCT scan	Crown impression (IP)	Crown Placement	Crown follow-up/ Final Visit
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Timeline				Baseline (BL)	14 D (+/- 3D)	28 D (+/- 3D)	Varied		4 (+/- 1) M after BL	3+ wks after IP	10 (+/- 2) M after BL
Informed consent	SIGN		X	X	X	X	X		X	X	X
Check BP, HR	X			X							
Med history review	X		X	X	X	X	X		X	X	X
Screen for adverse events				X	X	X	X		X	X	X
Eligibility Screen	X	X		X							
Impression and bite registration			X						X		X
CBCT Scan (a)		X						X			
Clinical measurements (b)			X	X	X	X				X	X
Periapical radiograph/ (S = Standardized)	X (optional)		X (S)	X (S)						X (S)	X (S)
Clinical photographs			X	X	X	X	X			X	X
Wound disinfection & suture removal (if any)					X	X	X				
Subject withdrawn by PI		Inadequate Bone		Inadequate Bone	Implant Loose	Implant Loose	Implant Loose		Implant Loose	Implant Loose	
Temp Crown for Test Group Only				X							
Bone Allograft				X							
Control Group – Temp Denture (at subject request)				X							

(a) The dental school only does CBCTs on certain days and at certain times. For subject convenience the first CBCT may be scheduled at the pre-implant visit and the second CBCT may be scheduled at the implant uncover surgery. However, one or both, may be done at separate visits due to dental school CBCT scheduling. Additionally, for the convenience of the subject, the Screening, first CBCT Scan and Pre-implant visit can be combined on the same day.

(b) Clinical measurements consist of plaque Index, gingival Index, probing depth, recession, PES/WES, width of keratinized tissue, thickness of keratinized tissue, gingival margin level and socket- and implant-related features. Not all measurements will be made in each visit. Specific parameters for each visit will be listed in CRF.

(c) Schedule for these visits is based on a per subject need for a visit, not for every subject. Conditions that require additional care for subject safety, such as premature wound exposure and slower healing might require

additional visits and will be followed as adverse events

IV. Statistical Analysis

Sample Size

A power analysis was performed using a statistical power calculator. This study will have a sample size of 40 subjects, 20 in each of the two groups. We estimate to have 80% power (with a Type I error rate of 5%) to detect a mean difference of 0.8mm mucosal recession, with the estimated standard deviation of 0.8mm.[22] This power calculation takes into account the estimated 10% of subjects drop out. A “p” value of less than 0.05 will be considered statistically significant.

Data Analysis

Mean values, standard deviations, and medians will be calculated for clinical and radiographic measurements. We will examine the univariate association of the defect size with the success of treatment using logistic regression. We will also attempt to examine the association of implant success with various combinations of clinical and radiographic parameters using multiple logistic regression, but acknowledge that we will be restricted by our sample size to at most two or three predictors in any model. Changes of the parameters over time within each group as well as differences between groups will be analyzed using the repeated measure of analysis of variance.

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