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TITLE: Factors Affecting Split Thickness Skin Graft Success Rates: A Randomized Control Trial

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AMENDMENTS/REVISIONS: None

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1.0 BACKGROUND AND HYPOTHESES

The radial forearm free flap (RFFF) and fibula free flap (FFF) are two of the most commonly used methods in head and neck reconstruction. The RFFF is a versatile flap. Its advantages include its thinness for intraoral reconstruction, long pedicle length with an average of 7.2 cm and longest length of 16 cm, option for using 2 veins, and reliability with a success rate of greater than 95%.[1,2] The FFF is also being increasingly used, usually to rebuild mandibular defects. Its advantages include providing a reliable long cortical bone for reconstruction, lengthy pedicle, and the option of dental implants in the future. [3–5] While both RFFF and FFF produce excellent functional and cosmetic results, their donor site cannot close primarily and oftentimes a split thickness skin graft (STSG) is needed.[6]

STSG are acquired using a Dermatome and placed over the intended donor site. A pressure dressing is then placed over the STSG to hold it in place. While STSG improves cosmetic and functional outcomes of the donor site, the failure of the STSG to completely take has been reported as high as 44.4% for RFFF and 42% for FFF.[7,8] However, both larger retrospective and prospective studies have placed estimated partial STSG loss at 15-20% range for both RFFF and FFF.[6,9,10] Factors associated with lower STSG take include diabetes, larger STSG, aspirin, STSG used for fibula donor sites, and graft sites that are casted. One hypothesis for why casting was associated with lower STSG take is because negative pressure dressing system may be superior to conventional bolster with or without casting for STSG success. [6] However, the data regarding this is mixed. Multiple prospective trials show no difference for STSG success rates for both RFFF and FFF between negative pressure systems and the conventional bolster, while retrospective trials show that negative pressure dressing system is superior.[7,8,11,12]

The duration of the bolster was also associated with percentage of STSG take. Longer bolster duration (14 days) was noted to be superior to the 5 day bolster with mean STSG uptake of 77.5% versus 59.9% respectively.[13] An extensive literature review was performed and no randomized control trials regarding this topic have been performed. Previously, a bolster over the STSG was thought to exert pressure and in this way reduce hematoma/seroma formation and improve take.[14] However, a 2003 study that placed pressure transducers in between the wound bed and the STSG and measured the pressure before and after the placement of the bolster found no difference in pressure with the bolster application. Hence, they hypothesized that bolsters improved STSG take by restricting movements and preventing sheering forces from being applied to the STSG. [15]

We would like to test this hypothesis in this study with a randomized control trial comparing STSG success rates between patients who have had a bolster and cast on for 10-14 days versus 5 days for radial forearm free flaps and 7 days for fibula free flaps (our current standard of care). Our hypothesis is that with both a bolster and cast, STSG movement would be further restricted and patients would have improved STSG take in the 10-14 day group when compared to the 5-7 day group.

2.0 OBJECTIVES AND PURPOSE

(a) AIM 1 – PRIMARY OBJECTIVE
To determine if patients who have a cast and bolster over their STSG for a longer period of time (10-14 days) will have better STSG take than those who have them on for 5 days for radial forearm free flaps and 7 days for fibula free flaps (our current standard of care). Our hypothesis is that patients with a longer cast and bolster duration will have better take as they will have reduced movement between the STSG and the wound bed.

(b) AIM 2 – SECONDARY OBJECTIVES
To determine if there are any consequences to longer duration of bolster and cast placement. We plan to administer a survey at the 1 month post-operative appointment to determine the duration of time local wound care was needed at the donor site, whether the patients suffered any complications at the donor site, and their perception of their health and self-esteem. Additionally, we will mail or email patients the surveys again at 3 month.

(c) AIM 3
To identify the characteristics such as demographics, comorbidities, social history, surgical techniques, and surgical complications that are associated with poor STSG take.

3.0 STUDY DESIGN

This will be a prospective randomized control trial with a recruitment goal of 220 patients. One hundred and ten (110) patients will have undergone a STSG to reconstruct the FFF donor site and another one hundred and ten (110) patients will be for those with a RFFF donor site. We anticipate this to be a 5 year study. Inclusion criteria include adult patients who underwent a RFFF or a FFF surgery and had a STSG placed over the donor site at Keck Hospital. Exclusion factors include patients who cannot make informed decisions and those who cannot make their one month appointment.

Either the principal investigator, co-investigators, or research assistants will recruit patients who meet the inclusion and exclusion criteria. In clinic, the principal investigators and co-investigators will discuss the research study and patients will have time to think about the study before surgery. The patient will be provided with the consent form to take home. Patients will be consented for this research study at the same time as their surgical consent on the day of surgery. A coronavirus screening questionnaire as well as the coronavirus nasopharyngeal swab will be performed before researchers will have direct contact with the patient. The consent will take place with proper social distancing and everyone will wear a surgical or N95 mask. Should the patient consent to the study, he will be asked to fill out two surveys – the Rosenberg self-esteem survey and the 36 item short form survey regarding his current quality of life.

Prior to initiation of participant recruitment, a randomization scheme will be developed using a computerized random number generator. Study participants will be randomized according to a block randomization scheme, with block size of 4. The randomization will be performed, with assignments placed in consecutively-numbered sealed, opaque envelopes attached to each consent.
The patients will then undergo surgery and receive routine post-operative care. After surgery on post operative day 1, one of the co-investigators will open the envelope which will reveal whether the patient is to have the cast for 5-7 days (5 days for radial forearm and 7 days for fibula free flaps) or 10-14 days. Patients who have their casts and bolsters on for 5-7 days will have them removed before discharge and those who are assigned to the longer group will have them taken off in clinic at their first post-operative visit.

At their one month follow up appointment, a picture will be taken of the donor site. Research assistants will be trained to take these pictures and one of the co-investigators will take their first picture with them. Each picture will be taken from a direct angle and will include only the entire donor site. The lighting will be the clinic overhead lights. The patient will also be asked to fill out a quality of life 36 item short form survey (SF 36) and a Rosenberg self-esteem survey directly on Redcap.[16] The patient does not have to make extra trips to the physician's office. These pictures and surveys will be administered at their routine office visits. At 3 month, the patient will receive the same surveys again by mail or email, per their preference. Once they have completed these surveys at 3 months, they will have completed their portion of the study.

The two co-investigators, Dr Daniel Kwon who is a head and neck attending and Liyang Tang who is a 4th year otolaryngology resident, will analyze the skin graft pictures on Adobe Photoshop. All of the photos of the grafts will be de-identified and the people analyzing the pictures will be blinded. They will estimate the percentage of the graft that has taken. Both have agreed that skin graft take means that the graft has successfully integrated into the donor site tissue, meaning that no underlying muscle or tendon is seen. If underlying muscle and tendon is noted on the picture, that region is noted as a skin graft failure region. Intrarater reliability will be optimized by having good training for picture taking and ensuring that the strict definition of successful graft take is used.

Data Collection

In addition to taking pictures of the STSG with a Canon clinic camera and administering surveys on the HIPAA compliant Redcap, the principal investigator, co-investigators, or research assistant will also collect demographic data, co-morbidities, social history, surgical techniques, and post-operative complications from the patient's chart and verify this information with the patient. Should any information be missing, we will gather this information from the patient. A Redcap form has been created to standardize the information gathered. All of this information will be stored in the HIPAA-compliant RedCap provided by the University of Southern California.

4.0 DRUG/DEVICE INFORMATION

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 **Inclusion Criteria:** Adult patients who underwent a RFFF or a FFF surgery and had a STSG placed over the donor site at Keck Hospital

5.2 **Exclusion Criteria:** Patients who cannot consent or cannot make it to their one month post-operative appointment

5.3 **Withdrawal Criteria:** Patients can withdraw at anytime for any reason.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

Prior to initiation of participant recruitment, a randomization scheme will be developed using a computerized random number generator. Study participants will be randomized according to a block randomization scheme, with block size of 4. The randomization will be performed, with assignments placed in consecutively-numbered sealed, opaque envelopes attached to each consent. Following surgery, assignment group will be determined by opening the sealed envelope on post operative day 1.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

The bolster that is placed over the STSG will be mineral oil soaked cotton balls wrapped in Xeroform. Then the arm is wrapped in Webril and casted with plaster. This is the standard of care for all of our patients who undergo STSG currently. Patients who will have this bolster and cast on for 5-7 days will be our control and those who will have it on for 10-14 days will be our experimental group.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Xeroform is well tolerated and not irritating to the skin. It is not classified as hazardous. Its safety information can be found here: https://www.ncmedical.com/wp-content/uploads/2011/06/Xeroform.pdf.

Plaster casting is also well tolerated. However, it can rarely lead to compartment syndrome, pressure sores, cellitis or dermatitis, and stiff joints.[18] Hence, we will be monitoring for signs and symptoms of these complications, especially compartment syndrome. We will monitor for numbness/tingling/decreased sensation, extreme pain, pallor, and decreased circulation with increased capillary refill time for that extremity. As per standard of care, we check capillary refill and motor functions once an hour immediately after surgery, which is later decreased to twice daily. If any of these signs or symptoms should occur, we will either loosen the cast or remove the cast. This will be reported to the IRB.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

The patients do not need any additional labs or office visits for this study. They will be consented in the pre-operative area. They will then have their surgery and routine post-operative care. Their cast will be

removed before discharge if they are in the 5-7 day standard group and at the office for their first post-operative visit if they are in the 10-14 day group. They will then be evaluated at 1 month for a quality of life survey, a self-esteem survey, and pictures of their skin graft. All these visits are routine, standard of care physician visits. The patient will not require any additional office visits. The patient will also be mailed or emailed a survey at 3 month.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The endpoint will be when the patient completes his or her 3 month survey.

11.0 SPECIAL INSTRUCTIONS: Not applicable

12.0 DATA COLLECTION AND MONITORING

The principal investigator, co-investigators, or research assistant will also collect demographic data, co-morbidities, social history, surgical techniques, and post-operative complications from the patient's chart and verify this with the patient. Should any information be missing, we will gather from the patient. A Redcap form has been created to standardize the information gathered Additionally, patients will complete their quality of life and self esteem surveys directly on RedCap. All this information will be placed into a HIPAA compliant USC Redcap database.

13.0 STATISTICAL CONSIDERATIONS

The study is powered to determine if a 10-14 day bolster with cast is superior in STSG take when compared to the tradition 5-7 day bolster with cast. This was calculated with an effect size of 0.632, per study by David.[13] The sample size calculation was reproduced at 80% power and two-sided alpha=0.05. According to this calculation, we will need 84 patients for the FFF group and another 84 patients for the RFFF.[17] Accounting for a 30% loss of follow up for a clinical trial, we will aim to recruit 110 patients for each group. Approximately 6-8 RFFF are performed each month at Keck. Hence it should take 18 months to finish collecting the data for the RFFF arm. Approximately 2 FFF are performed each month at Keck. Hence, we should finish data collection in 5 years for the FFF arm. This is a prospective randomized control study.
The primary outcome will be to determine if having the bolster and cast on for 5-7 days versus 10-14 days will affect split thickness skin graft take rates. This will be done with a Mann Whitney analysis.

The secondary outcome will be to determine if the duration of the bolster and cast affects the quality of life and self-esteem of our participates using the SF 36 quality of life and Rosenberg self esteem surveys. This will also be analyzed with a Mann Whitney. All p-values < 0.05 will be considered significant.

Other variables that will be analyzed are as follows:

1. Demographic characteristics such as age, ethnicity and gender
2. Use of chronic steroids or immunosuppressive agents
3. Charlson co-morbiditiey index
4. Social history such as alcohol, smoking, marijuana use, and betel nut use
5. Surgical techniques such as using muscle to cover the exposed tendon and taking multiple skin grafts
6. Other skin graft complications such as numbness/tingling, vascular compromise, pressure sores, cellulitis
7. General flap complications such as hematoma, flap failure, fistula, wound dehiscence, and death

An univariate analysis will be performed between these variables and split thickness skin graft take rates. Again, the Spearman, Mann Whitney, or Kruskal Wallis will be used depending on whether the independent variable is continuous or categorical. This will be done in STATA 15. All variable that have a p-value <0.1 will be placed into a multivariate linear regression. All p-values < 0.05 will be considered significant.

14.0 REGISTRATION GUIDELINE

The principal investigator and co-investigators will discuss the research study in clinic so that the patient will have time to think about the project. The patient will be consented in the pre-operative area at the same time as his surgical consent. Should the patient agree, an informed consent will be signed. The consent and the bill of rights will be provided to the patient. A telephone number will also be provided to the patient on his informed consent page.

15.0 BIOHAZARD CONTAINMENT

Not applicable.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

17.0 REFERENCES

1. González-García R, Rodríguez-Campo FJ, Naval-Gías L, et al. Radial forearm free flap for reconstruction of the oral cavity: clinical experience in 55 cases. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology*. 2007. doi:10.1016/j.tripleo.2006.09.026
2. Kruse ALD, Bredell MG, Lübbers HT, Jacobsen C, Grätz KW, Obwegeser JA. Clinical reliability of radial forearm free-flap procedure in reconstructive head and neck surgery. *J Craniofac Surg*. 2011. doi:10.1097/SCS.0b013e31820f36aa
3. Urken ML, Buchbinder D, Costantino PD, et al. Oromandibular reconstruction using microvascular composite flaps: Report of 210 cases. *Arch Otolaryngol - Head Neck Surg*. 1998. doi:10.1001/archotol.124.1.46
4. Pototschnig H, Schaff J, Kovacs L, Biemer E, Papadopulos NA. The free osteofasciocutaneous fibula flap: Clinical applications and surgical considerations. *Injury*. 2013. doi:10.1016/j.injury.2013.01.007
5. Okay D, Al Shetawi AH, Moubayed SP, Mourad M, Buchbinder D, Urken ML. Worldwide 10-Year Systematic Review of Treatment Trends in Fibula Free Flap for Mandibular Reconstruction. *J Oral Maxillofac Surg*. 2016. doi:10.1016/j.joms.2016.06.170
6. Hwang MS, Britt CJ, Vila PM, et al. Factors associated with skin graft take in fibula and radial forearm free flap donor sites. *Am J Otolaryngol*. 2020;(April):102536. doi:10.1016/j.amjoto.2020.102536
7. Chio EG, Agrawal A. A randomized, prospective, controlled study of forearm donor site healing when using a vacuum dressing. *Otolaryngol - Head Neck Surg*. 2010;142(2):174-178. doi:10.1016/j.otohns.2009.11.003
8. Ho MWS, Rogers SN, Brown JS, Bekiroglu F, Shaw RJ. Prospective evaluation of a negative pressure dressing system in the management of the fibula free flap donor site: A comparative analysis. *JAMA Otolaryngol - Head Neck Surg*. 2013;139(10):1048-1053. doi:10.1001/jamaoto.2013.4544
9. Richardson D, Fisher SE, David Vaughan E, Brown JS. Radial forearm flap donor-site complications and morbidity: A prospective study. *Plast Reconstr Surg*. 1997. doi:10.1097/00006534-199701000-00017
10. Momoh AO, Yu P, Skoracki RJ, Liu S, Feng L, Hanasono MM. A prospective cohort study of fibula free flap donor-site morbidity in 157 consecutive patients. *Plast Reconstr Surg*. 2011. doi:10.1097/PRS.0b013e318221dc2a
11. Vidrine DM, Kaler S, Rosenthal EL. A comparison of negative-pressure dressings versus bolster and splinting of the radial forearm donor site. *Otolaryngol - Head Neck Surg*. 2005;133(3):403-406. doi:10.1016/j.otohns.2005.04.028
12. Bach CA, Guilleré L, Yildiz S, Wagner I, Darmon S, Chabolle F. Comparison of negative pressure wound therapy and conventional dressing methods for fibula free flap donor site management in

patients with head and neck cancer. *Head Neck*. 2016. doi:10.1002/hed.23952
13. David AP, Heaton C, Park A, Seth R, Knott PD, Markey JD. Association of Bolster Duration with Uptake Rates of Fibula Donor Site Skin Grafts. *JAMA Otolaryngol - Head Neck Surg*. 2020;94115:E1-E6. doi:10.1001/jamaoto.2020.0160
14. Blair VP, Brown JB. The use and uses of large split skin grafts of intermediate thickness. *Plast Reconstr Surg*. 1968. doi:10.1097/00006534-196842010-00011
15. Seymour FK, Giele HP. Tie-overs under pressure. *Br J Plast Surg*. 2003;56(5):494-497. doi:10.1016/S0007-1226(03)00131-0
16. Salomé GM, Blanes L, Ferreira LM. The impact of skin grafting on the quality of life and self-esteem of patients with venous leg ulcers. *World J Surg*. 2014. doi:10.1007/s00268-013-2228-x
17. UCSF. Sample Size Calculators. http://www.sample-size.net/. Published 2019.
18. Boyd AS, Benjamin HJ, Asplund C. Principles of casting and splinting. *Am Fam Physician*. 2009.