Study Title: Prospective randomized clinical trial comparing outcomes of secondary intention wound care methods

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Lahey Hospital & Medical Center

Research Protocol

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Research Objectives / Specific Aims / Outcome Measures:

Objective:	To determine if debridement improves healing time for secondary intention wounds.
Hypothesis	Aggressive and frequent debridement of an acute post-surgical wound shortens healing time.
Outcomes Measures	The primary outcome measure will be time to healing. Secondary outcomes will include patient satisfaction (as assessed by the Patient Satisfaction Assessment Questionnaire) at time of complete healing, cosmetic appearance (Visual analog Scale) as rated by a blinded reviewer at time of complete healing, number of required debridements by time of complete healing, treatment failures at week 16, and number of complications (including pain, bleeding, infection, tumor recurrence) by time of complete healing or by week 16. The Patient Satisfaction Assessment Questionnaire is a validated questionnaire used standardly in Dermatology for assessing patient-based outcome measures of scarring. It consists of 5 subscales: appearance, symptoms consciousness, satisfaction with appearance and satisfaction with symptoms. Each subscale consists of a set of items with 4-point categorical responses, scoring 1 to 4 points (with 1 point assigned to the most favorable category and 4 assigned to the least favorable). It has been demonstrated to be a reliable and valid measure of patients' perception of scarring[12].

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The Visual Analog Scale is a validated image-based scale that is frequently used in the Dermatology and Plastic Surgery literature, that uses photographs for evaluation in 5 dimensions (pigmentation, vascularity, acceptability, observer comfort, and contour). "Observer comfort" measures the observer's "comfort level" when viewing the wound. The benefit of using this scale for the purposes of the study is because it is a photograph-based scale which can be evaluated later by a blinded physician rather than in the clinic at the time of the visit. The observer places a mark along the continuum and then that is measured from left to right and a corresponding score is given. The individual scores are tallied to obtain a single overall score ranging from "poor" to "excellent." It has been shown to have high observer reliability and internal consistency when evaluated by experts[13].

Background Information / Significance / Scientific Rationale:

Secondary intention is an established method of allowing post-surgical defects to heal. Previous studies have shown a positive association between the frequency of debridement and healing rates in chronic wounds, based on the belief that debridement initiates the first stage of wound healing, and transforms chronic wounds into acute wounds. [1-4] However, the effect of debridement on acute, post-surgical wounds is not well-described in the literature.

[5] One retrospective review of debridement and time to heal did include the analysis of surgical wounds and concluded that frequent debridement led to shorter healing times, but no prospective studies have been done investigating whether this subset of wounds show a propensity to heal without frequent and aggressive debridement.[6] Frequent debridement may unnecessarily strip the wound of macrophages, fibroblasts and keratinocytes that are valuable to wound healing in the acute, post-surgical wound. Additionally, while it is known that fibrin mediates many processes related to wound healing, it is not clear whether the presence of fibrin impedes or facilitates healing of the acute, post-surgical wound. Chronic wounds and wound care represent a major health burden in this country with significant associated costs.[4] Through this study, we hope to assess whether frequent debridement facilitates or impedes acute wound healing. Lastly, findings of this study may have implications on the number and frequency of follow-up clinical visit for patients, with direct effects on costs on the healthcare system, opportunity costs to the patient, as well as the availability of those appointments for

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other uses. Optimizing wound care methods in this era of accountable care organizations (ACO) therefore targets the triple aim of improving patient satisfaction, improving quality of care, and reducing overall system costs.[7]

Participant Selection / Eligibility:

Subjects

1) Dermatology patients at Lahey Clinic
2) who have undergone Mohs surgery or excision
3) who are older than 18 years
4) who are able to give consent
5) who had postoperative defects allowed to heal by secondary intention on the a) head and neck, b) trunk and upper extremities, c) lower extremities
6) who are willing and able to return to clinic in Peabody for all wound care visits

Exclusion Criteria

1) Unable to consent (due to language barrier, mental status)
2) Unable to perform daily wound care
3) Unwilling or unable to return for follow-up
4) Have baseline venous stasis or pitting edema of the affected limb
5) Wear compression stockings or require use of a compressive bandage (such as an Unna Boot) at baseline.

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Subject Enrollment: / Consent Process / Screening / Randomization:

Randomization

Block randomization using randomly-permuted block sizes of four and six will be used to ensure balanced enrollment in each arm as the trial progresses. Randomization will also be stratified by anatomic region. The three anatomic regions include: head and neck (5 per arm), trunk and upper extremity (5 per arm), and lower extremity (10 per arm). Randomization sequences will be generated in advance using an available web service and the list will be maintained by a research nurse not involved in patient enrollment. (Sealed Envelope Ltd. 2015. Create a blocked randomization list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 12 Oct 2015].) Treatment allocation assignment for each patient will be kept in sealed envelopes by the research nurse. As patients are being enrolled, the clinician seeing the patient will

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contact this research nurse to obtain the treatment assignment and will not have a priori knowledge of the randomization of the patient. In order to ensure a manageable caseload, only 10 patients will be enrolled in the study at any one time. Once 10 people are enrolled, then enrollment will stop until a patient completes the study, at which point randomized enrollment will resume.

Study Design / Procedures:

Randomized Clinical Trial

Enrollment

At the baseline visit, after the patient has signed consent and been randomized to their specific treatment arm, we will obtain basic demographic information including age, sex and race, as well as pertinent comorbidities that would affect wound healing such as diabetes, venous stasis, immunosuppression and tobacco use (if documented as problems in the patient's chart). Wound defect width, length, and depth will also be measured at baseline, prior to any intervention.

Intervention Arms:

1) Aggressive debridement: Aggressive and frequent debridement of fibrin and crust from the wound base down to pinpoint bleeding, both by the patient as part of daily wound care at home, and also by the clinician (either physician or experienced dermatologic surgery nurse) during follow-up visits. Silver nitrate will be used to treat excessive granulation tissue only if the granulation tissue is higher than the level of surrounding skin. Patients will return weekly until healed. Patients will be provided with detailed instructions and guidelines to help determine whether healing has taken place.

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2) Minimal debridement: No debridement of fibrin by the patient or the clinician. Exceptions include debridement of dried crust or eschar. Silver nitrate will be used to treat excessive granulation tissue only if the granulation tissue is higher than the level of surrounding skin. Patients will return every two weeks until healed. In between visits at weekly intervals, the patient will be contacted by phone to determine if healing has occurred in between clinic visits[11]. Patients will be provided with detailed instructions and guidelines to help determine whether healing has taken place.

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Notes:

- The following information will be recorded for each patient at each clinic visit for both treatment arms, using a standardized data collection form: Date of follow up; pain (0/10); episodes of bleeding (# and whether mild, moderate, or severe); amount of crust (mild, moderate, or severe); amount of fibrin (mild, moderate, or severe); size of wound (width, length, and depth); whether the wound is completely healed (completely re-epithelialized); any tumor recurrence (as determined by physician); if excess granulation tissue is present (as determined by being higher than the level of the surrounding skin); if there is infection (as determined by the physician); whether culture was taken; and degree of debridement (none, mild, moderate, or severe).
- At each visit, we will review the treatment method with the patient (i.e. whether aggressive or minimal debridement), reinforce the instructions, and give them another written copy of their wound care methods)
- We will measure time to 50% healing of the wound for all patients.
- *Both intervention arms (aggressive debridement and minimal debridement) are accepted methods of post-operative care for secondary intention wounds. While both methods are practiced at Lahey Clinic, there is no known, published "standard-of-care" in the literature for such wounds. This is because there have been no randomized controlled trials undertaken comparing efficacy of these two methods. That is the purpose of this study.*
- *It is the standard of care to have patients with wounds healing by secondary intention return to clinic for wound checks until the wounds is sufficiently healed; however, the exact interval period is up to the discretion of the provider. In this study, we will be following up weekly with patients receiving frequent debridement and biweekly with patients receiving minimal debridement. All patients will continue to be followed until their wounds are healed.*

Ongoing Care: The patient will return to clinic for evaluation until defect is completely healed, as determined by one of the study investigators.

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The follow-up intervals are as noted above.

- Patients will be asked to record the date on which their wound healed, and this will be reviewed over the phone or at their next clinic appointment.

- Once the wound is determined to be completely healed (full re-epithelialization), the patient will be asked to complete the Patient Satisfaction Assessment Questionnaire. The Patient Satisfaction Assessment Questionnaire is a validated questionnaire used standardly in Dermatology for

assessing patient-based outcome measures of scarring. It consists of 5 subscales: appearance, symptoms, consciousness, satisfaction with appearance and satisfaction with symptoms. Each subscale consists of a set of items with 4-point categorical responses, scoring 1 to 4 points (with 1 point assigned to the most favorable category and 4 assigned to the least favorable). It has been demonstrated to be a reliable and valid measure of patients' perception of scarring[12].

- Photographs of healed wounds will be provided to a third-party, blinded investigator, who will evaluate these photos using the validated Visual Analog Scale.
- If the patient's wound is not healed by 16 weeks, then the patient is deemed to be a treatment failure. The patient will be withdrawn from the treatment part of the study. The wound care instructions will be changed based on the patient's wound characteristics and medical comorbidities and they will continue to receive medical care until their wound is completely healed. We will continue to collect data on these patients until their wounds are completely healed and may describe their post-operative wound course in qualitative terms.

Statistical Issues

Sample Size/Power	Time to healing will be the primary outcome measure and will be compared between groups using a two-sided t-test. There is limited literature regarding similar patients to help guide estimates for a power analysis. Based on a review of the literature,[8-10] and a brief review of patients previously seen at our clinic, we powered the study to detect a difference in healing time between treatment groups of 14 days, and assumed a standard deviation (SD) of 15 days. To obtain 80% power to detect such a difference, assuming alpha=0.05 and a two-sided t-test, 20 patients per group (40 total) are required.
Anticipated Strengths	We performed a priori power analysis. We are using a randomized study design with validated survey instruments. We plan to use a blinded reviewer of the final cosmetic outcome.
Anticipated Limitations	Given the nature of our study, it will not be possible to conceal treatment arm to patients or providers, though assessment of the final outcome will be by blinded reviewer. If variability in wound healing is greater than anticipated, we may not have statistical power to detect differences between groups; however, the estimates we obtain will help inform future studies. The minimal debridement group will be seen by the clinician every two

weeks; while the aggressive debridement group will be seen weekly. It is therefore possible that ascertainment of time to wound healing will differ between groups. However, we hope to avoid this bias checking with the minimal debridement group by phone on weeks where they have no scheduled visit.

Study Calendar / Schematic / Schedule:

Day 1:

Eligible Dermatology patients at Lahey Clinic who have undergone Mohs surgery or excision and have postoperative defects allowed to heal by secondary intention, who satisfy the inclusion/exclusion criteria and who agree to enter the study and sign the consent form, are randomized to different intervention groups:

Aggressive Debridement Arm vs Minimal Debridement Arm.

Aggressive Debridement Arm:

Week 1-Week 16:

The patient returns to the clinic every week for evaluation until the wound is completely healed, as determined by one of the study investigators.

Minimal Debridement Arm:

Week 2-Week 16:

The patient returns to the clinic every two weeks for evaluation until the wound is completely healed, as determined by one of the study investigators.

Potential Risks and Discomforts:

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered during routine post-operative care, including the performance of routine physical or psychological examinations or tests. However, since this study is comparing two methods of treating post-surgical wounds, it is possible that one treatment method is significantly more effective than another. By participating in this study, there is the risk that the patients randomized to the less effective treatment method may delay their wound healing. It is also possible that one group of patients may have more side effects than the other. For example, patients in the aggressive debridement group may experience more bleeding, pain, and scarring than the minimal debridement group.

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Potential Benefits:

Improved knowledge of most effective post-operative secondary intention wound care methods.

Statistical Analysis:

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Analytic Plan	Differences in demographic and wound characteristics between groups will be compared to evaluate balance between groups. Differences between treatments arms for the primary (time-to-healing) and continuous secondary outcomes (patient satisfaction, cosmetic appearance, number of complications) will be analyzed using t-tests for independent groups. If time-to-healing is not distributed normally, or if there are censored observations (e.g., loss to follow-up, or not all patients have healed by the 16-week endpoint), a log-rank test will be used to test for differences in healing time instead of a t-test. Time to healing in both groups will be plotted using Kaplan-Meier curves. The proportion of treatment failures in each group will be compared using chi-square or exact tests, as appropriate. Exploratory subgroup analysis for the above outcomes stratified by anatomic site, will be performed to assess for between-group differences across wound location. All tests will be two-sided with alpha=0.05. Data will be analyzed using at Tufts CTSI using SAS or R software.

Data Management:

All primary data will be maintained by the Principal Investigator at Lahey Hospital & Medical Center. An electronic copy of de-identified study data will be provided to Dr. Liu, who will be the first author. De-identified electronic photographs (i.e. non-full-face photographs showing the scar only) of the final wound will be provided to Dr. Dabiri to rank using the Visual Analog Scale.

Data and Safety Monitoring and Quality Assurance:

Data and Safety Monitoring and Quality Assurance will be performed by the Principal Investigator. As the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered during routine post-operative care, there will not be a formal Data Safety Monitoring Board (DSMB) for this research.

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