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Novel Biomaterial Containing Gelatin, Manuka Honey, and Hydroxyapatite Enhanced Secondary Intention Healing vs. Standard Secondary Intention Healing in Mohs Surgical Defects on the Head and Distal Lower Extremities – A Randomized Clinical Trial

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1.0 Background

Brief Summary:

The purpose of this study is to elucidate if a novel biomaterial containing gelatin, manuka honey, and hydroxyapatite enhances secondary intention healing when compared to conventional secondary intention healing for surgical defects after Mohs micrographic surgery on the head and distal lower extremities (below the knee).

Detailed Description:

Secondary intention healing (SIH) is often underutilized and has several advantages compared to primary surgical repair.[1,2] Wound care is minimal, bleeding and infection are rare, and risks associated with primary closure (e.g. hematoma, suture granuloma, graft or flap failure) are non-existent.[3] Importantly, SIH facilitates surveillance of tumor recurrence, whereas flaps and grafts may bury residual tumor.[1,3] When used in appropriate anatomical locations, SIH leads to high patient satisfaction.[1,2,4] However, SIH requires regular wound care that can be cumbersome to patients.[3,5]

Prior studies utilizing biologic dressings have shown patients report better quality of life during the post-operative period related to less pain, decreased dressing changes, and faster healing times.[5,6] Biologic dressings provide an alternative to surgical autografts and eliminate the risks associated with graft harvesting (e.g. pain, infection, and scarring).[5,7] For many patients, the cosmetic outcome following healing is important. However, cosmetic outcome with SIH is variable and depends on many factors, namely location (e.g. concavities favorable), skin laxity, and underlying musculature.[1,2,8] Exuberant granulation tissue, hypopigmented and telangiectatic scars are the most frequent adverse cosmetic outcomes with SIH.[3,9]

The novel biomaterial APIS® (SweetBio, Inc. Memphis, TN) is an advanced synthesis of gelatin, manuka honey, and hydroxyapatite bioengineered to protect wounds, manage exudate, and maintain a moist environment. It is FDA cleared (FDA number K1827250) for wound management across 9 indications including surgical wounds. It has been used successfully in a small case series of 8 patients for post-operative Mohs surgical wounds on the head and distal lower extremities. Time to complete re-epithelialization was 6 weeks (42 days), suggesting a reduction in healing time compared to standard SIH times for the leg and head of 127 and 57 days, respectively.[10,11] Use of this novel biomaterial to enhance SIH is hypothesized to reduce healing times when compared to standard SIH wound care. This provides a useful option to aid SIH in sites like the lower legs, where healing can be prolonged due to intrinsic factors (e.g., cardiovascular disease, peripheral vascular disease, diabetes) or extrinsic factors (e.g., increased risk of surgical site infection following dermatologic surgery at sites below the knee).[10,12]

2.0 Rationale and Specific Aims

Randomized, comparative studies evaluating augmented SIH compared to conventional SIH in dermatologic surgery are limited. This study aims to evaluate whether use of a novel biomaterial enhances SIH, particularly in shortening time to complete re-epithelialization. Patients undergoing Mohs micrographic surgery amenable to SIH on the head and distal lower extremities will be randomized into one of four groups (standard SIH or biomaterial APIS® enhanced SIH on the head or distal lower extremities). Patients will have regularly scheduled follow-up with questionnaires at each visit. We aim to evaluate whether use of this novel biomaterial decreases complete re-epithelialization times, reduces infection rates, and improves cosmetic outcomes.

Outcome Measures
Primary:
1. Time to complete re-epithelialization

Patients will be seen in office 14 days post-operative, then every 14 days thereafter until complete re-epithelialization is achieved. Patients will also submit photos via Vanderbilt HIPAA compliant Box at regular follow-up intervals (post-operative day 7 then every 14 days thereafter until complete re-epithelialization is achieved). Time elapsed from surgery date to complete re-epithelialization will be noted in days.

Secondary:
1. Patient and Observer Scar Assessment Scale (POSAS) Patient Scale Score Version 2.0

Patients will complete the POSAS Patient Scale after complete re-epithelialization is achieved. The POSAS Patient Scale is a validated and widely accepted scar assessment tool. The patient scale has six questions assessing scar pain, itch, color, stiffness, thickness, and irregularity rated from 1 (no, not at all/normal skin) to 10 (yes, very much/worst imaginable). Scale from 6-60 with a final seventh question rating patient's overall opinion of scar quality (1-10).

2. Visual Analog Scale (VAS) – Provider Scar Ranking

Digital standardized photographs of scars after complete re-epithelialization is achieved will be assessed by two blinded dermatologists using the VAS. This scale ranges from 0 or normal skin to 10 or worst possible scar taking into account the scar's pigmentation, vascularity, contour, observer comfort, and overall severity. VAS scores of novel biomaterial will be compared to standard SIH.

3. Size of wound

Post-operative wounds will be measured at regularly scheduled follow-ups. The area and volume for each patient's wound will be calculated.

4. Pain score

Patients will self-report their surgical site/wound pain during in office follow-up visits via a questionnaire. Pain scale will range from 1 (no pain) to 10 (worst pain imaginable).

5. Infection

Post-operative wounds will be assessed for infection at regularly scheduled follow-ups. Any suspected infection (e.g. erythema, purulence, malodor) will be cultured and reported. Antibiotic usage for either prophylaxis peri-operatively or treatment will be recorded.

6. Bleeding

Patients will report any bleeding (yes/no) via questionnaires at regularly scheduled follow-ups. Additionally, if there was post-operative bleeding, was an intervention performed to achieve hemostasis (yes/no) and if yes, what intervention.

7. Ease of Wound Care

Patients will self-report the ease of wound care on a scale of 1 (very easy) to 10 (impossible) via questionnaires at regularly scheduled follow-ups.

3.0 Animal Studies and Previous Human Studies

APIS® was FDA cleared in 2019 (FDA number K1827250) for management of full and partial thickness wounds, pressure ulcers, venous stasis ulcers, diabetic ulcers, surface wounds, traumatic wounds, surgical wounds, abrasions, and donor site wounds.

A small case series of 8 patients used APIS® in SIH of Mohs surgical wounds on the head and distal lower extremities. Time to complete re-epithelialization was 6 weeks (42 days), suggesting a reduction in healing time compared to standard SIH times for the leg and head of 127 and 57 days, respectively.[10,11]

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- 18 years of age or older
- Post-operative wounds following Mohs surgery on the head or distal lower extremities
- Single Mohs post-operative defect
- Post-operative wounds greater than 1cm in width
- Depth of defect at least to subcutaneous tissue
- Patients have the ability to provide their own wound care
- Agreeable to regularly scheduled follow-up visits and transmission of photos via HIPAA compliant Vanderbilt University Medical Center Box
- Patients are able to provide informed consent

Exclusion Criteria:

- Under 18 years of age
- Unable to provide informed consent
- Unable to understand oral and written English
- Post-operative wounds not appropriate for secondary intention healing
- Sensitivity or allergy to APIS® biomaterial including collagen and its derivatives, porcine-derived materials or honey
- Immunosuppressed and organ transplant patients
- Post-operative wounds superficial to subcutaneous tissue

5.0 Enrollment/Randomization

Patient enrollment will occur at Vanderbilt University Medical Center One Hundred Oaks Department of Dermatology Mohs Surgical Unit. All patients eligible for study may be considered. Patients with Mohs surgical defects on the head and distal lower extremities amenable and conducive for SIH will be randomized to intervention or control by block randomization. Subjects will be randomized in a 1:1 ratio.

Address of enrollment:
Vanderbilt Dermatology One Hundred Oaks
719 Thompson Lane, Suite 26300
Nashville, TN 37204
(615) 322-6485

6.0 Study Procedures

Arms and Interventions
Two experimental groups

1) APIS® biomaterial on the head
2) APIS® biomaterial on the distal lower extremities

Two control groups

1) No intervention, standard SIH wound care on the head
2) No intervention, standard SIH wound care on the distal lower extremities

Experimental (40 patients): APIS® biomaterial. APIS® biomaterial placed on post-operative wound.

1) Head (20 patients)
2) Distal lower extremities (20 patients)
    a. Device: APIS® biomaterial. This biomaterial was FDA cleared in 2019 for management of full and partial thickness wounds, pressure ulcers, venous stasis ulcers, diabetic ulcers, surface wounds, traumatic wounds, surgical wounds, abrasions, and donor site wounds.
    b. One layer of APIS® will be applied to the post-operative wound covered by petrolatum impregnated gauze, a non-stick Telfa pad, gauze, and Opsite tape.

c. The biomaterial will be reapplied if it is completely absorbed at follow up and the wound depth below the epithelial level.

No intervention (40 patients): No APIS® biomaterial on post-operative wound.

3) Head (20 patients)
4) Distal lower extremities (20 patients)
    a. Post-operative wound will heal via conventional secondary intention. Application of petrolatum impregnated gauze, a non-stick Telfa pad, gauze, and Opsite tape.

This study may be deemed complete prior to reaching above enrollment numbers if statistical significance is achieved or at the discretion of the research team.

Mohs Surgery – Day 0
Patients eligible for study will be offered opportunity to enroll. After informed consent has been obtained, the patient's clinical history, medical history, social history, medication history, and vital signs will be reviewed and documented. Pre and post-operative photos will be obtained and stored in the Electronic Medical Record and Vanderbilt HIPAA compliant Box.

Patients on day of surgery will be provided with a post-operative wound care instruction sheet (for both control and experimental groups). They will also receive a detailed instruction sheet for uploading post-operative photos to Vanderbilt's HIPAA compliant Box.

Subsequent Post-operative Visits – Post operative Day 14 then every 14 days thereafter until complete re-epithelialization is achieved. Patients enrolled in study will be provided a brief questionnaire to complete at in-person office follow-up visits. Post-operative wounds will be assessed for any complications. Size of wounds in addition to photographs will be obtained until complete re-epithelialization is achieved. Patients will also upload post-operative photos to Vanderbilt's HIPAA compliant Box post-operative day 7 then every 14 days thereafter until complete re-epithelialization is complete.

7.0 Risks

Known and expected risks associated with the use of the intervention are the following:

- Allergic reaction to APIS® biomaterial
- Surgical site pain, infection, minimal bleeding, oozing, swelling, and/or itching
- Scar
- Loss of confidentiality
- Feeling uncomfortable answering questionnaire

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Participants will be instructed at the time of consent to contact a member of the study team should they experience any adverse event or unanticipated problem. An on-call

pager number will be provided to study participants. All adverse events and unanticipated problems will be reported to the VUMC IRB in accordance with the VUMC IRB policy. Additionally, all serious adverse events will be reported to the manufacturer of APIS®, SweetBio, Inc (Memphis, TN).

9.0 Study Withdrawal/Discontinuation

Participants have the ability to withdraw or discontinue from the study at any time. Subjects will be instructed to notify a member of the study team if they wish to withdraw, and any data collected for research will be discarded.

Participants enrolled in the study may be terminated from the study at the investigator's discretion including but not limited to the following:

- Lost to follow-up
- Nonadherence with wound care
- A participant's health status changes significantly which makes them not eligible for the study
- Trauma to the post-operative wound

10.0 Statistical Considerations

The primary endpoint is time to achieve complete re-epithelialization. The mean number of days required to achieve complete re-epithelialization between control and experimental groups will be analyzed with a Student's T-test. The null hypothesis is that there is no statistically significant difference between control and experimental complete re-epithelialization times. Secondary outcomes of patient and observer cosmetic outcome will be compared similarly.

11.0 Privacy/Confidentiality Issues

All data will be secured, and confidentiality will be upheld by all members of the research team. Participants will be assigned a study identification code in order to deidentify the study data. A crosslink will exist to link study identification codes to participant identifiers. This crosslink will only be accessible to a limited number of IRB trained and approved study personnel. Study data will be contained in a password protected Excel spreadsheet and stored on the Vanderbilt HIPAA compliant Box. Patients enrolled in this study may request to have all data removed/destroyed from the database if they elect to withdraw from the study.

12.0 Follow-up and Record Retention

Study duration expected to be 12 months. Study data will be maintained by the research team for a minimum of 7 years and potentially indefinitely. This data will continue to be stored in a password protected database file on the Vanderbilt HIPAA compliant Box, in compliance with Vanderbilt University Medical Center's record retention policies. A limited number of IRB trained, and approved study personnel will have access.

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