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Multifunctional In Situ Photopolymerized Semi-Interpenetrating Network System is an Effective Donor Site Dressing: A Cross Comparison Study in a Swine Model

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Abstract

Effective dressings for donor sites or other partial thickness wounds must promote removal of nonviable or necrotic tissue, eradication and prevention of microbial infiltrate, exudate absorbance, and regrowth of healthy epidermis and dermis. There are many commonly used products that facilitate these processes. Established properties of an in situ photopolymerizable semi-interpenetrating network (sIPN) suggest that it is also a viable treatment option. The widely varying material properties suggest that these dressing treatments may elicit different healing responses via different cellular mechanisms. In this study, we sought to resolve the differences in healing between Acticoat™, sIPN, nonadherent dressing with Tisseel™, and Xeroform™ dressing treatments in a porcine partial thickness wound model. Donor site wounds were produced on pigs at two cut depths and dressed with Acticoat™, sIPN, nonadherent dressing with Tisseel™, and Xeroform™ with alternatively placed autografts to provide a control area between each test site. Pigs were euthanized at 4, 7, 14, and 42 days for macroscopic examination and biopsy collection. Biopsies were analyzed histologically by two blinded observers for cellular densities and regional thicknesses within the tissue. sIPN- and Xeroform™-treated wounds were healed by 7 days, and Acticoat™- and nonadherent dressing with Tisseel™-treated wounds were healed by 14 days. Inflammatory responses were between comparable treatment type across all time periods. Dermal granulation features increased with time but were not significantly different. All dressing treatments elicited wound healing without outstanding toxicity or pathology indicating that sIPN is a comparable and viable treatment for partial thickness wounds.

Epidermal autograft donor site wounds provide major clinical challenges such as infection, pain, and long healing times. To facilitate healing in donor site wounds, dressing treatments should ideally meet four primary requirements; the removal of nonviable or necrotic tissue, eradication and prevention of microbial infiltrate, exudate absorbance, and regrowth of healthy epidermis and dermis.^{1,2} Established dressing treatments that are used clinically include Acticoat™, Xero-form™, or nonadherent dressings. Tisseel in this study was used as an adjunct to a nonadherent dressing.

Another experimental dressing treatment hypothesized to facilitate the key features of quality treatment is an in situ photopolymerized semi-interpenetrating network (sIPN). Each

of these dressing treatments varies in their approach to promoting healing. For example, Acticoat™ and Xeroform™ are both composed of absorbent gauze coated with different antimicrobial agents to promote exudate absorption and eradicate bacterial infiltrate. Acticoat™ contains nanocrystalline silver, whereas Xeroform™ contains bismuth tribromophenate in petrolatum. sIPN is an in situ photopolymerizable hydrogel composed of poly(ethylene glycol) diacrylate (PEGdA) and gelatin acting as a tissue scaffold. Key properties of sIPN include absorbance, tissue adhesiveness, contour conformation, biocompatibility, elasticity, readily modifiable for cell-material interactions, and the ability to function as a drug delivery matrix.³⁻⁸ These suggest that the sIPN may be a viable treatment for partial thickness wounds.

The widely varying material properties of the treatments used in this study suggest that they may elicit different healing responses via different cellular mechanisms. In this study, we sought out to resolve the differences in healing between Acticoat™, sIPN, a non-adherent dressing, and Xeroform™ dressing treatments in a porcine partial thickness wound model. Throughout the course of healing, cell types active in epithelialization, extracellular matrix remodeling, and inflammation were qualitatively and quantitatively analyzed as key indicators of healing.

MATERIALS AND METHODS

Treatments

Acticoat™ was obtained from Smith & Nephew (Hull, UK). Tisseel™ was obtained from Baxter (Deerfield, IL). Telfa™ and Xeroform™ were obtained from Kendall (Mansfield, MA). Starting materials for sIPN preparation were purchased from Sigma-Aldrich (St. Louis, MO). Unpolymerized sIPN solutions were prepared at 20% gelatin and 30% PEGdA in water at 60°C in H₂O. Approximately 0.045% 2,2-dimethoxy-2-phenylaceto-phenone, dissolved in PEGdA, was added to this solution within an hour of application to the wound.

Surgical Methods

Approximately, 40 lbs Yucatan pigs (Sinclair Research Center Inc., Columbia, MO) were used for this study in accordance with University of Wisconsin (UW)-Madison Research Animal Resource Center protocol M1653. Anesthesia was induced with Telazol® (4.4 mg/kg IM) and xylazine (2.2 mg/kg IM), then maintained with isoflurane while monitoring pulse oxygenation and heart rate. Pig backs were shaved and prepped with Betadine®. Subcutaneous injections of 0.25% bupivacaine with 1:100,000 epinephrine solution were given over the entire surgical region to assist with analgesia and hemostasis. A thin layer of mineral oil was applied immediately before wounding. Two wounds were produced using a Zimmer® electric dermatome set at 0.016" and 0.022" settings covering 5.4% (330 cm²) total body area wound. Epinephrine solution was applied to wound bed with nonadherent gauze for hemostasis. Dressing treatments, Acticoat™, sIPN, Telfa™ with Tisseel™, and Xeroform™ were applied over epidermal autograft-separated regions as shown in Figure 1. Autografts separated treatments to prevent overlap of the dressing and facilitate the identification of each treatment type. sIPN solution was applied to wound dropwise under simultaneous UV light exposure (Clearstone Technologies CF1000 with 365-nm LED head) until initial film is polymerized (approximately 1–2 minutes). Then, additional sIPN solution is added and polymerized to thicken the dressing. Tisseel™ was applied using specified two-chamber syringe and covered with Telfa™ gauze. Autografts, Acticoat™, Telfa™, and Xeroform™ were immobilized with surgical staples. Treatments were overlaid with burn gauze, then wrapped in Coban™ (3M, St. Paul, MN) and tape. Animals were treated with IM buprenorphine twice daily until dressing removal.

Pigs were housed independently with unrestricted movement in cages at the UW-Madison Medical Sciences Center and fed daily with no diet restrictions per our standard protocols for animal research. Secondary dressings were removed for observation (ie, for incident of infection) on postoperative day 10. No additional primary and secondary dressings were reapplied thereafter. On the day of euthanasia, pigs were injected with Beuthanasia-D, 0.2 ml/kg IV.

Histologic Observation and Measurement

At days 4, 7, 14, and 42 after euthanasia, multiple tissue biopsies were taken from unwounded tissue, and each wounded tissue at both cut depths. Tissues were fixed in 10% buffered formalin, paraffin embedded, sliced, and stained with hematoxylin and eosin, Masson's trichrome, and Giemsa stains (UW-Madison Research Animal Resource Center). Tissue slides were examined by two independent blinded observers. Ten regions of each tissue slice were observed; half from the epidermis and half from the dermis. Viewing regions were evenly spaced across the length of the biopsy. Unwounded, autografted-treated, and dressing-treated tissues were observed. For epidermal cell counts and measurements, data was collected for analysis of keratinocyte density (normalized to stratum spinosum area as an observable histologic feature because it is consistently the only region containing viable, nonbasal keratinocytes), stratum spinosum thickness, stratum corneum thickness, and melanocyte density (normalized to stratum basale length). For dermal cell counts and measurements, viewing regions were positioned toward the outermost surface of viable dermis or region of extracellular matrix remodeling (granulation tissue). In slides that contained the region of extracellular matrix remodeling deep within the dermis (ie, autograft biopsies), the region was centered in the field of view. These regions were aligned and oriented in the same manner for every section examined to ensure the consistency in analysis of notoriously variable data. Data was collected for polymorphonuclear leukocyte (PMN) density, macrophage density, lymphocyte density, remodeling tissue thickness, and fibroblast density (all densities normalized to area of viewing region). Thicknesses, lengths, and areas were all calculated using National Institute of Health ImageJ image processing and analysis software.

Statistical Analysis

Two pigs were used for each time period. Data from all five viewing regions and both pigs at each time point, treatment type, and cut depth were analyzed as a pooled mean $\pm$ standard error. Data was compared using student's *t*-tests. Statistical significance and the corroboration of both observers are noted in text. A lack of statistical significance is noted where $P > .1$. An infection developed under an autografted 0.022" dermatome cut depth wound at 7 days. Data from all the treatments on this wound were not included in analysis. Therefore, data from 0.022" dermatome cut depth wound at 7 days were gathered from a single pig and were compared with all other data using Welch's *t*-test for unequal variance.

RESULTS AND DISCUSSION

Epidermal Healing

Epidermal healing was examined as an indicator of initial healing. Biopsies taken from wounds treated with epidermal autograft, Acticoat™, sIPN, Tisseel™ with Telfa™, and Xeroform™ after 4, 7, 14, and 42 days showed persistent changes in multiple features of the epidermis in a time-dependent manner (Figure 2). At 4 days, none of the dressing treatment groups appeared healed in contrast to the autograft group. This can be seen in the examples given in Figure 3, which applies Masson's trichrome stain to emphasize the border between remaining viable tissue in the wound bed and the dead and necrotic tissue associated with the fibrin clot. Keratinocyte density counts and spinosum thickness measurements confirmed

the lack of re-epithelialization outside of regions immediately adjacent to hair follicles (Figure 2A,B). Autografts appeared to lack flush adhesion, which suggested that these also may not have integrated into adjacent healthy tissue in 4 days. By 7 days, all dressing treatments elicited varying degrees of epidermal healing. sIPN- and Xeroform™-treated wounds showed complete epidermal coverage, unlike Acticoat™ and Tisseel™ with Telfa™ (Figure 4). Acticoat™ and Tisseel™ with Telfa™ showed some regions with developing spinosum and others with an apparent lack of any organized keratinocytes. Keratinocyte density and spinosum thickness were especially low for Tisseel™ with Telfa™ in comparison with all other treatments ($P < .01$ and $P < .05$, respectively, from both observers). All autografts were sufficiently integrated into underlying tissue by 7 days, except for a single case of infection that presented as a blister of odorous exudate beneath an autograft on a wound cut at 0.022" (data excluded from analysis). The variety of epidermal healing seen at 7 days suggested that it is the most critical stage of development for wound covering with new epidermis.

At 14 days, all treatments elicited complete epidermal coverage (Figure 5). Furthermore, all treatments supported the production of stratum corneum and at least some repopulation of melanocytes in the basal layer (Figure 2C,D). These are known hallmarks of the wound bed restoring a number of critical protective functions such as a physical protection from percutaneous absorption of toxins and bacterial infiltration, and melanin activity inhibiting DNA damage from UV light.⁹ sIPN showed the greatest stratum spinosum thickness at both cut depths, although not statistically significant. However, all dressing treatments had lower keratinocyte density and thicker stratum spinosum than unwounded ($P < .0001$ and $P < .05$, respectively, from both observers) and autograft-treated ($P < .05$ and $P < .1$, respectively, from both observers) biopsies at both cut depths. All dressing treatments showed a higher incidence of sporadic epidermis organization with thin projections into the dermis, and pods of dermis appeared within the epidermis in the two-dimensional plane of the slides. This coincided with the appearance of broad extracellular spaces between spinosum keratinocytes which boldly resolved desmosome linkages that were not visible in unwounded and autograft treatments. Autograft treatment continued to appear integrated and stable, but an increase in melanocyte density was observed ($P < .05$, from both observers). As time progressed, melanocyte density was a good indicator of the melanin granule production. Therefore, though healed, all treatments were continuing to remodel the wound bed at 14 days.

At 42 days, the epidermis showed signs of continued remodeling (Figure 6). Keratinocyte and melanocyte densities increased to their peak levels in response to all treatments (Figure 2A,D). Increased melanocyte density was consistent with macroscopic observation of increased pigmentation from 14 days (Figure 7). However, sIPN elicited lower levels than unwounded tissue, although not statistically significant, whereas all other treatments, including autograft, elicited much higher levels than unwounded tissue ($P < .05$). The response to non-sIPN treatments coincided with studies which have indicated a tendency for hyperpigmented hypertrophic scars in Duroc and Yorkshire pigs.¹⁰ For example, one pig treated for 42 days was 35 days older than all other pigs. The older pig showed much higher melanocyte density (11.6 cells/mm stratum basale) than the younger pig (0 cells/mm stratum basale) in response to sIPN ($P < .001$), whereas this discrepancy was not observed with other treatments. Spinosum thickness receded from 14-day levels in response to all treatments at both cut depths (Figure 2B). The epidermis of dressing treatments appeared to flatten without restoration of rete ridges, unlike unwounded and autograft biopsies. Lack of rete ridge restoration is a known indicator of scarring.¹¹ Corneum thickness reached its peak at 42 days for all dressing treatments except Acticoat™ at 0.016" cut depth (Figure 2C). Corneum thicknesses with dressing treatments were higher than that of unwounded tissue, although not statistically significant. Thickening of the corneum in scarred wounds may be

related to the low lipid content of immature desquamating keratinocytes, which increases water holding.¹² In summary, all treatments healed wounds of 0.016" and 0.022" cut depths, but the end-stage healing indicated that scarring characteristics may differ between treatments.

Inflammation

Inflammation was examined as indicator of the relative material biocompatibility of each dressing type. Within the first 4 days after wounding and treatment, a thick mixture of fibrin clot, dead PMNs, and degraded extracellular matrix components were observed at the interface between all dressing treatments and the healthy underlying dermis (Figure 3). This mixture at the dermis-clot interface sloughed off after epidermis formation. Viable inflammatory cells within the dermis indicate the resolution of inflammation after the formation of dermis-clot interface (Figure 8). In general, PMN density decreased with increasing treatment time for all test groups. PMN density showed a general trend with respect to time where densities peak at 4 to 7 days and decreased until 42 days with few exceptions (Figure 8A). At 4 and 7 days, all dressing-treated wounds showed higher densities than unwounded tissue ($P < .1$, from both observers). Furthermore, all dressing treatments elicited higher densities than autograft treatment although not statistically significant due, in part, to the consistently low densities observed with the latter. Also, at 4 days only, 0.022" cut depth elicited slightly higher PMN densities than 0.016" in response to all treatments (not statistically significant). Upon reepithelialization, observed by 14 days, there was a decrease in PMN density among dressing-treated wounds vs 7 days. Low densities were generally observed by 14 and 42 days. These data suggested that PMN recruitment is more extensive in treatments that heal after formation of an extensive dermis-clot interface and require re-epithelialization.

Macrophage and lymphocyte densities did not show an obvious dependency with respect to treatment time, treatment group, or cut depth between treatments (Figure 8B). Macrophages are known to play multiple roles in inflammation and granulation. At 4 and 7 days, when re-epithelialization had not been fully established, macrophages were localized near the dermis-clot interface. However, at later time points, macrophages appeared to be evenly distributed throughout the widening remodeling tissue. Even at 42 days, densities from all treatments did not recede to the levels observed in unwounded tissue as determined by both observers. These observations indicated that macrophages are participating in the neutralization of the dermis-clot interface and in the remodeling of the dermal extracellular matrix.¹³ Differences in macrophage response to cut depth between dressing and autograft treatments were observed. At 4 days, dressing treatments elicited slightly higher macrophage densities than autograft at 0.022" cut depth, although not statistically significant, whereas autograft treatment elicited higher densities at the 0.016" cut depth. This increased macrophage density among dressing treatments with respect to cut depth coincided with the same trend in PMN density. PMNs and macrophages would have acted cooperatively toward the removal of debris and neutralization of microbial infiltration as a major role in acute inflammation. In general, each treatment elicited relatively low lymphocyte density at 4 days, which increased at 7 or 14 days, then receded again at 42 days (Figure 8C). The exception to this was Xeroform™ treatment of a 0.016" cut depth wound on one of the two pigs. These data suggest that none of the treatments consistently elicited a pathologically enhanced immune response. Although leukocyte infiltration is not novel with respect to commonly used dressings, the observed similarity between sIPN and other dressings with regards to the presence of leukocytes suggests similar wound healing response to these different treatments and biomaterials.

Dermal Extracellular Matrix Remodeling

The remodeling of the dermis was observed as a potential indicator of the magnitude of new extracellular matrix production and organization. Remodeling tissue thickness increased from 4 days to a maximum at 7 or 14 days in response to all dressing treatments ($P < .005$) (Figure 9A). A concomitant increase was observed in fibroblast density from 4 days to a maximum at 7 or 14 days in response to all dressing treatments ($P < .05$) (Figure 9B). At 42 days, remodeling tissue appeared to have continued widening, receded in thickness, or blended in with surrounding dermis well enough to appear as normal, mature tissue. At each timepoint after 7 days, dressing treatments consistently elicited wider remodeling tissue thicknesses (not statistically significant) and higher fibroblast densities ($P < .1$) relative to autograft treatments at both cut depths. Notably, after 7 days, remodeling tissue thicknesses (not statistically significant) and fibroblast densities ($P < .1$) from dressing treatments did not return to unwounded or autograft levels. These coinciding data suggested that remodeling tissue thickness was a function of infiltrating fibroblast density in the processes of remodeling dermal connective tissue. Also, remodeling tissue thickness and fibroblast density served as indicators of a permanent abnormality in the thickness, composition, and structure of the dermis that is known to resolve as a hypertrophic scar.¹⁴

CONCLUSION

Differences in the structures and cells associated with wound healing have been observed among treatment types. All treatments elicited healing without outstanding, untoward effects. Through the observation of effective healing, each of the treatments facilitated the removal of dead tissue from the dermis–clot interface, protected from infection, and absorbed moisture sufficiently to support timely re-epithelialization. The exception was the infection of an autograft-treated wound. Although material compositions varied widely between dressing treatment types, the wound healing response was generally comparable suggesting that sIPN treatment is a viable option for future use and development.

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Figure 1.

Example of wound treatment arrangement on pig wounds. Wounds cut at 0.016" or 0.022" in dermatome cut depth settings were treated with Acticoat™ (left), semi-interpenetrating network (sIPN) (left-middle), Tisseel™ and Telfa™ (right-middle), Xeroform™ (right), and alternating epidermal autografts.

Figure 2.

Epidermal features of wounds dressed with various treatments examined histologically at 4 (■), 7 (▨), 14 (□), and 42 (▩) days. The 0.016" dermatome cut depth wounds are shown on the left, whereas 0.022" wounds are on the right. Viable keratinocyte density within epidermis(A), thickness of stratum spinosum(B), thickness of stratum corneum(C), and melanocyte density(D) are displayed. Data from one observer is reported as average of 10 total viewing regions in biopsies from two separate pigs $\pm$ standard error, except for a single pig at 7 days 0.022" cut depth. "u" indicates significant difference from unwounded tissue, "a" indicates significant difference from autograft treatment, and "t" indicates significant difference from previous time point ($P < .001$).

Figure 3.

Representative histologic photomicrographs of tissues 4 days after treatment. The 0.016" dermatome cut depth wounds are shown on top, whereas 0.022" wounds are on bottom. Tissue are aligned so that approximately the top 3rd of each photo contains dead or necrotic tissue such as stratum corneum, fibrin clot, dead cells, or degraded extracellular matrix. (Masson's trichrome stain to clearly resolve dead/necrotic tissue and viable tissue in assessing that no epidermis formation was observed, objective magnification $\times 10$).

Figure 4.

Representative histologic photomicrographs of tissues 7 days after treatment. The 0.016" dermatome cut depth wounds are shown on top, whereas 0.022" wounds are on bottom. Tissue are aligned so that approximately the top 3rd of each photo contains dead or necrotic tissue such as stratum corneum, fibrin clot, dead cells, or degraded extracellular matrix. (Giemsa stain, objective magnification $\times 20$).

Figure 5.

Representative histologic photomicrographs of tissues 14 days after treatment from single animal. The 0.016" dermatome cut depth wounds are shown on top, whereas 0.022" wounds are on bottom. Tissue are aligned so that approximately the top 3rd of each photo contains dead or necrotic tissue such as stratum corneum. (Giemsa stain, objective magnification $\times 10$).

Figure 6.

Representative histologic photomicrographs of tissues 42 days after treatment from single animal. The 0.016" dermatome cut depth wounds are shown on top, whereas 0.022" wounds are on bottom. Tissue are aligned so that approximately the top 3rd of each photo contains dead or necrotic tissue such as stratum corneum. (Giemsa stain, objective magnification $\times 20$).

Figure 7.

Example of healed wound appearance from 0.022" cut depth at 42 days. Treatments were arranged as Acticoat™ (left), Tisseel™ and Telfa™ (left-middle), semi-interpenetrating network (sIPN) (right-middle), Xeroform™ (right), and alternating epidermal autografts.

Figure 8.

Dermal inflammation features of wounds dressed with various treatments examined histologically at 4 (■), 7 (▨), 14 (□), and 42 (▩) days. The 0.016" dermatome cut depth wounds are shown on the left, whereas 0.022" in wounds are on the right.

Polymorphonuclear leukocyte (PMN) density, including neutrophils, basophils, and eosinophils (A), macrophage density (B), and lymphocyte density (C) are displayed. Data from one observer is reported as average of 10 total viewing regions in biopsies from two separate pigs $\pm$ standard error, except for a single pig at 7 days 0.022" in cut depth. "u" indicates significant difference from unwounded tissue, "a" indicates significant difference from autograft treatment, and "t" indicates significant difference from previous time point ($P < .001$).

Figure 9.

Dermal extracellular matrix remodeling features of wounds dressed with various treatments examined histologically at 4 (□), 7 (▨), 14 (▩), and 42 (■) days. The 0.016\"