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RESEARCH ARTICLE

An Electrospun Poly-Ethylene Oxide/ Cerium (III) Nitrate Dressing for Delayed Debridement and Improved Wound Healing of Warfighter Contact Burns

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ABSTRACT

Introduction: Thermal burns account for 5-10% of casualties sustained in present-day conflicts and are expected to be one of the most common wounds to occur in future conflicts. Timely debridement of necrotic burn tissue can greatly reduce the chances of mortality and late-stage complications. However, future conflicts are anticipated to occur in austere environments where surgical debridement may not be plausible and casualty evacuations significantly delayed. Without access to prompt surgical interventions and standard treatment, burn wounds can progress (become deeper and more extensive) and become highly susceptible to infection. Several studies have demonstrated that topical applications of Cerium (III) Nitrate (CeN) can be used to delay the need for surgical eschar removal, a delay which may be forced upon injured warfighters in austere environments. The proof-of-concept studies described herein suggest that an electrospun dressing with a Polyethylene Oxide (PEO) shell and CeN core could prolong the time before surgical intervention is required and/or mitigate late-stage burn pathophysiologies in Prolonged Field Care (PFC) scenarios.

Materials and Methods: Coaxially electrospun PEO dressings with a CeN payload were synthesized for application in a swine burn model. Dressings were first evaluated *ex vivo* using a Lactate Dehydrogenase (LDH) assay to confirm that no cytotoxic effects were present. Then, one female Yorkshire pig was anesthetized and received ten 5 cm x 5 cm contact burns with a brass burn device that was heated to 100°C. The deep-partial thickness wounds were randomly assigned to one of five treatment groups: 1) 1-Layer of the PEO/CeN dressing, 2) 4-Layers of the PEO/CeN dressing, 3) 4-layers of a control electrospun PEO dressing, 4) Flammacerium® cream (silver sulfadiazine 1%, cerium nitrate 2.2%), or 5) the PFC standard of care (SOC; gauze). Wounds were observed over an 18-day period, with surgical debridement occurring on Day 4 for all wounds. Transepidermal water loss, depth to debridement, and histologic measurements of necrosis were utilized to assess the burns. Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AAALAC International. Experimental design and statistical comparisons were approved by an accredited epidemiologist and biostatistician.

Results: The PEO/CeN dressings did not elicit a cytotoxic response *ex vivo*. Compared to the PFC SOC, treatments containing CeN reduced the amount of necrotic tissue produced by second-degree thermal injuries, as evidenced both histologically and in the depth required to reach viable tissue during surgical debridement. Importantly, the dressing did not adversely impact the live tissue surrounding the burn site.

Conclusions: There are currently no field dressings that can delay the need for immediate debridement and thereby promote burn wound healing. This proof-of-concept study strongly suggests that the electrospun PEO/CeN dressing could fulfill this unmet medical need and advocates for further evaluation for use in imminent PFC scenarios.

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INTRODUCTION

Thermal burns account for 5–10% of casualties sustained in present-day military conflicts via flame or contact burns and are expected to be one of the most common wounds to occur in future conflicts [1,2]. Timely debridement of wound eschars can greatly reduce mortality and late-stage complications. However, the current military standard of care for thermal injuries incurred in the field is to stabilize the casualty, wrap the injury with gauze or a silver-based dressing, and then evacuate the casualty for advanced care. While this is sufficient given the current combat environments, future conflicts may necessitate Prolonged Field Care (PFC) operations that could delay casualty evacuations for 72 hours. Without access to prompt surgical interventions or effective treatments, burns can progress (become deeper and more extensive) and become highly susceptible to infection.

Several studies have demonstrated that a single topical application of Cerium (III) Nitrate (CeN) can delay the need for eschar removal [3,4]. Burn eschars treated with CeN become firm and leather-like, but do not spontaneously separate from the wound. Once excised, the tissue beneath the treated eschar is generally healthy and has a high rate (>90%) of graft acceptance [5]. Although the mechanism of how CeN hardens the burn eschar is not fully understood, various works suggest that it could be used to prolong the time before surgical intervention is required and potentially mitigate late-stage burn pathophysiologies.

Scientists at the Naval Medical Research Unit San Antonio (NAMRU-SA) recently generated a core-shell fiber electrospun dressing with a Polyethylene Oxide (PEO) shell and CeN core as the basis of a PFC burn wound dressing [6]. The dressing is lightweight and can deliver the CeN payload within an hour of application. The proof-of-concept studies described herein characterize this PEO/CeN dressing for cytotoxicity, its ability to impact burn eschars, and its potential to improve deep-partial thickness burn outcomes when combined with delayed standard surgical interventions.

MATERIALS AND METHODS

Dressing fabrication

Coaxially electrospun dressings were fabricated as described previously. Briefly, Polyethylene Oxide (PEO - Sigma) was dissolved in a mass ratio of 1:1 in 2:1 (v/v) acetone:dichloromethane to obtain a 5% (w/v) total polymer content. CeN (Ce(NO₃)₃ hexahydrate; Sigma) (5% w/v) was solubilized in acetone. To obtain the core-shell fiber, the solutions were connected to different inlets of an 18/16 gauge coaxial needle. Flow rates were initially set to 1.5 mL/hr and 0.15 mL/hr for PEO and Ce(III) solutions, respectively, and slowly increased to 5 mL/hr and 0.5 mL/hr for PEO and Ce(III) solutions, respectively. For these

samples, variability was mitigated by electrospinning the same volume of polymers for each batch. Solutions were spun at 28kV with a flight distance of 12 cm onto a mandrel rotating at 25rpm. Control PEO dressings were electrospun through an 18-gauge spinneret, with a flight distance of 15 cm and 0% relative humidity.

Ex vivo viability assay

Full-thickness Yorkshire Cross pig skin was resected within one hour of euthanasia and preserved in ice-cold sterile saline until processing. Samples either remained unburned or received a 15 second contact burn from a 100°C thermo-coupled brass block [5,6]. Burned tissue was allowed to cool for 15 minutes to prevent adverse effects on treatments. Tissue biopsies (6 mm) were taken and placed in a 96-well plate (Corning) containing Hanks Balanced Salt Solution (Gibco) [7]. The epidermal surface was treated with one of six treatments (no treatment, 1-Layer PEO/CeN, 4-Layers PEO/CeN, 4-Layers of the electrospun PEO dressing, Flammacerium® (silver sulfadiazine 1%, cerium nitrate 2.2%), or an aqueous solution of 2% CeN) and incubated at 37°C with 5% CO₂. Optimization was required to prevent post application CeN precipitation, which is known to occur in the presence of phosphate buffers and cell culture media [4,8,9].

Tissue viability was assessed using the Pierce LDH Cytotoxicity Assay® (ThermoFisher) after 24 hours and after 72 hours. LDH absorbance was read on a Synergy HTX multimode plate reader (Agilent Technologies, Santa Clara, CA). LDH values were normalized and compared to their respective untreated controls using a two-way Analysis of Variance (ANOVA) with QQ and homoscedasticity post-hoc analyses. Technical triplicates were taken from each tissue sample.

Animals

One female Yorkshire pig weighing approximately 50 kg was procured from a USAISR approved vendor and used in this pilot study. The animal was housed, with ad libitum access to water, and was acclimated to the facilities for at least seven days before any procedures. Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by the AAALAC.

Anesthesia and analgesia

The animal was fasted the night before anesthetic events to prevent gastrointestinal complications or vomiting during procedures. On the day of thermal insult and surgical debridement, the animal was pre-medicated with glycopyrrolate (0.01 mg/kg, IM), induced with tiletamine-

zolazepam (4–6 mg/kg, IM) and anesthetized with 3–5% isoflurane in oxygen via tracheal intubation. Anesthesia was maintained with 1–3% isoflurane in oxygen. Analgesia was administered prior to wounding and/or dressing changes, with sustained release buprenorphine (0.1–0.24 mg/kg) administered subcutaneously in the lateral neck.

Thermal Injury and treatment

The burn wound procedure has been described previously [10,11]. Briefly, hair was removed and the skin was rinsed. Then ten contact burns were made 4 cm from the spine and 3 cm from each other. Five 5 cm x 5 cm burns were made on each side of the spine of the anesthetized animal with a brass burn device (100°C for 15 seconds) [5–7,12,13]. A 1.7 kg ring was added to the device to deliver constant and consistent pressure during insult (~0.4 kg/cm²).

Wounds were allowed to cool for one hour and randomly assigned to one of five treatment groups: 1) 1-Layer PEO/CeN (n = 3), 2) 4-Layers PEO/CeN (n = 3), 3) 4-Layers of a control electrospun PEO dressing (n = 2), 4) Flammacerium® (n = 1), or 5) the PFC SOC(gauze; n = 1). All wounds were then covered with an occlusive dressing (Tegaderm™, 3M) and sterile nonadherent gauze (Telfa, Kendall, Mansfield, MA). Vetwrap (3M) was wrapped around the trunk of the body to cover the entire wounded area. Finally, a fabric vest (DeRoyal, Powell, Tennessee) was applied for additional protection.

Two days later, wounds were cleaned, patted dry, and measured for Transepidermal Evaporative Water Loss (TEWL), treatments re-applied, and the animal was re-dressed.

Debridement and wound care

On Day 4 post-burn, all burns were tangentially excised to punctate bleeding using a dermatome (Zimmer Biomet, Warsaw IN). Punctate bleeding is indicative of a viable tissue and is the clinical standard to indicate complete removal of dead tissue. Total debridement depth was defined as the thickness of tissue removed until punctate bleeding was observed.

Debrided wounds were covered with Silveron® (Argentum Medical, Geneva IL), wet gauze, and an occlusive dressing. This was followed by gauze, Vetwrap, and a fabric vest. Silverlon® dressings were changed twice per week. At each dressing change, wounds were rinsed with diluted 4% chlorhexidine gluconate, sterile water, and patted dry with sterile gauze. Wounds were imaged during each dressing change.

Wounds were biopsied using an 8 mm biopsy punch 14 days after debridement. A strip biopsy (4.0 x 0.5 cm) spanning the wound bed was also taken on the final day of the experiment.

Transepidermal Evaporative Water Loss (TEWL)

On Day 2 post-burn, TEWL data was obtained from the top, middle, and bottom of each wound using a digital, multiple probe adapter (MPAS-6) system (Courage Khazaka Electronic, Cologne, Germany). This probe system uses the MPA software to operate the Tewameter® TM 300 and Mexameter® MX 18 probes (Courage Khazaka Electronic, Cologne, Germany).

Histologic wound assessment

Tissue samples were fixed in 10% neutral buffered formalin for at least 48 hours and processed for paraffin embedding. Tissue sections (~4 µm thick) were cut, cleared in xylene, and rehydrated with an ethanol gradient (100%, 95%, 70% ethanol and deionized water). Sections were stained with Hematoxylin and Eosin (H&E) or Caspase-3 (Cas-3) to observe remodeled collagen and re-epithelialization or the depth of necrotic tissue, respectively. A blinded, clinical pathologist scored the slides for cell phenotypes and indicators of wound healing.

Statistical analyses

Data is presented using means and standard deviation, unless otherwise noted. All statistical comparisons use a 2-way Analysis of Variance (ANOVA). Cytotoxicity measurements employed a linear regression analysis with data normalcy validated by QQ and homoscedasticity plots.

RESULTS

Dressing fabrication and Ex vivo evaluation

Preliminary analyses demonstrated that dressings released ≥90% of the CeN payload within the first hour of solubilisation, which was similar to previously characterized dressings. All dressings were sterilized via UV irradiation, which did not significantly decrease CeN content per gram of dressing (data not shown) [14].

To test for cytotoxicity, treatments were placed atop freshly excised porcine tissue. The media was assessed for LDH levels 24 or 72 hours post treatment. These treatments included: 1) no treatment, 2) 1-Layer PEO/CeN, 3) 4-Layers PEO/CeN, 4) 4-Layers of the electrospun PEO dressing, 5) Flammacerium® and 6) an aqueous solution of 2% CeN. None of the treatments produced significant increases or decreases in LDH at either time point, indicating the dressings did not convey cytotoxic or cytoprotective effects.

Effect of CeN on burn wound eschars

Deep Partial Thickness (DPT) burn wounds were made along the dorsum of a female Yorkshire pig. Two days later, dressings were removed and the burns were assessed for TEWL (Figure 2). Unburned (control) skin had a low TEWL score, whereas the gauze-treated burn had a much

higher TEWL score. This is indicative of the difference in moisture retention between undamaged skin and burned skin. Burns treated with Flammacerium[®] showed a TEWL score similar to unburned skin ($36.4 \text{ gm}^{-2}\text{h}^{-1}$ and $22.3 \pm 18.2 \text{ gm}^{-2}\text{h}^{-1}$, respectively), as did those treated with the PEO dressing ($57.4 \pm 38.6 \text{ gm}^{-2}\text{h}^{-1}$). Burns treated with either the 1-Layer PEO/CeN or the 4-Layer PEO/CeN dressing also had significantly lower TEWL readings ($77.1 \pm 5.32 \text{ gm}^{-2}\text{h}^{-1}$ and $73.9 \pm 14.7 \text{ gm}^{-2}\text{h}^{-1}$, respectfully) than the burns treated with gauze ($101.2 \text{ gm}^{-2}\text{h}^{-1}$), albeit still greater than the control group. After TEWL readings, a biopsy sample was taken from each wound, and new dressings were applied. Two days later, the dressings were removed, the wounds were imaged, and then the wounds were surgically debrided until punctate bleeding was evident.

Depth of necrotic burn tissue

The average depth to achieve punctate bleeding was recorded for each burn (Figure 3A). The PFC SOC treated burn required the greatest amount of debridement ($2159 \mu\text{m}$) and was the only treatment that necessitated more than $2000 \mu\text{m}$ of tissue to be removed. As the amount of PEO/CeN dressing applied increased from 1-Layer to 4-Layers, the depth to debridement decreased from $1981 \pm 76 \mu\text{m}$ to $1778 \pm 0 \mu\text{m}$, respectively. There was no significant difference among the burns treated with the PEO/CeN dressings, the PEO dressing ($1727 \pm 279 \mu\text{m}$), and the Flammacerium[®] cream ($1778 \mu\text{m}$). Of note, the debridement surgeon (blinded to treatment groups) noted that two of the treated burns felt “desiccated and leathery.” These burns were later identified as being treated with either 1-Layer PEO/CeN or 4-Layer PEO/CeN.

As an independent measure of necrotic tissue depth, biopsies collected prior to debridement were assessed for Cas-3 expression. Cas-3 is a crucial mediator of apoptosis, and is frequently utilized to delineate the depth of severe tissue damage following thermal insult [12,15,16]. Burns treated with the PEO dressing marginally reduced the depth of tissue necrosis compared to the SOC gauze treatment ($2348 \pm 653 \mu\text{m}$ and $2692 \pm 382 \mu\text{m}$ respectively) (Figure 3B). As the PEO/CeN dressing treatment increased from 1-Layer to 4-Layers, the depth of necrotic tissue decreased ($2185 \pm 301 \mu\text{m}$ and $1247 \pm 791 \mu\text{m}$, respectfully). The Flammacerium[®] cream, which contained the largest composition of cerium nitrate (2.2% w/v), conferred the shallowest depth of necrotic tissue ($1028 \pm 59 \mu\text{m}$), suggesting that cerium-based products can have a considerable therapeutic effect on burn progression.

Biopsies were collected 0, 2, and 4 days post-burn and stained for H&E. There were no discernable differences in burn depth or acute inflammation among the treatment groups (Supplementary figure 1).

Post-debridement wound healing

After surgical debridement, all burns were covered

with a silver-based dressing. During the twice-per-week dressing changes. Burns were also biopsied once per week to assess histological indicators of wound healing, such as granulation tissue, fibroplasia, and epidermal hyperplasia (Figure 4). Three days after debridement, granulation tissue was present in all groups, and epidermal regeneration/hyperplasia was present in all groups except for the PFC SOC. Except for the Flammacerium[®]-treated burn, there was moderate fibroplasia three days after debridement (Day 7), which increased to marked fibroplasia at 7 and 10 days after debridement. Typically, fibroplasia is more severe in more extensive dermal injury due to the amount of denatured collagen that needs to heal. Conversely, epidermal hyperplasia, which progresses from epidermal regeneration, was noted at 7 and 10 days after debridement for the Flammacerium[®]-treated samples and may suggest faster wound healing compared to the other groups. Decreases in neutrophils and lymphocytes were also observed in all treatments, compared to the PFC SOC, beginning as early as 10 days after debridement (Figure 4).

Finally, H&E stained sections of tissue at Day 18 demonstrate the formation of a near complete or progressing layer of epidermis in all treatments. All three post-debridement burns treated with the 4-Layer PEO/CeN dressings displayed prominent bands of remodeled collagen that span virtually the entire wound space. However, few conclusions can be drawn from this data until a larger sample size is achieved.

DISCUSSION

Burns treated with CeN creams such as Flammacerium[®] can convert burn eschars into a leathery layer that prevents the invasion of external factors while retaining valuable wound moisture [3,5,8]. Similarly, the proof-of-concept studies in this paper strongly suggest that an electrospun PEO/CeN dressing can achieve similar effects. The electrospun dressing did not negatively impact cell viability *ex vivo* and, when compared to the PFC SOC *in vivo*, the dressing 1) reduced the TEWL of DPT burn wounds and 2) decreased the overall amount of necrotic tissue that developed. There were also no significant differences in acute inflammatory cell infiltrate. Interestingly, the PEO-only dressings facilitated wound moisture retention to a greater extent than CeN-loaded dressings (Figures 1, 2). This may be due to the absorptive properties of PEO, which exists in a higher overall fraction in unloaded dressings compared to CeN loaded dressings, as well as the high surface area-to-volume ratio found in electrospun dressings [17,18]. However, in contrast to the burn treatments with higher CeN concentrations the PEO-only dressing did not reduce the amount of necrotic tissue formed by the burn (Figure 3). Together, these data strongly suggest that the lightweight, electrospun dressing effectively delivered CeN to the necrotic burn tissue and reduced the overall tissue loss associated with thermal injury.

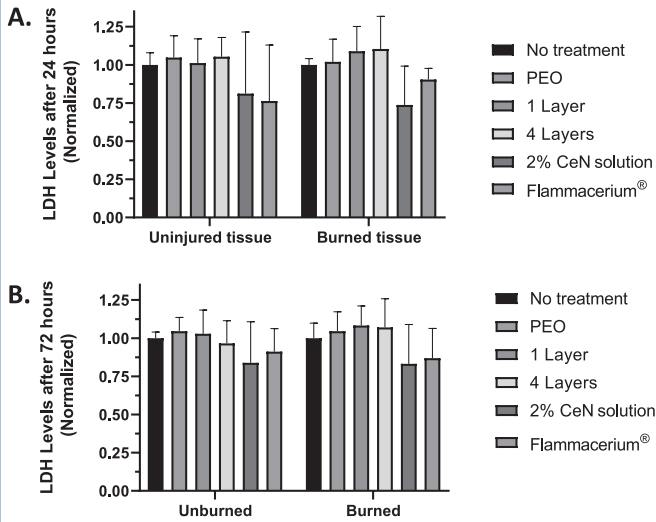


Figure 1 *Ex vivo* treatment with cerium nitrate-containing treatments does not significantly affect cell viability. Treatments were applied to the epidermal surface of isolated pig tissue and incubated at 32°C with 5% CO₂ for 24 (A) or 72 (B) hours. Data are representative of four independent experiments with technical triplicates; mean with standard deviation. Polyethylene Oxide (PEO); Cerium (III) Nitrate (Cen); Lactose Dehydrogenase (LDH).

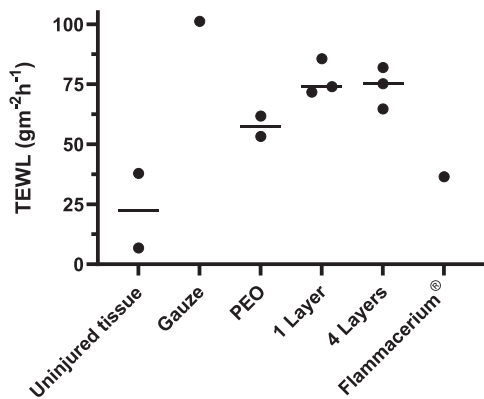


Figure 2 Electrospun cerium nitrate dressings reduce Transepidermal Water Loss (TEWL) by Day 2. Burns were assessed for TEWL after one dressing treatment. Measurements greater than those of the uninjured tissue suggest that the wound surface is damaged and/or more susceptible to dehydration. Data points show the average value of three measurements taken from each wound; mean values are indicated by solid lines. Polyethylene Oxide (PEO).

While these results strongly advocate for further evaluation of this CeN dressing for combat casualty care in PFC scenarios, there are two significant drawbacks to note. First, the limited number of test subjects precludes us from drawing any statistically powered conclusions from the *in vivo* study. The limited number of wounds also put a constraint on which wounds received the various treatments. Because porcine skin can differ in thickness and healing capacity along the cranio-caudal axis, it is possible that the perceived differences in necrotic tissue depth and/or healing capacity could be dependent on where the burns were located. To address this possibility, a blinded pathologist scored the burn depths and found no differences amongst the individual wounds.

The second drawback of these studies is that the CeN content the electrospun dressings was considerably lower than that of Flammacerium®. Each layer of electrospun PEO/CeN dressing contained 11.0 ± 2.9 mg of Ce(III). This means that burns treated with the 1-Layer CeN dressing received 11.0 mg Ce(III) and the burns treated with the 4-Layer dressing received approximately 44.0 mg Ce(III). This is in sharp contrast to the burn treated with Flammacerium®, which received approximately 110 mg Ce(III). An equivalent Ce(III) delivery would have required treatment with 10 layers of the electrospun fiber. Nonetheless, the ~44 mg Ce(III) delivered by the CeN dressings was sufficient to cause a decrease in necrotic tissue depth.

Given the limited sample size of this pilot study, it is not possible to statistically determine if the electrospun dressing can achieve similar results as the Flammacerium® cream. However, there is a strong inverse correlation between the amount of CeN used to treat the burn and the final depths of the burn injury. Increased concentrations of CeN is inversely correlated with the depth of Cas-3 staining, which suggests that the electrospun dressing and Flammacerium® have the capacity to reduce the amount of necrotic tissue that develops after a thermal injury. These

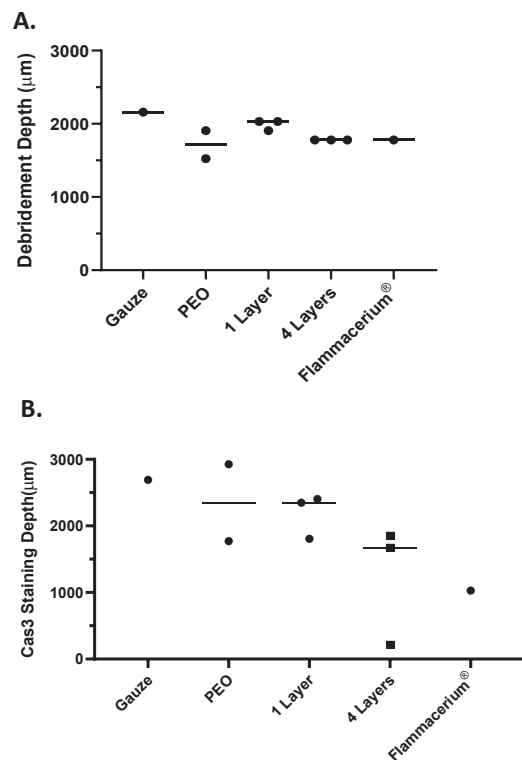


Figure 3 Comparison of surgical debridement depths and depths of necrotic tissue. (A) Four days after injury, a blinded operator surgically debrided all burns until punctate bleeding was observed. The total depth of debridement was recorded for each wound. (B) Immediately before surgical debridement, each burn was biopsied with an 8 mm biopsy punch. Samples were stained for Caspase 3 (Cas3). The distance from the wound surface to the bottom of Cas3 staining were recorded for each sample. Polyethylene Oxide (PEO).

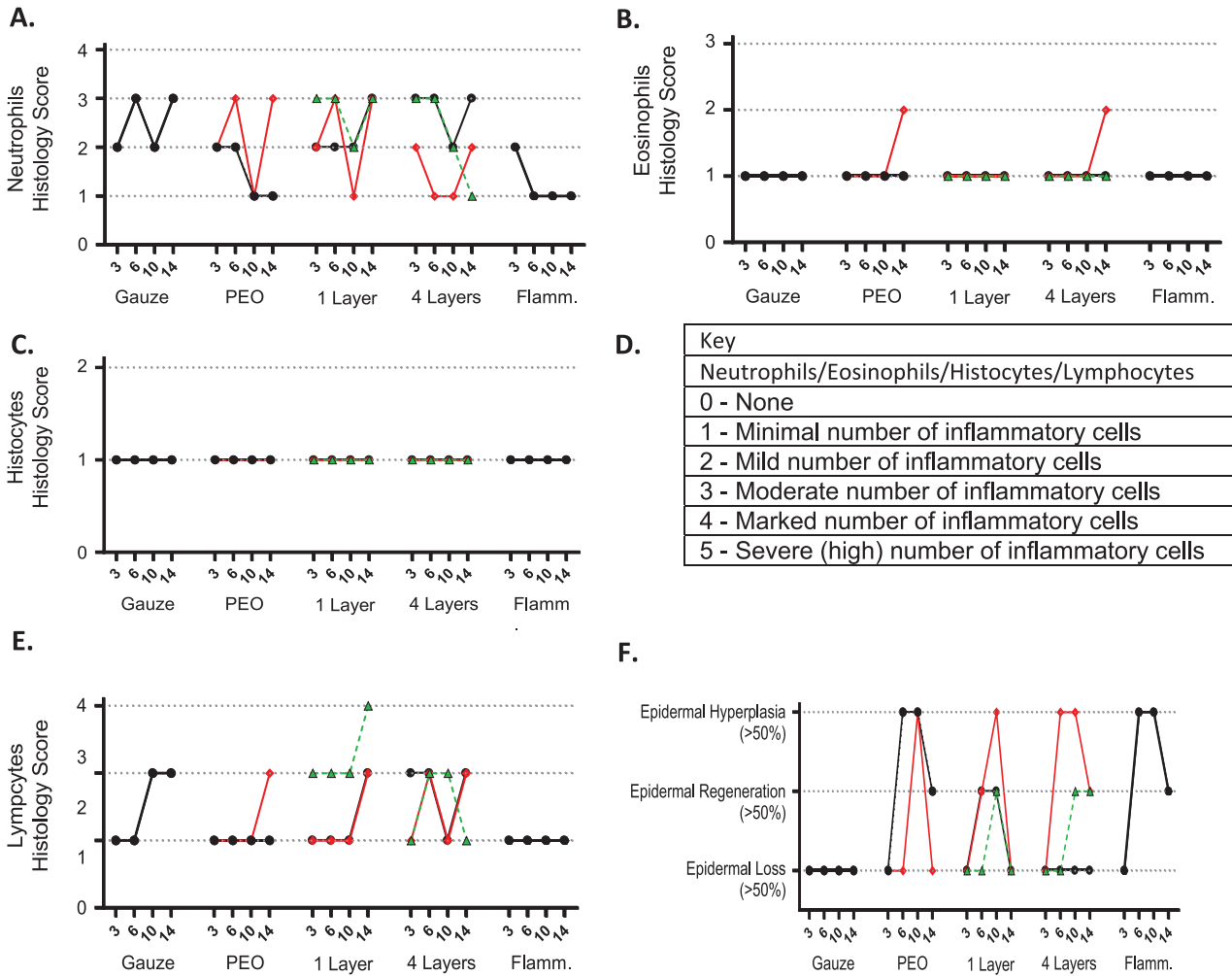


Figure 4 Electrospun cerium nitrate dressings reduce pro-inflammatory cell infiltrates and may heal faster than to the prolonged field care standard of care. Biopsy samples were collected 3, 6, and 10 days after surgical debridement. A blinded pathologist scored all samples for neutrophil infiltrate (A), Eosinophil infiltrate (B), Histocyte infiltrate (C), Lymphocyte infiltrate (D), and extent of epidermal regeneration (F), The histological scorecard is included (E). Individual wounds are indicated by the different colored lines. No difference in histology scores were observed prior to surgical debridement on Day 4. Polyethylene Oxide (PEO); Flammacerium® (Flamm.).

results also correlate with the recorded depths of surgical debridement. Furthermore, these studies demonstrate that DPT burns are not adversely impacted by PEO/CeN dressings during the critical period for immediate interventions in PFC scenarios. Compared to the current SOC all treatments decreased the depth of debridement to achieve punctate bleeding, by approximately 250 μm. This is a substantial difference in debridement depth considering that uninjured dermal tissue thickness ranges between 2-3 mm, and that there is a strong correlation between debridement depth and the rate of wound healing.

CONCLUSIONS

Effective burn care in the combat arena is a challenging problem. Compounding this issue is the fact that future conflicts are anticipated to delay access to Role 2 care by 72 hours. Limited access to medical facilities and standard burn wound treatments within this 72-hour window can

negatively impact burn prognoses and hinder the recovery of potentially salvageable burn tissue. The light-weight nature and simplistic application procedures of electrospun dressings, compared to bulkier and potentially more difficult to handle cream formulations, allows for more advantageous transport in already heavily weighted combat packs; similarly, these dressings are not simply consigned to field medics but can also be applied by untrained soldiers as well, at the point of injury. The ability to simultaneously delay the need for debridement and promote an advantageous wound healing environment, as displayed by the electrospun PEO/CeN dressings, could prove invaluable in future PFC scenarios.

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DISCLAIMER

The views expressed in this article are those of the author(s) and do not reflect the official policy or position of the U.S. Army Medical Department, Department of the Army, Department of the Navy, the DoD, or the U.S. Government.

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