Wireless Electroceutical Dressing for the Treatment of Biofilm Infected Burn Patients

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ABSTRACT

Introduction: Biofilms are clinically frustrating structures because within their extracellular polymeric substance (EPS) cocoons, bacteria are protected from antimicrobial attack and natural host defenses. The CDC estimates that 65% of all human infectious disease is caused by bacteria with a biofilm phenotype and NIH estimates that this number is closer to 80%. Despite advances in the use of topical and parenteral antimicrobial therapy and the practice of early tangential burn-wound excision to manage bacterial load, bacterial infection remains a major problem in the management of burn victims. The purpose of this clinical trial was to investigate the efficacy of an FDA cleared wireless electroceutical dressing (WED) against burn wound biofilm infection. The hypothesis was that a low electric field (~1V) generated by the moisture-activated WED would reduce biofilm severity and infection load. **Methods:** A phase I, prospective, randomized, controlled clinical trial was performed to evaluate the efficacy of the WED dressing compared to the standard of care (SoC) control dressing to prevent and disrupt biofilms. Subjects were screened from inpatient admissions to the Brooke Army Medical Center and US Army Institute of Surgical Research Burn Center in San Antonio, TX. Traumatic burns >300cm2 in size and distributed either in one contiguous area or two separate but similar areas were selected. In total 38 subjects were enrolled to the study. After obtaining informed consent, subject burn wounds were divided into two parts and randomized to receive either the SoC dressing or the WED dressing. Dressings were changed on day 4 and removed on day 7. Biopsies were collected on days 0 and 7 for blinded scanning electron microscopic (SEM) examination of biofilm and for semi-quantitative bacteriological analyses. **Results:** The results showed that short-term WED treatment significantly decreased biofilm severity in all burn wounds (grafted and non-grafted) analyzed. Furthermore, bacterial load was significantly lower in non-grafted burn wounds. The incidence of opportunistic pathogens such as Ralstonia pickettii and Serratia marcescens were significantly lower in WED treated wounds compared to SoC. **Conclusion:** This phase I clinical trial demonstrated that the WED promoted biofilm infection clearance better than SoC alone.

BACKGROUND

- Burn injuries (BI) are common to all military conflicts and historically constitute approximately 5 to 10% of all military casualties. American Burn Association (ABA) National Burn Repository shows that complications caused by infection represent 6/10 most common complications after burn injury. 42-65% of the mortality following thermal injuries is related directly to infections. Despite advances in antimicrobial therapy and the practice of debridement to manage bacterial load, bacterial infection remains a major problem in the management of burn victims
- Local management of infected burn wounds includes cleansing, debridement, topical antimicrobial agents (e.g. silver sulfadiazine (SSD), combination antibiotics, chlorhexidine), and dressings (e.g. compresses, biosynthetics, biologics). SSD, a common treatment in burn care, could be detrimental to wound healing and increase hypertrophic scar formation. Another concern with silver-based treatments is the emergence of resistant pathogenic strains.
- Biofilm infection is directly implicated in numerous human soft tissue and device-related infections. The estimates of infections with a biofilm phenotype are at 65%-80%. The current management of biofilm infection includes systemic antimicrobial therapy combined with sharp debridement to a healthy tissue bed as determined by the surgeon who cannot visualize the biofilm or decides based on standard clinical microbiological tests.
- Electrical principles influence fundamental processes in bacterial biology and influences bacterial growth and survival. Preclinical porcine studies where a wireless electroceutical device (**WED**) was tested on bacterial or fungal biofilm infected burn wounds showed that WED: (i) disrupted biofilm infection and (ii) restored skin barrier function. The effect of WED on wound healing was consistent with the beneficial effects seen in keratinocyte and other cellular studies.

Objective

Determine the efficacy of WED against biofilm infection in human burn wounds

Methods

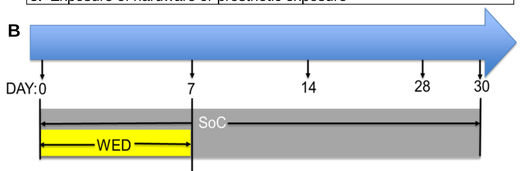
- The study was designed as a phase I, single-center, prospective, randomized, controlled clinical trial. The trial protocol was developed by the authors and was performed under an approved Institutional Review Board (IRB) protocol (C.2018.065) at the Brooke Army Medical Center (BAMC) and US Army Institute of Surgical Research (USAISR) Burn Center in San Antonio, TX. The study was registered in clinicaltrials.gov as NCT04079998.
- N=38 subjects were enrolled and randomized for treatment. Baseline assessments: infection assessment and wound photography. 3 mm punch biopsies of the treatment areas were obtained on d0, 4 and 7 for biofilm analysis (SEM). For rigor, sample collection and analyses were performed blinded.
- Primary outcome: short-term impact of WED on biofilm severity and eradication compared to SoC after seven days of treatment as analyzed by SEM (gold standard for biofilm analysis).

Methods (contd.)

A

Inclusion Criteria
Patients 18-65 years of age
Patient is willing and able to provide informed consent
Patient has acute wound(s) caused by trauma or burns meeting the following parameters:
1. Single wound ≥ 300 cm^2 in size in one contiguous area or two separate wound sites ≥ 150 cm^2
2. Exposure of deep dermis, subcutaneous tissue, muscle, fascia, tendon or bone.
Exclusion Criteria
Pregnancy
Prisoner
Current systemic steroid use
Active malignancy or immunosuppressive therapy
Know allergy or sensitivity to silver or zinc
Patient's proposed study wound site has any of the following conditions:
1. Location is on the hands, face or feet
2. Exposure of visceral organs
3. Exposure of hardware or prosthetic exposure

B



Note: WED treatment was stopped at d7. Subjects continued to participate in research visits at d14 and 30 and wound closure (visual and TEWL) measurements and scar assessments was performed. These data are not shown.

A.Inclusion/Exclusion criteria

B.Study enrollment, randomization, and follow up. Treatment design: For the first seven days following burn, following randomization, patients received either SoC or WED at the site of burn. After this period of treatment, WED was discontinued and SoC alone was applied until completion of the study at d30.

C. Research Procedures.

C
assessment of eligibility
informed consent
medical history
physical exam
vital signs
dressing application/change
wound & infection visual assessment
wound photography
wound biopsy
assess for adverse events

Results

WED significantly decreased biofilm severity in all human burn wounds

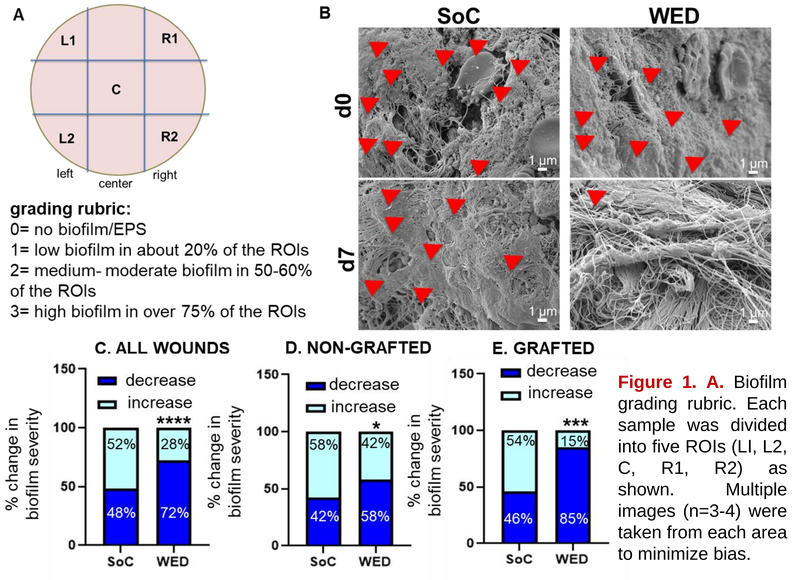


Figure 1. A. Biofilm grading rubric. Each sample was divided into five ROIs (LI, L2, C, R1, R2) as shown. Multiple images (n=3-4) were taken from each area to minimize bias.

Grading was performed following a 0-3 grade rubric where 0=no biofilm or EPS and 3=abundant biofilm and EPS in >75% of the sample. **B.** Representative SEM images from d0 and 7 of SoC or WED treated burn patients. Red arrowheads point to biofilm EPS matrix containing bacteria. Blinded biofilm grading was performed on SEM images obtained from **C.** all wounds (n=25), **D.** non-grafted wounds (n=12), and E. grafted wounds (n=13). Change in grade between d0 and 7 are represented as percentages in the graphs. WED treated burn patients had significantly lower biofilm grade compared to SoC alone. Contingency analysis using Fisher's exact test was performed. *P<0.05, ***P<0.0001, ****P<0.00001.

WED significantly decreased bacterial load in human non-grafted burn wounds

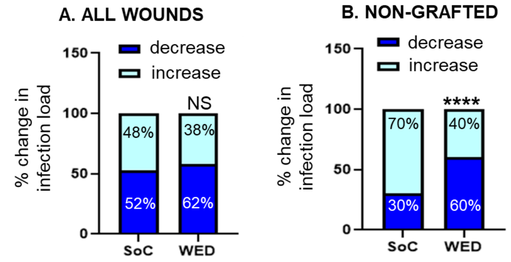


Figure 2. Blinded semi-quantitative scoring of bacterial load was performed on **A.** all wounds (n=19) and **B.** non-grafted wounds (n=10). Change in score between d0 and 7 are represented as percentages in the graphs and showed that non-grafted, WED treated burn patients had significantly lower bacterial load compared to SoC alone. Contingency analysis using Fisher's exact test was performed. ***P<0.0001; NS=not significant..

WED significantly decreased the incidence of specific opportunistic bacterial pathogenic strains in human burn wounds

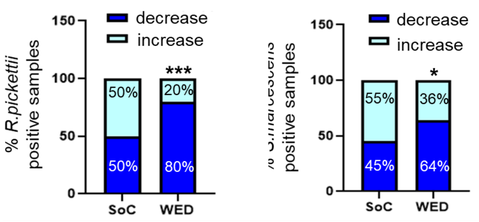


Figure 3. Blinded semi-quantitative scoring of incidence of **A.** Ralstonia pickettii (n=5) and **B.** Serratia marcescens (n=11) was performed. Percentage of samples containing the bacterial strains between d0 and 7 are represented in the graphs. WED treated burn patients had significantly fewer R. picketti (***P<0.0001) or S.marcescens (*P<0.05) compared to SoC alone. Contingency analysis using Fisher's exact test was performed.

Summary of Observations

1. **Fewer burns treated with WED had biofilm (*p<0.04*)**
2. **WED decreased biofilm in burn wounds (*p<0.05*)**
3. **WED decreased biofilm severity in all burn wounds (*p<0.05*)**
   - **WED decreased biofilm severity in non-grafted wounds (*p<0.0001*)**
   - **WED decreased biofilm severity in grafted wounds (*p<0.0001*)**
4. **WED decreased bacterial load in non-grafted wounds (*p<0.0001*)**
5. **WED decreased incidence of *Ralstonia pickettii* and *Serratia marcescens* (*p<0.01*)**

Conclusion

This work corroborates the anti-biofilm efficacy of WED in burn and trauma wounds and supports the safety of use in the context of human subjects. A larger clinical trial with longer duration of treatment investigating the impact on wound healing outcomes is warranted.

Acknowledgments

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