The Modular Adaptive Electrotherapy Delivery System (MAEDS): An Electroceutical Approach for Effective Treatment of Wound Infection and Promotion of Healing

Kath M. Bogie*†

ABSTRACT Background: Infected wounds are painful and cannot heal, with antibiotics showing reduced efficacy. Appropriate wound electrotherapy may limit incident planktonic and polymicrobial colonization, inhibit biofilm formation and accelerate healing. Methods: The Modular Adaptive Electrotherapy Delivery System (MAEDS) is a lightweight, flexible, battery-powered disposable bandage which delivers controlled reliable electrotherapy to the wound for up to 7 days. Large full-thickness excisional wounds (6 cm diameter) were created in a porcine model and freshly cultured 0.5 McFarland green fluorescent protein–labeled Pseudomonas aeruginosa evenly applied to the wound bed. Control wounds received standard wound care, Tegaderm HP Transparent Dressing (3 M Health Care, St. Paul, MN, USA) applied in a sterile fashion. Treatment wounds received MAEDS electrotherapy for up to 28 days or until healed. Onboard Bluetooth facilitated remote real-time monitoring of MAEDS function. Dressing changes occurred on postoperative day (POD) 1, 3, 5, 7, 10, 14, 21, and 28. Punch biopsies were taken at the wound margin and center. Bacterial samples were processed to determine infection status. Results: Acute infected wounds treated with MAEDS electrotherapy were 92% smaller than baseline by POD21. Healing rate was significantly faster (p < 0.01) and infection significantly decreased (p < 0.0001) at POD10, relative to control wounds. Conclusion: The MAEDS electrotherapy can significantly inhibit infection and enhance healing rate in acute infected wounds.

INTRODUCTION

Infected wounds are painful and cannot heal. Infected wounds increase scarring, extend hospital stays and can cause sudden death. All military injuries have some degree of bacterial colonization and are prone to infection.1 This complication delays healing and provides a source for cross-contamination both across the local patient population and across wounds for the patient with multiple injuries. Antibiotics are showing reduced efficacy in the face of multi-resistant bacteria. The increasing prevalence of multi-resistant bacteria indicates that novel approaches to infection control are needed.2 There is also a very high mortality rate for people who develop recurrent infections. Thus, there is a critical clinical need for interventions that can reduce incident infection, clear existing infection and accelerate healing.

Traumatic wounds, and in particular blast injuries, are much more complex than acute surgical wounds. Murray et al have found that almost half of all military wounds have some degree of bacterial colonization acutely.3,4 This complication adds further to the challenges of optimal wound management. A preliminary animal study of small fragment wounds by Bowyer et al found that while acute intramuscular inflammation and edema occur, it is critically important for successful healing that bacterial colonization is controlled.5 Increased bacterial activity decreases local tissue oxygenation, inhibiting angiogenesis and re-epithelialization thus prolonging the inflammatory phase. In severe infection, an acute wound may fail to heal and become chronic. When infected wounds do progress through the healing, the granulation tissue formed is more edematous and fragile than in non-infected wounds. Overall, when an infected wound does eventually heal, it will have decreased final wound strength and increased contraction and scarring.

Many infections will respond to therapy but a number will become re-infected with new strains of bacteria negatively impacting care at a critical stage of treatment.4,6 The disturbingly high mortality rate among military personnel who develop these recurrent infections highlights the need for early interventions to prevent and/or diminish wound infections.4,7 Novel approaches to enhance tissue viability, including infection control and modulation of inflammation, are needed as both alternative and adjunctive therapies to standard antibiotic regimes.

The presence of endogenous wound electrical currents in human wounds has long been known. It has also been shown in vitro that electrotherapy has the potential to reduce wound infection and can effectively inhibit several of the bacterial strains relevant to complications of military wounds, including Pseudomonas aeruginosa.6,9 Wound electrotherapy thus has the potential to address the multifaceted clinical challenge of wound infection in the combat-related or trauma-induced
wound. Both planktonic and biofilm bacterial wound infections can be positively impacted by electrotherapy to improve healing rates in acute infected wounds. Electrotherapy increases local metabolic activity and tissue oxygenation, inhibiting biofilm formation.\textsuperscript{12,13} These effects may be due to electrolysis products, or to increases in bacterial membrane permeability.\textsuperscript{10,11} Sustained application of electrotherapy has been found to be bactericidal when applied to infected but unwounded skin and to increase blood flow and capillary density in compromised wounds.\textsuperscript{14,15} Efficacy appears to vary with stimulation profile, with the primary electrotherapeutic factor being current density, implying that the bactericidal effect is electrochemically mediated.

Our group has developed the patented Modular Adaptive Electrotherapy Delivery System (MAEDS).\textsuperscript{16} This lightweight, flexible, battery-powered disposable device provides sustained delivery of controlled reliable electrotherapy to effectively minimize infection and maximize healing. The portable self-contained MAEDS was initially developed to in order to systematically evaluate the effects of varying electrotherapy treatment paradigms in a small animal model.\textsuperscript{17} The device is constructed using substrate materials that are biocompatible for sustained contact with the skin and wound, specifically liquid crystal polymer, and an adaptable architecture that facilitates functional adaptation.\textsuperscript{18}

MAEDS for large animal use is programmable and enables biphasic charge-balanced stimulation to be applied intermittently or continuously, for duty cycles (active stimulation period) from 5 min/day to 24 h/day. MEADS for large animal use can remain in situ delivering reliable electrotherapy as required for up to 7 days (Fig. 1).

METHODS

A porcine infected wound model was used for proof-of-concept testing. Three female Yorkshire pigs (30–35 kg) were co-housed prior to surgery in steel cages with a 12-hour light dark cycle. The animals were fed antibiotic-free food and water ad libitum throughout the study protocol. All pigs were observed for signs of infection or altered health at least 7 days prior to surgery as per protocol.

On the surgery day, the pigs were sedated in their cages by intramuscular injection of Telazol, 3–4 mg/kg (Wyeth Pharmaceuticals, Madison, NJ, USA). They were then transferred to the operating suite and an airway was secured with endotracheal intubation. General anesthesia was then induced and the pig was placed in a prone position so that their entire dorsal region would be accessible for surgery. The back hair was shaved and six wound sites were marked over the paraspinal region using a prefabricated stencil. The pig’s paraspinal region was then sterilely prepped with chlorhexidine scrub. In order to assist with local analgesic and hemostasis, the areas of skin to be excised were injected subcutaneously with a mixture of 1% lidocaine with 1:100,000 epinephrine (7cc at each excision site). Bilateral full-thickness excisional wounds (6 cm diameter) were then created. Hemostasis was achieved using limited electrocautery and manual pressure with sterile 4 × 4 cm gauze (Kendall Curity, Covidien, Mansfield, MA, USA).

Following creation of each wound, 150 μL of a freshly cultured 0.5 McFarland solution of a green fluorescent protein-labeled \textit{P. aeruginosa} was evenly applied to each wound bed by pipette. This strain of bacteria was selected for initial testing because it is known to cause both acute and chronic infection, due to the formation of stable biofilms within the wound.

Control wounds received standard wound care, specifically Tegaderm HP Transparent Dressing (3 M Health Care, St. Paul, MN, USA) applied in a sterile fashion. Treatment wounds received electrotherapy delivered by MAEDS for 6 minutes every hour (a 10% duty cycle) for up to 28 days or until all treatment wounds appeared to be fully healed. Electrotherapy was initiated immediately following wound creation and inoculation with pulse width 100 ms, and pulse amplitude 16 mA to provide a current density of 6.7 μA/cm\textsuperscript{2}.

To minimize extrinsic contamination a multi-layer dressing designed to withstand the pig’s tendency to scratch their back was designed based on a similar dressing described by Branski \textit{et al.}\textsuperscript{19} The second layer of the dressing consisted of an elastic bandage (Vetrap, 3 M Health Care, St. Paul, MN, USA). The final layer of coverage was Goat tube (Sullivan Supply, Hillsboro, TX, USA). Following surgery, the pigs were housed adjaently but individually to minimize interference with the MAEDs device and dressings.

The MAEDS function was remotely monitored every 30 seconds using the onboard Bluetooth radio. Data were stored locally on an SD card and uploaded to a secure Internet server every 10 minutes using a Wi-Fi connection.

Dressing changes occurred on postoperative day (POD) 1, 3, 5, 7, 10, 14, 21, and 28 with the substrate being discarded and the power/control module affixed to a fresh sterile substrate.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Large animal use MAEDS (Overall size 8 × 8 cm). (a) bio side hydrogel stimulation electrodes. (b) top-side connective traces power/control module in situ.}
\end{figure}
A culture swab was taken of the wound using a standard technique. Specifically, a double swab packaging was used to obtain the bacteria for culture (BBLTM CultureSwab, Franklin Lakes, NJ, USA). The double culture swab was applied with a gentle pressure to the wound’s surface. The entire wound was then swabbed from top to bottom using a back and forth motion. The swab was then rotated 180 degrees and the entire wound swabbed again using the same technique. The sterile cap was then placed back onto the swab and labeled accordingly. All processing was initiated within 24 hours of bacterial collection. If it is not possible to begin within 3 hours, the swabs were kept cool by placing them in a sealed plastic bag on ice in a cooler. Swab processing began with plating the bacteria onto a MacConkey agar using the standard quadrant streaking method. The swab tip was then placed into a tube with sterile phosphate buffered saline and used to create serial dilutions, which were plated onto blood, MacConkey and Mannitol salt agar plates, using 10 μL samples for each dilution. Plates were then incubated and read the following day. Outcomes variables included colony counts, color (when applicable) and appearance (if abnormal).

In vivo wound healing was monitored by digital stereophotogrammetry (LifeViz 3D system, Quantificare Inc., San Mateo, CA, USA). Wound bed cultures were obtained in a standardized sterile fashion using a double culture swab immediately following dressing removal on the individual wound. Bacterial samples were processed within 24 hours to determine MacConkey, blood and agar colony counts.

RESULTS
The MAEDS function was reliably monitored throughout the intervention. An average received signal strength (RSSI) of −65 dBm was achieved at a distance of 3.05 m. Local SD card data were concordant with remote server data.

Data could not be assumed to be normally distributed, thus the Mann–Whitney test was applied to determine significant differences between treatment and control groups (nine wounds per group).

Blood agar plates indicated that intermittent electrotherapy consistently reduced total bacterial load from POD1 to POD10, whereas untreated wounds had increased bacterial load. Acute infected full-thickness wounds treated with intermittent electrotherapy delivered at a 10% active duty cycle showed significantly decreased infection \((p < 0.0001)\) at POD10, relative to untreated wounds (Fig. 2).

The healing rate was significantly faster \((p < 0.01)\) for electrotherapy treated wounds compared to untreated infected wounds (Fig. 3). By POD21, electrotherapy treated wounds were 92% smaller than baseline (Fig. 4).

DISCUSSION
Infectious disease data gathered from the current study characterized bacterial infection associated with acute wounds. Results indicated that differences in both total bacterial load and \(P. aeruginosa\) bacterial load between wounds treated with intermittent electrotherapy and control wounds.

A physiologically appropriate moist wound environment is essential for wound healing. Exposure of the wound bed disrupts the moist wound environment, increasing the risk of drying out. Frequent dressing changes have been reported to cool the wound bed and inhibit healing. A moist wound environment is also essential to maintain effective electrotherapeutic current delivery to the wound bed. Systems using disposable surface electrodes require wound dressing to be removed so the electrodes can be placed at each treatment session and removed post-treatment. This introduces the
potential for non-uniform treatment delivery due to errors in repeatability of electrode placement and increases infection risk due to repeated wound exposure.

Appropriate and repeated delivery of electrotherapy to the wound bed has the potential to limit incident planktonic and polymicrobial colonization and accelerate healing.

It is also becoming clear that the wound biome is a complex environment. Not only do bacteria colonize wounds planktonically but they also attach to the wound bed and form biofilms. Standard clinical microbiology focuses on a monospecies planktonic bacterial load to determine infection status. However, it has been recognized for some time that many wound infections are typically polymicrobial and that biofilms often inhibit healing. Biofilm forms rapidly in nearly all traumatic wounds and is present in most acute surgical wound infections. Once established, the removal of a wound biofilm is very difficult, not least because biofilms are intrinsically resistant to antibiotics. The application of intermittent electrotherapy has the potential to inhibit biofilm formation and provide an alternative to topical antibiotics.

Future studies using MAEDS will elucidate the efficacy of appropriate and repeated delivery of intermittent electrotherapy to the wound bed to potentially limit incident planktonic and polymicrobial colonization and inhibit biofilm formation.

CONCLUSION
Pre-clinical investigation using an appropriate large animal model indicates that electrotherapy using MAEDS can significantly inhibit infection and enhance healing rate in acute infected wounds. The MAEDS can be configured to treat wounds of any size and dimension. It is envisioned that the MAEDS device can reliably deliver electrotherapy to reduce complications of soft tissue trauma and improve healing in acute infected wounds. Integration of innovative remote monitoring capabilities will enable wound status to be remotely monitored to ensure the wound is tracking the path to healing and providing early detection of infection.

In addition to promoting wound healing, electrotherapy has the potential to address the challenges of increasing antibiotic resistance and managing the wound bioburden.

Further development of this technology will integrate customized electrotherapy together with wound monitoring in the SmartMAEDS system. SmartMAEDS will enable real-time remote monitoring of wound status, minimizing unnecessary dressing changes and wound bed disruption, improving healing outcomes, and increasing safety.

PREVIOUS PRESENTATIONS
Presented as poster # MHSRS-17-0344 at the 2017 Military Health System Research Symposium, Kissimmee, FL August 2017.

FUNDING
This work has been supported by Department of Veterans Affairs Rehabilitation Research & Development Service Grant# F7129R and the Case Western Reserve University/STERIS Corp Infectious Diseases Research Program.

ACKNOWLEDGMENTS
The author wishes to acknowledge the contributions of Dr CA Zorman and Dr DS Howe in technical development of the MAEDS system. Ms J Graebert provided support for management of the animal model. I have obtained written permission from all persons named in the Acknowledgment.

REFERENCES


