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Major Article

Preliminary analysis of the antimicrobial activity of a postoperative wound dressing containing chlorhexidine gluconate against methicillin-resistant *Staphylococcus aureus* in an in vivo porcine incisional wound model

Thriveen Sankar Chittoor Mana MD [a], Curtis Donskey MD [b], Neal Carty PhD [c], Larry Perry RN [d], David Leaper MD [e], Charles E. Edmiston Jr,PhD [f,*]

[a] *Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH*
[b] *Geriatric Research, Education and Clinical Center, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH*
[c] *Avery Dennison, Chicago, IL*
[d] *Pluris Research, Franklin, TN*
[e] *Institute of Skin Integrity and Infection Prevention, University of Huddersfield, Huddersfield, United Kingdom*
[f] *Department of Surgery, Medical College of Wisconsin, Milwaukee, WI*

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Background: Surgical site infection is a major postoperative complication after surgical procedures. The effectiveness of postoperative antimicrobial dressings in reducing surgical site infections is unclear and limited information is available on the efficacy of chlorhexidine gluconate (CHG)-impregnated postoperative dressings.

Methods: A pilot study was conducted to examine the efficacy of an innovative CHG-impregnated postoperative dressing in reducing the burden of methicillin-resistant *Staphylococcus aureus* (MRSA) in an in vivo porcine, incisional-wound model. Sutured incisional wounds were contaminated with MRSA and then covered with a CHG wound dressing, a placebo control, or a nonantimicrobial gauze. The surviving MRSA population was quantitatively cultured 3 days postprocedure.

Results: MRSA was not recovered from any of the 8 wounds that were treated with the CHG dressing (limit of detection, approximately 1.7 $\log_{10}$ colony-forming units [cfu]/g tissue). In contrast, the average microbial recovery from wounds treated with the placebo dressing was 4.2 $\log_{10}$ cfu/g and the average microbial recovery from wounds treated with the gauze dressing was 3.2 $\log_{10}$ cfu/g.

Conclusions: An innovative CHG dressing provided significant antimicrobial activity against MRSA contaminating a surgical wound in a porcine, incisional-wound model. Future clinical studies are needed to assess the efficacy of the CHG dressing to reduce the bacterial burden in postoperative wounds of surgical patients.

Surgical site infection (SSI) is a major postoperative complication that increases morbidity, mortality, and length of stay for surgical patients.[1-3] In the United States, 300,000-500,000 patients develop an SSI annually.[4] Preoperative skin antisepsis is an important part of the care bundle for reducing the risk of SSIs and is supported by several national, international, and societal guidelines (Centers for Disease Control and Prevention, National Institute for Health and Clinical Excellence, World Health Organization, European Network for Health Technology Assessment, and the American College of Surgeons).[5-10] The use of postoperative dressings, particularly those with an antiseptic content, to aid in the reduction of SSI is less clear. The Centers for Disease Control and Prevention, National Institute for Health and Clinical Excellence, and World Health Organization

* Address correspondence to Charles E. Edmiston Jr, PhD, Department of Surgery, Medical College of Wisconsin, 9200 West Wisconsin Ave, Milwaukee, WI 53226.
E-mail address: edmiston@mcw.edu (C.E. Edmiston).

Conflicts of interest: Curtis Donskey has received research funding from Avery Dennison, Clorox, GOJO, and PDI. Neal Carty is an employee of Avery Dennison Corporation, the manufacturer of the chlorhexidine gluconate dressing described in the study. Larry Perry is the proprietor of the commercial laboratory, Pluris Research, which received a study grant from Avery Dennison for this investigation. Thriveen Sankar Chittoor Mana, Charles E. Edmiston Jr, and David Leaper have no conflicts of interest to declare.

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guidelines recommend keeping the original incisional wound dressings in place for 24-48 hours postoperatively, but these dressings may become a source of infection if not kept clean and dry.[6-8,11] Therefore, the application of a postoperative dressing has become common practice for protecting the wound and as an SSI risk reduction strategy.[12] Historically, a variety of antimicrobial wound dressings have been used postoperatively, including silver-based dressings, polyhexamethylene biguanide dressings, honey-based dressings, and povidone-iodine-based dressings.[13-17]

Surgical wounds, especially traumatic wounds, are fertile for bacterial contamination.[18] The efficacy of selective antimicrobial-impregnated dressings in reducing the burden of bacteria causing SSI has been demonstrated in limited clinical studies, animal wound models, and in vitro models of wounds.[19-24] However, a Cochrane Systematic Review in 2016 found that the evidence for effectiveness of existing postoperative dressings such as silver- or polyhexamethylene biguanide-based dressings in reducing SSIs was inconclusive, stimulating clinicians to call for more definitive evidence-based studies.[25,26]

Chlorhexidine gluconate (CHG) is a broad-spectrum antiseptic commonly used for preoperative skin preparation.[27,28] CHG-impregnated intravenous dressings have been shown to be effective in reducing the risk for catheter-related bloodstream infections.[29-32] However, limited information is available on the efficacy of CHG-impregnated postoperative dressings in reducing bacterial bioburden and preventing SSIs. Therefore, the present pilot study examines the efficacy of an innovative CHG-impregnated postoperative dressing in reducing the burden of methicillin-resistant *Staphylococcus aureus* (MRSA) in a porcine, incisional-wound model.

METHODS

Wound dressings

Three different postoperative wound dressings were compared. A transparent adhesive CHG dressing (ReliaTect Post-Op Dressing with CHG, Avery Dennison, Chicago, IL and Eloquest Healthcare, Ferndale, MI), measuring 8 cm x 15 cm, included CHG embedded within an acrylic adhesive. A placebo dressing was a nonantimicrobial dressing of identical design, but manufactured without CHG. The third comparator was a gauze dressing, which was a gauze pad, representing a common standard of care.

The CHG dressing is intended to cover and protect a wound caused by percutaneous medical devices such as drains, chest tubes, orthopedic pins, fixtures, and wires. It may also be used to cover and secure primary dressings. It inhibits microbial growth within the dressing and prevents external contamination. Reduction in the colonization or microbial growth on the device has not been shown to correlate with a reduction in infections in patients. Clinical studies to evaluate reduction in infections have not been performed.

Experimental animals

Five female domestic swine, aged 6-9 weeks and weighing between 14 and 18 kg, were used. The animals were treated in accordance with the regulations outlined in the US Department of Agriculture Animal Welfare Act (9 CFR, Parts 1, 2, and 3) and the conditions specified in *The Guide for Care and Use of Laboratory Animals*.[33] The animals were housed individually and maintained in a 12-hour light-dark cycle within a room-temperature environment (16°C-27°C, 20%-70% relative humidity), fed once per day, and allowed access to water ad libitum. Animals were acclimated to this housing environment for 7 days prior to commencing the experimental protocol.

Microbiological methods

Freshly-prepared MRSA (ATCC 33591) cultures were washed and resuspended with 0.85% sterile saline solution to a final concentration of approximately 5×10^4 colony-forming units (cfu)/mL. This diluted inoculum was applied to the sutured wounds postoperatively, after suturing but before dressing application. Enumeration of bacterial suspensions was accomplished by a plate counting technique using 1:10 serial dilutions on mannitol salt agar plates selective for *S aureus*. Before enumeration, tissue-and-dressing samples were homogenized in a sterile tissue grinder and suspended in 5 mL of Dey/Engley (D/E) broth to neutralize the antimicrobial activity of the CHG. D/E broth has been previously demonstrated to be an appropriate neutralizing medium for MRSA culture in the presence of the CHG-containing adhesive.[34] The actual concentration of the inoculum suspension was quantified by enumeration without predilution into D/E broth.

Microbiological method validation

A control experiment using porcine cadaver skin was conducted to prove the accuracy of the bacterial recovery and enumeration procedure, including the effectiveness of D/E broth as neutralizer. Abdominal-ventral swine skin (Tissue Source, Lafayette, IN) was brought to room temperature, cleaned, and allowed to dry. The skin flap was then antiseptically prepared using 2% CHG/70% isopropyl alcohol solution (ChloraPrep, CareFusion, El Paso, TX) and allowed to air dry for approximately 3 minutes. Eight linear incisions, approximately 0.5 cm deep and 2.5 cm in length, were made on each skin flap, extending through the dermis, using a #15 scalpel blade. The wound margins were approximated and closed with 3 simple interrupted 4-0 polyamide sutures. Four of the sutured incisions were dressed using CHG dressings, and the other 4 were dressed with placebo dressings. Immediately thereafter, a tissue sample weighing between 0.80 and 0.9 g was harvested from each sutured wound that included the incision and approximately 2-3 mm of surrounding skin, together with the dressing left intact. The tissue samples were weighed in a sterile Petri dish, then placed in a sterile tissue homogenizer together with a 0.1 mL inoculum of MRSA suspension. The inoculated sample was homogenized and neutralized with 5 mL of D/E broth, then plated for bacterial enumeration as described earlier.

In vivo experimental procedures

On the day of surgery (day 0), each animal was anesthetized, and the entire dorsolateral region was prepared by clipping the hair followed by light shaving to ensure a clean and smooth skin surface. The skin was then antiseptically prepared using 2% CHG/70% isopropyl alcohol solution, allowing at least 3 minutes drying time, then draped for surgery. Eight linear, full thickness incisions, approximately 0.5 cm deep and 2.5 cm in length, were made on each animal (4 per side) using a #15 scalpel blade. After hemostasis, the wound margins were approximated and closed using 3 simple, interrupted 4-0 polyamide sutures. Each sutured wound was challenged with an inoculation of 0.1 mL of the MRSA inoculation suspension and spread over the incision site with a surrounding skin margin approximately 0.5 cm wide. The inoculum suspension was allowed to dry for approximately 3 minutes before applying a postoperative wound dressing to cover each incision (Fig 1).

Each sutured, inoculated incisional wound was dressed with 1 of the 3 postoperative wound dressings (CHG dressing, placebo dressing, or gauze dressing) according to a predetermined randomization schedule. Foam pads (Reston self-adhering foam, 3M Health Care, St Paul, MN) were placed in-between the dressed incision sites, and then a protective, occlusive pad was secured using an elastic bandage

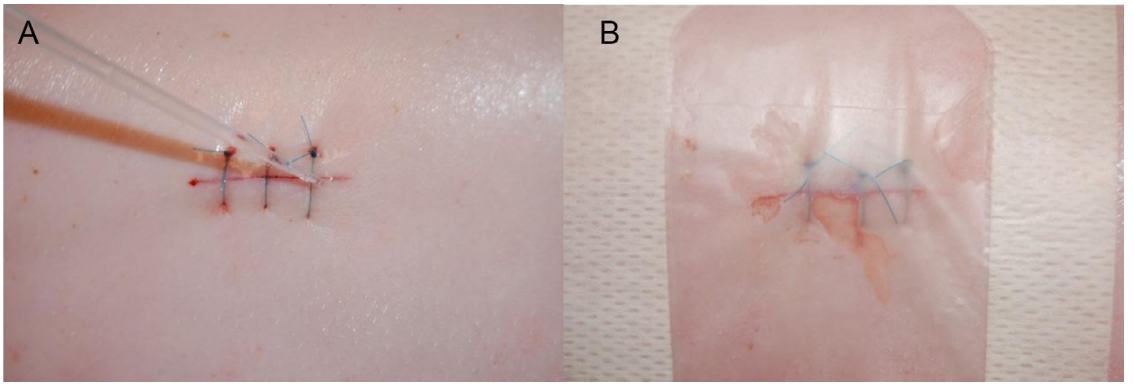

Fig 1. (A) Representative photograph of a sutured incision being inoculated with methicillin-resistant *Staphylococcus aureus* suspension. (B) Photograph of postoperative wound with chlorhexidine gluconate dressing applied.

over the entirety of the surgical sites to protect the dressings from external contamination. Animals were returned to their cages, and the dressings were left in place undisturbed for 72 hours.

On day 3, the animals were returned to the operating room and euthanized. A tissue sample, weighing between 0.90 and 1.1 g, was harvested from each wound that included the incision and approximately 2-3 mm of surrounding skin, together with the dressing left intact. The tissue samples were weighed in a sterile Petri dish, homogenized in a sterile tissue grinder, and then enumerated using the procedure described earlier. The number of surviving cfu in each sample was normalized by the sample mass to yield final data in units of cfu per gram. Under this methodology, the minimum detectable number of surviving colonies is approximately 1.7 $\log_{10}$ cfu/g, estimated based on detection of 1 cfu in the first (undiluted) plating of a 1 g sample.

Statistical techniques

Statistical analyses were performed using the Minitab software package version 16.2.4 (Minitab Inc, State College, PA). A power and sample size analysis was conducted assuming that a meaningful difference between the treatment groups would be at least 1 $\log_{10}$ cfu/g. A standard deviation of 0.5 $\log_{10}$ cfu/g was assumed based on previous pilot studies. Using a one-way analysis of variance with $\alpha = 0.05$ and $\beta = 0.10$, this analysis concluded that a sample size of N = 8 would be required to achieve the desired statistical power.

A one-sample t test was used to analyze the data: one-way analysis of variance of all 3 treatment groups was not appropriate because the data from the CHG dressing group were below the limit of detection. Data for the other 2 treatment groups in units of cfu/g were log-transformed before performing statistical analysis. The sample mean and 95% confidence interval were computed, and then a one-sided hypothesis test was performed under the null hypothesis, H_0, that the population mean (μ) is less than or equal to the limit of detection and the alternative hypothesis, H_A, that the population mean is greater than the limit of detection (H_0:$\mu \leq 1.7$ $\log_{10}$ cfu/g, H_A: $\mu > 1.7$ $\log_{10}$ cfu/g).

RESULTS

Quantitative microbiology, undertaken 3 days postoperatively, did not recover any detectable numbers of surviving cfu of MRSA in any of the 8 wounds treated with the CHG dressing: all 8 data points were below the experimental limit of detection of approximately 1.7 $\log_{10}$ cfu/g. In contrast, the average microbial recovery from wounds treated with the placebo dressing was 4.2 $\log_{10}$ cfu/g (range: 3.7-4.9 $\log_{10}$ cfu/g), and the average microbial recovery from wounds treated with the gauze dressing was 3.2 $\log_{10}$ cfu/g (range: 3.0-3.4 $\log_{10}$ cfu/g) (Fig 2). Both placebo and gauze average recoveries were statistically significantly greater than the minimum detection threshold of 1.7 $\log_{10}$ cfu/g ($P < .001$).

Two different batches of inoculum suspension were evaluated. The concentration of the first suspension was measured to be 5.2×10^4 cfu/mL, whereas the second was 5.6×10^4 cfu/mL. In the control experiment on porcine cadaver skin flaps, the inoculum concentration was quantified to be 3.00×10^4 cfu/mL. Surviving MRSA recovery

Fig 2. MRSA recovered from the wound specimens excised 3 days postoperatively. Individual data points are represented with open circles. The means and 95% confidence intervals are represented by black squares and lines. All 8 of the CHG dressing data points were below the LOD. *cfu*, colony-forming units; *CHG*, chlorhexidine gluconate; *LOD*, limit of detection; *MRSA*, methicillin-resistant *Staphylococcus aureus*.

from inoculated CHG dressing samples ranged from 3.45×10^3 cfu to 4.10×10^3 cfu, whereas the recovery from placebo dressings ranged from 3.05×10^3 cfu to 4.05×10^3 cfu. This equates to an average recovery from CHG dressings of 120% of what was inoculated, and 125% recovery of what was inoculated from placebo dressings.

DISCUSSION

The present pilot study documented that an innovative CHG dressing compared with controls provided a significant antimicrobial activity against MRSA contaminating the sutured incisional surface of a surgical wound. The 0.1 mL inoculation was spread over a 1.0 cm x 3.5 cm area resulting in an inoculation density of 3.2 $\log_{10}$ cfu per cm^2 of skin, which is similar to the microbial skin surface density of human skin flora (dry abdominal surface).[35,36] We did not include a comparison of the CHG dressing with other antimicrobial wound dressings. However, the level of suppression of MRSA in the current study is comparable to previous data for silver-based postoperative dressings.[22,23] In addition, the findings are consistent with previous studies, demonstrating that CHG dressings can be effective in preventing catheter-related infections.[29-32]

Currently, there is no standard of practice for postoperative wound care and the choice of dressing remains physician preference. Although many antiseptic agents have been used in postoperative wound care, these studies in general have been poorly designed, and often fraught with bias and limited in power. The current pilot in vitro and in vivo study suggests that a transparent dressing in which CHG is incorporated within the acrylic adhesive was effective in suppressing the growth of a multidrug-resistant strain of *S aureus* (ie, Methicillin-Resistant Staphylococcus aureus). A tangible benefit associated with a transparent surgical dressing is the ability to observe the wound as it transitions from the inflammatory to maturational phase of wound healing. Finally, there is a strong evidence-based argument for the development of an effective antimicrobial dressing that provides topical broad-spectrum activity against both gram-positive and gram-negative surgical wound pathogens.[37] Although the results of this study are encouraging, further studies are warranted, including a well-designed randomized-controlled clinical study in a postoperative surgical patient population.

Our pilot study had several limitations. The first stage in the development of an innovative surgical wound dressing involves assessing the impact of the antiseptic (ie, chlorhexidine-gluconate) activity on the kinetics of microbial growth following contamination of a sutured wound with MRSA. The current protocol was not designed as an infection resolution study. Furthermore, the limit of detection for MRSA was approximately 1.7 $\log_{10}$ cfu/g, and we cannot exclude the possibility that MRSA was present in lower concentrations. In addition, the wounds were only sampled at 3 days postprocedure, and therefore it is not clear if suppression of MRSA would continue for longer periods. Finally, only 1 pathogen was studied; however, *S aureus* is the leading cause of SSIs and CHG does have broad-spectrum activity against other bacterial and fungal pathogens. Future investigations will assess the clinical benefit of using an innovative CHG-impregnated surgical dressing for superficial surgical wounds.

CONCLUSIONS

In a porcine incisional wound model, a CHG dressing was effective in significantly reducing the burden of MRSA for 3 days when compared with a placebo and the standard of care (gauze). Future studies are needed to assess the efficacy of this innovative CHG dressing in reducing the bacterial burden on skin of surgical patients. There is also a need for additional evidence-based studies to determine if antimicrobial dressings represent an effective adjunctive intervention for reducing the risk of SSI.

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