

Reduction of Bacterial Burden and Pain in Chronic Wounds Using a New Polyhexamethylene Biguanide Antimicrobial Foam Dressing—Clinical Trial Results

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ABSTRACT

OBJECTIVE: A randomized controlled trial to evaluate the effectiveness of a polyhexamethylene biguanide (PHMB) foam dressing compared with a similar non-antimicrobial foam for the treatment of superficial bacterial burden, wound-associated pain, and reduction in wound size.

SETTING AND PARTICIPANTS: This study was conducted in 2 wound healing clinics—a university hospital-based clinic and a community-based clinic. Forty-five chronic wound subjects, stratified to either foot or leg ulcers, were followed for 5 weeks.

METHODS: A multicenter, prospective, double-blind, pilot, randomized controlled clinical trial with 3 study visits (Weeks 0, 2, 4) documented pain and local wound characteristics using NERDS and STONEES clinical criteria to determine superficial bacterial damage or deep/surrounding infection.

RESULTS: The use of PHMB foam dressing was a significant predictor of reduced wound superficial bacterial burden ($P = .016$) at week 4 as compared with the foam alone. Pain reduction was also statistically significant at week 2 ($P = .0006$) and at week 4 ($P = .02$) in favor of the PHMB foam dressings. Polymicrobial organisms were recovered at week 4 in 5.3% in the PHMB foam dressing group versus 33% in the control group ($P = .04$). Subjects randomized to the PHMB foam dressing had a 35% median reduction in wound size by week 4, compared with 28% in the control group.

CONCLUSIONS: PHMB foam dressing successfully reduced chronic wound pain and bacterial burden.

KEYWORDS: polyhexamethylene biguanide foam dressing, antimicrobial foam dressing, reduction of bacterial burden and pain in chronic wounds

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INTRODUCTION

Normal cutaneous ulcer healing usually follows a well-orchestrated trajectory. A complex network of biochemical pathways and sequential cellular interactions ensure an integrated progression of hemostasis, inflammation, proliferation (matrix deposition), and remodeling. However, wound healing is often stalled at the inflammatory or proliferative stage, producing chronic wounds that do not heal at the expected rate.^{1,2} These chronic nonhealing wounds are not inconsequential, and they constitute a significant burden for patients and the healthcare system contributing to substantial patient-centered disability (eg, decreased quality of life, restricted activities of daily living), morbidity (eg, amputations), and healthcare costs.³ The exact mechanisms that contribute to poor wound healing remain elusive but likely involve an interplay of systemic and local factors. Converging evidence suggests that wound healing can be noticeably delayed when the bacterial burden crosses a certain colonization threshold to overcome host resistance, causing local damage.^{4–6} The exact mechanism is not known, but bacteria may trigger the release of proteases that destroy growth factors and wound matrix, compete with nutrients in the wounds, or produce endotoxins and exotoxins that are toxic to the cellular wound microenvironment.

IMPORTANCE OF BACTERIAL BALANCE

All chronic wounds are colonized by microorganisms usually from external contamination. *Contamination* refers to the presence of nonreplicating microorganisms on the wound surface and evoking no clinical host response. As the microorganisms continue to proliferate and attach to the tissue within the wound, *colonization* is established in the absence of any detectable host injury. The concept of *critical colonization* (*covert infection, localized infection, increased bacterial burden*) connotes a

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replicating microbial burden in the wound surface compartment with subtle clinical signs of host injury. *Wound infection* occurs when the level of microbial burden or virulence has overwhelmed the host responses, and the microorganisms invade the host tissues locally (surrounding or deep) or systemically, causing clinical host injury. The susceptibility of the host to wound infection is a function of a symbiotic relationship between the host resistance and the bacteria number and their virulence.^{4–6} According to Sibbald et al,⁵ bacterial damage can be conceptualized and separated into superficial or deep/surrounding compartments that necessitate different management strategies.

The superficial compartment extends approximately 1 to 3 mm below the wound surface. Certain bacteria favor the superficial compartment because of its poor blood supply and relatively hypoxic environment. To reduce bacterial burden and its deleterious effect on wounds, a plethora of topical antimicrobial agents have been developed. Many active ingredients are impregnated in dressings that may be released into the wound in the presence of wound fluid or exudate.^{6,7} Alternatively, bacteria can be entrapped and sequestered in the microarchitecture of a dressing and ultimately inactivated. For bacterial damage that involves the surrounding and deep compartment in a chronic wound, systemic agents are usually recommended. An effective topical antimicrobial may still be considered to eliminate the bacteria that migrate to the superficial compartment where the circulation may be less than optimal.^{7,8} With the emergence of bacteria such as methicillin-resistant *Staphylococcus aureus* that are resistant to commonly used oral antibiotics, the use of topical antimicrobial agents has become a propitious local alternative. Ideally, these topical antimicrobials should be effective against a broad spectrum of pathogens, are low in cytotoxicity, and are safe with a low sensitization potential.⁵

Polyhexamethylene biguanide (PHMB) (Cosmocil CQ; Avecia Biocides, Wilmington, Delaware) is a common antimicrobial agent deployed in cosmetics, baby wipes, contact lens cleaning solutions, and swimming pool cleaners. PHMB, which is related to chlorhexidine digluconate, consists of a hydrophobic backbone with multiple cationic groupings (biguanides) separated by hexamethylene chains.⁹ PHMB initially binds to the positively charged surface of the bacteria and then travels to the bacteria's inner cytoplasm and the cytoplasm membrane, disrupting the integrity and permeability of the phospholipid structure, leading to cell death. Although PHMB has been demonstrated to be lethal to a broad spectrum of bacteria in vitro, it has very low toxicity to human cells that possess a more complex and protective structure. Using an ex vivo model, Werthén et al¹⁰ documented that *Pseudomonas aeruginosa* extracted from infected wound fluid was effectively eliminated by PHMB. In a prospective randomized controlled trial,¹¹ 50 patients were ran-

domized to gauze dressings moistened by either PHMB solution (Lavasept; Fresenius AG, Bad Homburg, Germany) or Ringer's solution for the treatment of surgical wounds. According to microbiology results from bacterial swabs, wounds that were treated with PHMB solution for 15 days in the study demonstrated faster and significant reduction in bacterial count. In another randomized controlled study, Motta and Trigilia¹² demonstrated that tracheotomy sites were relatively free of pathogens for 11 days in subjects assigned to the PHMB dressing compared with a shorter duration of 6 days in subjects randomized to the regular drain sponge. To examine the effectiveness of PHMB for deep wounds, Motta et al¹³ recruited 21 subjects with wounds that required gauze packing for 5 weeks in a study using a randomized controlled design. At baseline, 15 isolates were recovered from the PHMB study group versus 12 isolates in the control group. One week later, 6 isolates were recovered from wounds that were treated with PHMB versus 10 isolates in the control group. Overall study results demonstrated that the group randomized to the PHMB dressing "exhibited a greater reduction in the total number of microorganisms recovered throughout the study duration."¹³

However, the gauze material is suboptimal as a wound dressing because of its poor fluid-handling capacity, inferior moisture balance properties, and low tensile strength, which tends to leave debris/fibers on the wound base upon dressing removal.

An innovative dressing (Kendall AMD antimicrobial foam dressing; Tyco Healthcare Group LP, DBA Covidien, Mansfield, Massachusetts) was developed characterized by a foam matrix that is impregnated with PHMB as an antimicrobial agent. The PHMB in the dressing serves as a chemical barrier against bacterial invasion from the environment and as a bactericidal agent to thwart bacterial proliferation within the wound bed. The use of foam provides a highly absorbent, nonlinting platform that is designed to handle moderate to heavy exudate. A moist wound environment is facilitated by the foam dressing without causing damage to periwound skin, while enabling autolytic debridement and reducing pain. The open cell structure of the dressings also allows the exchange of gases, such as oxygen and water vapor.

A multicenter, prospective, double-blind, pilot, randomized controlled clinical trial was conducted to more closely examine the PHMB-impregnated foam dressing's performance with chronic wounds, specifically diabetic foot ulcers and leg ulcers.

CLINICAL TRIAL

Study Objectives

The primary objective of this clinical trial was to compare the efficacy of PHMB-impregnated foam (Kendall AMD antimicrobial foam dressing) versus a regular foam dressing without

the antimicrobial agent (Kendall foam dressing, Tyco Healthcare Group LP, DBA Covidien) in reducing superficial bacterial burden and promoting healing (surface area change) in chronic wounds.

Secondary objectives were to

- evaluate surface colonization of the wound bed using swab culture (bacteriology),
- examine pain and other clinical signs of increased bacterial burden (pain, wound, and periwound assessments), and
- document any potential adverse effects (see Results).

Methods

In this prospective, double-blind, pilot, randomized controlled clinical trial, 45 subjects with leg ($n = 23$) and foot ($n = 22$) ulcers were recruited from 2 wound clinics in Canada. After signing an informed consent document, subjects were screened for eligibility and then followed prospectively for 4 weeks at the clinic every 2 weeks (weeks 0, 2, and 4). A total of 40 subjects completed the clinical trial per protocol. Subjects who did not complete the study protocol cited the following reasons: 2 subjects withdrew from the study for reasons not related to wound care or an adverse event, 2 subjects were lost to follow up, and 1 subject withdrew because of an adverse event. This adverse event was an infection (moderate severity) that resolved in 30 days after withdrawal with antibiotic therapy. All wounds were at least 1 cm^2 in size with adequate vascular supply to support healing as indicated by either a palpable pulse (approximately ≥ 80 mm Hg), ankle brachial index greater than 0.5, or a toe pressure greater than 50 mm Hg. Subjects with a known allergy to chlorhexidine gluconate were excluded from the study.

After written consent was obtained, eligible subjects were randomized to either PHMB-impregnated foam (Kendall AMD antimicrobial foam dressing) or the regular, nonantimicrobial foam (Kendall foam dressing). Randomization schedules were generated by a computer program. Block randomization ensured that comparable numbers of subjects with leg and foot ulcers were stratified into either the intervention or the control groups. Treatment assignments were kept in sealed envelopes that were opened only after consents were obtained. To ensure allocation concealment, all dressings and packages appeared the same, with the exception of a letter X or Y printed on the front of the package as the only identifier for treatment assignments. All clinical investigators and assessors of the study were blinded to the group assignments and their corresponding letters.

Ethical Approval

Each study site received approval from its respective research ethics board. Written informed consents were obtained from all participating subjects.

Study Protocol

After randomization, the assigned dressings were applied over the study wound after cleansing with sterile water or normal saline. Dressings were changed up to 3 times per week during the course of the study. Follow-up evaluations were conducted by the research team at weeks 2 and 4 (the final visit). The ulcer characteristics, wound surface area, periwound skin condition, and pain levels were documented at each visit (baseline/week 0, week 2, week 4). Where appropriate, wounds were debrided to remove debris in accordance with best practice. Wound swabs were obtained after cleansing and debridement using the Levine technique at weeks 0 and 4 for quantitative culturing. Although other topical antimicrobial agents and cleansing solutions were excluded, systemic antibiotics were prescribed for the treatment of deep infection as needed.

Wound Surface Area

The percentage decrease in wound surface area was calculated by measuring the wound surface area during each study visit (week 2, week 4) and comparing that visit's value to the baseline wound measurement (week 0). Wound surface areas were measured by multiplying the longest length by the widest width that were perpendicular to each other ($\text{length} \times \text{width} = \text{cm}^2$).

Pain

Subjects were asked to rate their current levels of pain at the study wound prior to dressing removal on a 5-point Likert verbal descriptor scale. The verbal descriptor scale was made up of 5 word adjectives, "none," "mild," "moderate," "severe," and "extreme," thus describing increasing severity of pain. The purpose for this scale was to assess the level of pain localized at the study wound.

In addition, subjects were requested to indicate their pain levels 5 minutes after the randomized foam dressing was applied to the study wound. This pain assessment utilized the visual analog scale (VAS), with the objective being to assess for any stinging or burning sensations. The VAS is the most commonly used instrument to evaluate pain with a ratio scale property.¹⁴ It is unidimensional, consists of a continuous 100-mm vertical or horizontal line with anchors of "no pain" on one end and "worst pain" on the other end, representing the 2 extremes of pain intensity. Subjects were asked to place a mark on the line (VAS) that best represented their pain intensity.

Wound and Periwound Skin Assessments

Wound characteristics were documented using a standardized tool (NERDS and STONEES checklist, Table 1).⁸ Periwound skin condition was evaluated and described as intact, macerated, erythematous, or blistered.

Table 1.

NERDS AND STONEES MNEMONIC

S	↑ Size
T	Temperature difference by 3° F by infrared thermometry
O	Probe/exposed bone
N	New satellite area breakdown
E	Erythema and edema
E	↑ Exudate
S	Smell
N	Nonhealing
E	↑ Exudate
R	Red Friable Granulation
D	Debris on the surface
S	Smell

Bacteriology

Wound swabs were obtained at baseline and at week 4 to determine the microbiological profile. After dressing removal, the wounds were irrigated with sterile water or normal saline, and all patients received appropriate debridement. The bacterial swab was obtained by rotating the swab tip 360 degrees in a 1-cm² area of the cleanest part of the wound (Levine technique). The swab was then placed in the transport media to be sent to a Clinical Laboratory Improvement Amendments–certified central laboratory for susceptibility testing, identification of microbes, and quantitative cultures. To provide quantitative culture data, the bacterial swabs were placed in a known aliquot of liquid (1 mL) and then serially diluted. Wound infection was equated to the equivalent of greater than 10⁵ colony-forming units per milliliter. The number and types of bacterial species cultured were calibrated.

Statistical Methods

An additional purpose for this pilot study was to establish a statistically significant sample size and confirm study end points and methodology for a pivotal clinical trial. Thus, there were no formal sample size calculations conducted for this pilot; a sample size of 40 evaluable subjects was deemed sufficient to meet these study objectives.

The statistical analysis was conducted per protocol; however, adverse event data were analyzed using the intention to treat principle.

Nonparametric tests (eg, 2-sample Wilcoxon-Mann-Whitney test, Kruskal-Wallis test) were applied to compare the percentage decrease in wound surface area at each study visit to baseline wound measurements, the difference in pain ratings, and the number of bacterial species and bacterial count between baseline and the end of the study (Table 2). Logistic regression analysis was used to evaluate potential factors that contributed to changes in the wound surface bacterial count.

RESULTS**Study Subjects/Disposition**

Forty subjects with leg (n = 20) and foot (n = 20) ulcers completed all study visits; data generated from 21 subjects randomized to the control foam dressing and 19 subjects randomized to the antimicrobial foam dressing are reported in the final analysis.

Overall, 82% of these subjects were men, with a mean age of 55.8 (SD, 13.13) years. The mean body mass index was 52.6 (SD, 11.95) kg/m², with 95.6% of the subjects categorized as obese. The 2 study groups were comparable with no statistically significant differences noted on baseline characteristics and comorbidities (eg, smoking, diabetes mellitus, peripheral vascular disease, hypertension, and recent surgery).

A larger proportion of subjects randomized to the control foam dressing (61.9%) was prescribed antibiotics prior to the study versus those randomized to PHMB foam dressing (31.6%); the difference did not reach a significant level (*P* = .067).

Wound Surface Area

The wound surface areas between the 2 study groups were similar at baseline: median of 3.8 cm² (1.1–94.8 cm²) for the

Table 2.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Parameter	Kendall Foam (n = 23)	Kendall AMD Foam (n = 22)	Total (n = 45)	<i>P</i> ^a
Age, y				0.3680
No. of patients	23	22	45	
Mean (SD)	55.1 (11.01)	56.4 (15.28)	55.8 (13.13)	
Median	55.0	57.5	55.0	
(Minimum, Maximum)	(36.0, 83.0)	(20.0, 79.0)	(20.0, 83.0)	
Sex, n (%)				0.4591
Male	20 (87.0)	17 (77.3)	37 (82.2)	
Female	3 (13.0)	5 (22.7)	8 (17.8)	
Race, n (%)				0.7682
Asian/South Asian	1 (4.3)	2 (9.1)	3 (6.7)	
Black/African American	2 (8.7)	1 (4.5)	3 (6.7)	
White	20 (87.0)	18 (81.8)	38 (84.4)	
Other	0 (0.0)	1 (4.5)	1 (2.2)	
BMI				0.5071
No. of patients	22	22	44	
Mean (SD)	52.8 (7.73)	52.4 (15.26)	52.6 (11.95)	
Median	53.9	53.2	53.8	
(Minimum, Maximum)	(35.4, 70.6)	(27.3, 94.0)	(27.3, 94.0)	
Weight status				
Overweight (25–29.9)	0 (0.0%)	1 (4.5%)	1 (2.2%)	
Obese (≥30)	22 (95.7%)	21 (95.5%)	43 (95.6%)	

^a*P* for age and BMI obtained using 2-sample Wilcoxon-Mann-Whitney test. *P* for sex and race obtained using 2-sided Fisher exact test. *P* for weight status obtained using Kruskal-Wallis test.

PHMB foam dressing group compared with 4.5 cm² (21.0–21.9 cm²) for the foam dressing group ($P = .55$). At week 2, the PHMB study group exhibited a 32% (32.0 cm²) median decrease in wound surface area as compared with the 21% (21.1 cm²) median reduction observed in the control group ($P = .31$). Upon completion of the study, subjects randomized to the PHMB foam dressing had a 35% median reduction (34.9 cm²) in wound surface area by week 4, compared with 28% (27.8 cm²) in the control group ($P = .85$).

Bacteriology

At baseline, there was no difference in the number of microorganisms recovered from wounds between the 2 study groups. At week 4, polymicrobial organisms were detected in 5.3% of wounds treated with PHMB foam dressing compared with 33% with the control foam dressing ($P = .04$). Logistic regression analysis was performed to examine the factors that contributed to the reduction of bacterial burden on the wound surface. A number of independent variables were selected, such as treatment assignment, wound location, age of wound, diabetes, and so on. The PHMB-impregnated foam dressing was the only significant predictor of the reduction of wound superficial bacterial burden ($P = .016$) at week 4.

Wound and Periwound Characteristics

Wound scores, NERDS and STONEES checklists, and periwound skin assessments were similar between the 2 subject groups at baseline. The percentage of maceration at the periwound demonstrated a similar trend during the study period in both study groups. From baseline to week 4, periwound maceration of the subjects allocated in the PHMB group increased from 36.8% to 57.9%, and subjects allocated to the control group increased from 47.6% to 61.9%.

Pain

Baseline pain assessments were also comparable between the 2 study groups (33.3% no pain PHMB foam vs 31.6% control, $P = .79$). At week 2, a higher proportion of subjects in the PHMB foam group (78.9%) reported no pain prior to dressing change than in the control group (33.3%), as measured by the 5-point Likert scale. The difference was significant ($P = .0006$). Pain ratings remained consistently lower through week 4, with 73.7% in the PHMB group reporting no pain ($P = .02$) versus 38.1% in the control group. At week 2, pain levels 5 minutes after dressing application were also measured via the VAS; the same trend in pain reduction was apparent, with subjects randomized to the antimicrobial foam dressing reporting greater comfort ($P = .05$).

Minimal adverse events were reported during this trial, and none were assessed as being related to the study dressings or procedures. Events of interest include 2 subjects in the control group who developed infections localized at the study wound. One subject in the control group required a new prescription for systemic antibiotic related to the study wound. None of the subjects randomized to the PHMB foam dressing developed wound infections. Periwound infection was defined as the presence of 3 or more criteria from the STONEES mnemonic (Table 1).

DISCUSSION AND OVERALL CONCLUSIONS

Wound-related bacterial damage and infection can result in poor wound healing and other adverse patient outcomes. Among patients with diabetic foot ulcers, several studies^{15–18} suggest that wound infection was one of the major risk factors that heralds amputations. Length of hospital stay and mortality were significantly increased in surgical patients who had wound infection. Although Gram-positive organisms predominate in wounds initially, they are combined with Gram-negative organisms and anaerobes (polymicroorganisms), which are usually detected in chronic wounds. Wound healing has been found to be noticeably compromised when the bacterial burden crosses a certain colonization threshold (1.0×10^6 or higher number of colony-forming units per gram of tissue) or incorporates 4 or more pathological bacterial species.^{4–6} Together, multiple microorganisms may aggregate to produce biofilms and exchange virulence factors, rendering them even more difficult to be eliminated over time. Although there are numerous antimicrobial products available, not one product is going to be appropriate for all patients. Results of this clinical trial suggest PHMB-impregnated foam dressing as a viable option for the treatment of critically colonized chronic wounds.

These study findings indicate that a significantly lower number of bacterial species were recovered from wounds that were randomized to the PHMB dressing versus the control dressing. Moreover, the use of the PHMB foam dressing was the sole significant predictor of reduced wound superficial bacterial burden. Pain was also significantly reduced with the antimicrobial dressing. Cutting and Harding¹⁹ originally proposed that the presence of unexpected pain/tenderness along with other criteria is indicative of infection in granulating wounds. More recently, an international Delphi panel of 54 members arrived at a consensus²⁰: changes in the nature of pain should indeed raise the suspicion of infection in a variety of acute and chronic wounds. Gardner et al²¹ evaluated the validity of a checklist of 12 clinical signs and symptoms to identify localized chronic wound infection ($n = 36$). Quantitative biopsy cultures equal to or greater than 10^6 colony-forming units per gram of

wound tissue were used as the criteria to determine the infection status of each study wound. For wounds that were not infected, none of the subjects complained of increasing pain. Pain was a useful indicator of bacterial damage and infection with high specificity value (100%) and interrater reliability ($\kappa = 0.73$) in this study population. The mechanism linking infection to pain remains elusive. One theory links the wound-related pain to irritation from proinflammatory mediators via Toll-like receptors, a family of pattern recognition receptors that mediate innate immune responses to pathogenic stimuli.

Although the change in wound surface area was nonsignificant, wounds that were treated with PHMB foam dressings exhibited faster healing rates than wounds managed by the control foam dressing. This trend warrants further investigation in a randomized controlled clinical trial of a larger sample size, with selection criteria enforcing a more uniform wound size upon study entry for closer scrutiny.

Overall, results from this double-blind, randomized controlled clinical trial demonstrated that the PHMB dressing significantly reduced polymicrobial organisms, decreased pain levels, and was a significant predictor for reduced wound superficial bacterial burden. Perhaps equally important, both the subjects and nursing staff stated that they were highly satisfied with the PHMB dressing's performance with chronic wounds. ●

CASE STUDY

Week 0



A 67-year-old man developed a wound on the lateral aspect of his left malleolus approximately 18 months ago. His medical history includes venous insufficiency, hypertension, smoking, and chewing tobacco. Medications upon study entry were specific to his hypertension. Baseline wound surface area calculated on length \times width was 7.2 cm². The periwound area presented with maceration and stasis dermatitis. The subject reported his baseline pain level as "moderate" using the 5-point Likert scale. He was randomized to the antimicrobial foam dressing.

Week 2



The wound surface area decreased by 62% to 2.72 cm². Periwound assessment demonstrated both healthy/intact skin and redness with continuing dermatitis. The subject reported his pain level as "none."

Week 4



The wound surface area was 0.5 cm², resulting in a total reduction of 93% from study baseline (Week 0). Periwound assessment reported some maceration with continuing dermatitis. The subject again reported his pain level as "none." He did not experience any adverse events during this clinical trial.

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