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Major Article

Efficacy and safety of a novel skin cleansing formulation versus chlorhexidine gluconate

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Health care–associated infections
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noninferiority study

Background: This study evaluated whether a multi-ingredient surfactant colloidal silver technology was noninferior to a 4% chlorhexidine gluconate (CHG) antiseptic on immediate and persistent antimicrobial activity.
Methods: The inguinal regions of 81 healthy adults were demarcated into 4 quadrants, and 3 were used for testing each product at baseline, 10 minutes, and 6 hours postapplication. The log of the number of colony forming units was obtained using a cylinder sampling technique. The 95% confidence interval of the test product to the control product with a margin of 0.65 was established as the upper limit of noninferiority.
Results: A total of 81 individuals were enrolled. The colloidal silver product was found to be noninferior to 4% CHG at both 10 minutes and 6 hours postapplication.
Conclusions: The colloidal silver-based product was noninferior to the 4% CHG product at 10 minutes and 6 hours postapplication.

BACKGROUND

Health care–associated infections (HAIs) continue to plague patients in the United States. Annually, there are >1.7 million HAIs in the United States resulting in almost 100,000 deaths and costs to the medical care system of $6.5 billion.[1] The Centers for Disease Control and Prevention estimate that 1 in 25 patients will contract an HAI during their inpatient hospitalization,[2] underscoring the need for novel prevention strategies.

The recent compendium of strategies to prevent HAIs strongly recommends the use of topical antiseptics for HAI risk reduction in acute care settings.[3] Chlorhexidine gluconate (CHG) has been widely used as an antiseptic for decolonizing the skin before surgery and for daily bathing while hospitalized[4-6] because of its proven immediate and persistent antimicrobial activity after skin application.[7] However, not all trials have been positive,[8] and reports have implicated CHG in cases of site irritation, allergic and anaphylactic reactions, and patient discomfort.[9-11] This is problematic, particularly for already compromised skin. Further, continued antimicrobial resistance has been documented,[12,13] suggesting greater control may be necessary from an antimicrobial stewardship perspective.[14,15] In particular, establishing antisepsis in the inguinal area before urinary catheter insertion is important in preventing urinary tract infections.[16] Because of this, it is important to continue to explore skin antiseptics that provide broad-spectrum antimicrobial activity.

The objective of this study was to evaluate if a novel, multi-ingredient surfactant colloidal silver technology was noninferior to a commonly used 4% CHG containing skin antiseptic in terms of immediate and persistent antimicrobial activity.

MATERIALS AND METHODS

This was a noninferiority study evaluating the antimicrobial activity of 2 products, a surfactant, multi-ingredient colloidal silver technology (Theraworx Specialty Care Pack; Avadim Technologies, Asheville, NC) and a 4% CHG antiseptic (Hibiclens; Molnlycke Health

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Care, Norcross, GA), with respect to immediate and persistent antimicrobial activity on the skin. This study was conducted to identify if the colloidal silver technology was an effective antiseptic and could be used prior to insertion of a urinary catheter to clean the inguinal area.

Pretest period

The 14 days prior to the test portion of the study was defined as the pretest period. During this time, subjects avoided using medicated soaps, lotions, deodorants, shampoos, and skin contact with solvents, detergents, acids and bases, or any other products known to affect the normal microbial populations of the skin.

Baseline screening sampling and inclusion and exclusion criteria

Adult subjects ≥18 years of age were invited to participate and were recruited using a convenience sample at Bioscience Laboratories, Bozeman, Montana, between January 10, 2017, and January 30, 2017. Inclusion criteria included the following: (1) ability to read and provide written informed consent; (2) in good health without a medical diagnosis of a current or recent severe illness, medicated or controlled diabetes, hepatitis B or C virus infection, prior organ transplant, mitral valve prolapse with heart murmur, fibromyalgia, ulcerative colitis, Crohn disease, or an immunocompromised condition, such as HIV infection, lupus, or medicated multiple sclerosis; (3) skin within 15.24 cm of the test sites free from tattoos, dermatoses, abrasions, cuts, lesions or other skin disorders; and (4) minimal hair density at test sites. Skin samples were taken on the day after the pretest period using the cylinder sampling technique in the center of the sampling areas at the inguinal evaluation sites. A minimum of 72 hours elapsed between the end of the screening period and the beginning of the experimental period. Baseline criteria for including the inguinal site consisted of ≥5.0 $\log_{10}$ and ≤7.5 $\log_{10}$ colony forming units (CFU)/cm^2. Failure to document these counts resulted in exclusion from the study.

Cylinder sampling techniques

A sterile cylinder (Fig 1, marker A) with an inside area of 3.46 cm^2 was held firmly onto the test site for sampling. Three milliliters of sterile stripping fluid with product neutralizers (SSF++) (1.167% w/v lecithin, consumer grade; 10.0% v/v Polysorbate 80 [bioWORLD]; 0.04% w/v KH_2PO_4 [Sigma Aldrich]; 1.01% w/v Na_2HPO_4 [Sigma Aldrich]; 0.01% v/v Triton X-100 [JT Baker]; 0.5% w/v sodium thiosulfate pentahydrate [Sigma Aldrich]; 0.1% v/v Tamol SN [Rohm Haas], 1.25 mL Butterfield's Phosphate Buffer Diluent Stock Solution [3.4% w/v KH_2PO_4; Sigma Aldrich], pH 7.8-7.9; Bioscience Laboratories, Bozeman, MT) was placed into the cylinder, and the skin area inside the cylinder was massaged in a circumferential manner for 1 minute with a sterile rubber policeman (Fig 1, marker B). The SSF++ was removed with a sterile pipette and transferred into a sterile test tube. A second 3.0-mL aliquot of SSF++ was placed into the cylinder and completed in the same manner, therefore pooling the aliquots for microbial enumeration.

Test period

Clinical efficacy testing was performed based on procedures outlined in the Food and Drug Administration's (FDA) Tentative Final Monograph[9] and the ASTM Method E1173-15 for a simulated preoperative skin preparation.[10]

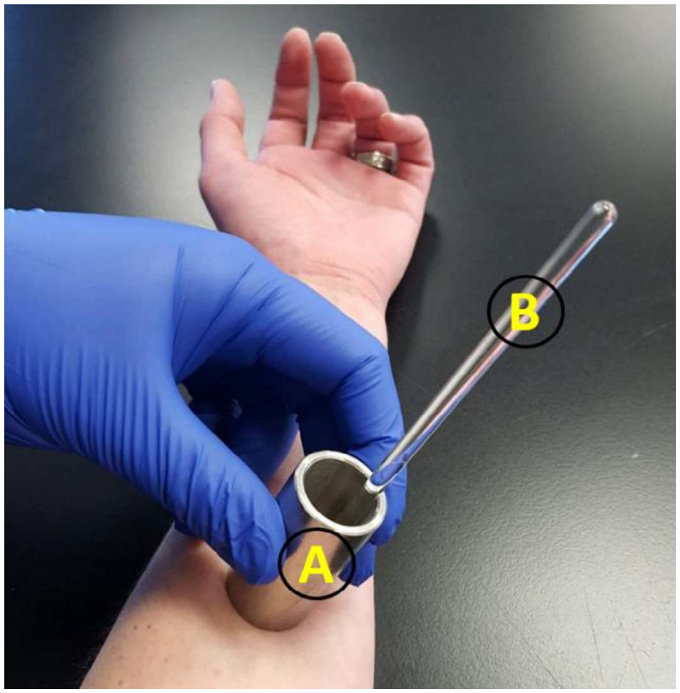

Fig 1. Cylinder sampling technique. Marker A shows the cylinder, and marker B shows the rubber-tipped policeman.

On each subject's inguinal region, 4 areas were demarcated (2 × 5 in) using a sterile surgical marker, on each inguinal side. Only 3 of the 4 sites were sampled (one at baseline, one at 10 minutes, and one at 6 hours). All areas were chosen visually to be of similar physical condition. Bilaterally, 2 areas (one for each product) were used for testing. Products under evaluation were randomly allocated using a computer-generated randomization scheme for each of the inguinal test sites, such that both products were used on each subject. Sites were sampled for microbial loads 10 minutes ± 30 seconds postproduct application using the cylinder sampling technique. The 6-hour sites were covered with sterile gauze and semi-occlusive bandages and were sampled 6 hours ± 30 minutes after product application using the cylinder sampling technique.

Diluting and plating

Aliquots of the microorganism suspension (10^0 dilution) were serially diluted in Butterfield's Phosphate Buffer Solution with product neutralizers (1.167% w/v lecithin, consumer grade; 10.0% v/v Polysorbate 80 [BioWORLD, Irving, TX]; 0.0523% w/v KH_2PO_4 [Sigma Aldrich]; 1.673% w/v K_2HPO_4 [EMD Chemicals]; 0.01% v/v Triton X-100 [JT Baker, Pittsburgh, PA]; 0.5% w/v sodium thiosulfate pentahydrate [Sigma Aldrich, Milwaukee, WI]; 0.1% v/v Tamol SN [Rohm Haas, Philadelphia, PA]; 1.25 mL Butterfield's Phosphate Buffer Diluent Stock Solution [3.4% w/v KH_2PO_4; Sigma Aldrich]; pH 7.8-7.9; Bioscience Laboratories), as appropriate. Duplicate pour plates were prepared from each of these dilutions on tryptic soy agar with neutralizers for each product (Tryptic Soy Agar with Lecithin and Polysorbate 80; Hardy Diagnostics CRITERION Tryptic Soy Agar with 0.07% w/v Lecithin and 0.5% w/v Tween 80; Bioscience Laboratories) and incubated at 30°C ± 2°C for approximately 72 hours. Microbial colonies were manually counted, and data were recorded on data collection forms.

Statistical analyses

The estimated $\log_{10}$ number of viable microorganisms per square centimeter recovered from each sample site was designated as the *R* value. To convert the volumetric sample measurement into the number of CFU per square centimeter, the following formula was used:

$$R = Log_{10}\left[\frac{F\left(\frac{\sum_{i=1}^{n} c_i}{n}\right)10^{-D}}{A}\right]$$

where *R* is the average CFU count in the $\log_{10}$ scale per square centimeter of sampling surface; *F* is the total number of milliliters of stripping fluid added to the sampling cylinder (in this study, $F = 6$ mL); $\frac{\sum_{i=1}^{n} c_i}{n}$ is the average of the duplicate colony counts used for each sample collected; *D* is the dilution factor of the plate counts; and *A* is the inside area of the cylinder in square centimeters (in this study, $A = 3.46$ cm^2).

Counts of <1 CFU/cm^2 were treated as 1 CFU/cm^2, so that the $\log_{10}$ transformation was zero instead of a negative number. The *R* values were the values used in this study for baseline, 10 minutes, and 6 hours.

A noninferiority test required by the FDA[17] was conducted for both immediate (10 minutes) and persistent (6 hours) activity. If the upper limits of the 95% confidence interval (CI) of the average treatment effect (colloidal silver minus 4% CHG), estimated by a multiple linear regression, was equal to or below the noninferiority margin (0.65), noninferiority was established. The multiple regression equation used was the $\log_{10}$ recovery data as the dependent variable and the $\log_{10}$ baseline count as the continuous predictor variable and the two products as the categorical predictor variables. The 2 products as the qualitative independent variable were also in the model. The equation used is as follows:

$$\hat{y} = b_0 + b_1x_1 + b_2x_2 + e$$

where $\hat{y}$ is the $\log_{10}$ recoveries; b_0 is the standard *y* intercept; b_1 and b_2 are the computed values using the least squares method; x_1 is the $\log_{10}$ baseline value; $x_2 = 1$, if the test product (colloidal silver) was used, and $x_2 = 0$, if the control product (Hibiclens) was used; and *e* is the error term.

Minitab version 18 (Minitab, State College, PA) was used for analysis.

RESULTS

A total of 40 subjects were enrolled and tested in the colloidal silver arm and 41 were enrolled in the 4% CHG arm. For efficacy 10 minutes after application, the mean recovery for the colloidal silver product was 3.83, whereas the mean recovery for the 4% CHG was 3.64. The average treatment effect was 0.21, with the upper limit of the 95% CI at 0.58. Because the upper bound of the 95% CI for the noninferior statistic was 0.58 (Table 1), this was lower than 0.65, so the colloidal silver was noninferior to the 4% CHG. For efficacy of the 6-hour time point, the mean for the recovery of the colloidal silver was 3.49 and for the 4% CHG it was 3.34. The average treatment effect was 0.18. The upper bounds of the 95% CI was 0.61, which was within the limit of 0.65, so the colloidal silver was noninferior to the 4% CHG (Table 2).

Table 1
Results from 10-minute kill studies

Product	Sample size	Recovery	Average treatment effect	95% Confidence interval (upper limit)
Colloidal silver	40	3.83 (0.82)	0.21	0.58
4% CHG	41	3.64 (0.96)		

CHG, chlorhexidine gluconate.

Table 2
Results from 6-hour kill studies

Product	Sample size	Recovery	Average treatment effect	95% Confidence interval (upper limit)
Colloidal silver	40	3.49 (0.97)	0.18	0.61
4% CHG	41	3.34 (1.18)		

CHG, chlorhexidine gluconate.

DISCUSSION

This study indicates that a novel, multi-ingredient colloidal silver-based skin cleanser and antiseptic was noninferior to a 4% CHG-based agent with respect to recovery in microbial flora in the inguinal region at 10 minutes and 6 hours. Therefore, it could be used as a replacement for common uses of 4% CHG-based skin antiseptics, particularly in the inguinal region.

For the 10-minute time point, upper limit of the 95% confidence interval was 0.58, well within the error margin of 0.65. For the 6-hour time point, the upper limit of the 95% confidence interval was 0.61, again well within the limit of 0.65. However, because only 40 and 41 subjects were used, the 95% CI was very wide. Had more subjects been used in this study, it would have narrowed the 95% CI to be within the 0.5 limit, which is customarily used.

One important implication of these results stems from the recent guidance from the FDA that CHG-containing products have greater safety concerns. This rule took effect December 20, 2017.[18] Given the many facilities using CHG for various practices from peri-care to daily bathing, this change in the protocol substantially impacts daily practice. Given the limited alternatives to CHG, the results of this study suggest that this colloidal silver-containing product may be a suitable replacement.

The results of this study regarding the efficacy of the test product are supported by other studies showing its efficacy against various microorganisms such as carbapenem-resistant *Enterobacteriaceae*.[19] Additional work conducted by Schultz et al[20] at the University of Florida Institute for Wound Research confirmed the test formulation has demonstrated activity against mature biofilms (methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* sp). Furthermore, the product includes several active ingredients that result in an antiseptic effect by multiple purported mechanisms. The acidic pH enhances the skin's permeability barrier by activating a suite of enzymes that generate lipids that mediate this function.[21] Finally, the low pH also enhances the skin's cohesion, adhesion, and integrity by downregulating another group of enzymes that leads to the shedding of the stratum corneum that becomes activated in high pH environments, such as incontinence-associated dermatitis or moisture-associated skin damage. A more cohesive stratum corneum, replete with intercellular lipids, prevents the penetration of pathogens into the skin.[21]

The pH of the colloidal silver product is acidic (4.6-4.8), mimicking the pH of normal skin. This acidic characteristic can be attributed to its citrus-based ingredient. Undiluted grapefruit extract or Citricidal (GSE, Ripton, VT), which is enriched in citric acid, exhibits a pH of 2.0-3.0, which is designed to support the naturally acidic environment of the skin. In a prior review,[22] the authors concluded that Citricidal displays antimicrobial activity against a wide variety of gram-negative and gram-positive organisms, even at low concentrations (1:128), specifically by disrupting the integrity of the pathogen cell membranes. In a more recent comprehensive review of the literature, Nagoba et al[17] concluded that topical applications of various, mildly acidic compounds, such as citric acid, facilitate the health of the skin cells and accelerate wound healing by controlling wound infection, increasing antimicrobial activity, altering protease activity, releasing oxygen, reducing the toxicity of bacterial end products, and enhancing epithelialization and angiogenesis. Therefore, the grapefruit extract supports the acid mantle of the skin by inhibiting colonization of skin by pathogens, while simultaneously facilitating the growth of the skin's normal healthy microbiome.

CONCLUSIONS

The results of this study indicate that the colloidal silver-based product was noninferior to the 4% CHG product for the immediate sample time of 10 minutes and at the persistent sample time of 6 hours. This product may be an alternative to topical CHG, particularly for inguinal site care in hospitalized settings.

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