Journal of Hospital Infection 102 (2019) 256–261

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Ex vivo and *in vivo* evaluation of residual chlorhexidine gluconate on skin following repetitive exposure to saline and wiping with 2% chlorhexidine gluconate/70% isopropyl alcohol pre-operative skin preparations

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ARTICLE INFO

Article history:
Received 5 June 2018
Accepted 8 October 2018
Available online 16 October 2018

Keywords:
Skin antisepsis
Surgical site infection
Chlorhexidine gluconate
Film-forming copolymer
Ex vivo
In vivo

SUMMARY

Background: Skin antisepsis is performed before surgery to minimize the risk of surgical site infections. Chlorhexidine gluconate (CHG) is routinely used in this application, but it may be removed during surgery when prepped areas are exposed to fluid and repeated blotting.

Aim: This work evaluated the effect of adding a film-forming acrylate copolymer to a CHG-containing skin preparation on minimizing CHG loss during a simulated surgical irrigation and wiping procedure. The results were compared with those obtained with a commercially available water-soluble CHG preparation.

Methods: Two studies using excised porcine skin and one study on human volunteers were performed. In each study, the CHG preparations were applied and the treated sites were challenged with repetitive saline soaks and gauze dabbing to simulate surgical conditions. Challenged and unchallenged sites were analysed either for CHG content by high-performance liquid chromatography, or for bacterial log recovery after seeding an indicator organism (reflecting remaining CHG activity).

Findings: After irrigation and wiping, skin treated with the film-forming CHG preparation had more CHG remaining both on excised pig skin and in the human model. In the pig model, there was a lower recovery of inoculated bacteria with the CHG preparation containing the film-forming copolymer. No skin irritation or adverse events were reported in the human study.

Conclusions: The addition of a film-forming copolymer has the potential to improve the retention of CHG on skin throughout a surgical procedure compared to a water-soluble preparation. This improved retention may lead to better antimicrobial activity.

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https://doi.org/10.1016/j.jhin.2018.10.004

Introduction

Pre-operatively, skin is treated with antiseptic products to reduce the microbial load and minimize the risk of surgical site infections. Chlorhexidine gluconate (CHG) is an antimicrobial used in pre-operative skin preparations because of its broad-spectrum activity and persistent properties. It is often used with isopropyl alcohol (IPA) to combine the fast action of alcohol and the residual activity of CHG [1,2]. Ideally, the antimicrobial activity is maintained at and around the incision site for the entire duration of the surgical procedure and until the incision is closed. However, the prepped skin can be exposed to irrigation fluids and mechanical challenges such as wiping with gauze throughout the surgery. Because CHG is water-soluble, some of it could be removed during surgery when prepped areas are repeatedly exposed to fluid and blotted.

A new pre-operative surgical CHG preparation has been developed, containing a film-forming copolymer to minimize CHG loss during surgery. This formulation is different from existing CHG preparations and is expected to better resist wash-off, which may improve the antimicrobial efficacy throughout the surgical procedure. The literature describes how CHG binds to the skin and mucous membranes through electrostatic interactions; the positively charged molecule binds with the negatively charged surface of the skin [3–5]. This binding of CHG to skin can occur in any formulation. The formulation described here contains a copolymer that also binds to the epidermis, as is typical of acrylate polymers (many wound dressing adhesives are based on acrylate polymers [6]). This proprietary copolymer has hydrophobic and hydrophilic functionalities, but no overall charge. It was hypothesized that the copolymer confines CHG, providing additional retention of CHG at the skin surface compared to a water-based formulation. In the absence of ionic interactions, the CHG is confined through non-specific interactions with the polymer. Multiple interactions are possible due to the relatively large size of the CHG molecule.

The studies presented here compare this new investigational formulation composed of 2% CHG/70% IPA with a copolymer, to a commercially available preparation, 2% CHG/70% IPA without copolymer (positive control) for the amount of CHG deposited on the skin and the amount of CHG remaining after a soaking challenge simulating exposure to fluid during surgery in an *ex vivo* model (pig skin) and in an *in vivo* model (human volunteers). In addition, the *ex vivo* model was also used in a separate experiment to determine CHG activity remaining by looking at bacterial recovery.

Methods

The formulations tested were a new investigational skin preparation under development (CHG/IPA Film-Forming Skin Prep; tinted for pig studies and colourless for human study; active ingredients 2% CHG and 70% IPA in combination with a proprietary acrylate copolymer; 3M, St. Paul, MN, USA) and a commercially available skin preparation serving as a positive control (ChloraPrep® Patient Preoperative Skin Preparation, with Hi-Lite Orange® tint for pig studies and clear for the human study, CareFusion Inc, San Diego, CA, USA, which contains 2% CHG and 70% IPA). In all cases a 10.5-mL applicator was used.

The excised pig skins (pig skin studies 1 and 2) were procured from the University of Minnesota Meat Science Department according to their Institutional Animal Care and Use Committee (IACUC) -approved protocol. Pig skin study 2 used *Staphylococcus aureus* (ATCC 27217, tetracycline resistant) for the bacterial recovery assay. These studies were performed at 3M. The human volunteer study was performed by an independent laboratory (Microbac Laboratories, Inc., Sterling, VA, USA). The protocol and informed consent form were approved by the Institutional Review Board (MicroBioTest IRB). The human study was conducted in accordance with the principles of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and the Food and Drug Administration.

Ex vivo pig skin studies

Pig skin study 1

This study was performed on five excised porcine abdominal skins. Each skin was immobilized on to a board and the hair removed by clipping. The skins were disinfected with copious amounts of 70% IPA to decrease endogenous flora, repeating several times with clean sterile gauze and fresh IPA. One side was designated for the investigational skin preparation, the other for the control skin preparation. Each side was divided into three sections (preparation areas ~70 square inches each, approximate coverage area for 10.5-mL applicators). There were three test sites within each section: one unchallenged (control) site and two challenged sites, or two unchallenged (control) sites and one challenged site for an overall balanced design. One preparation was applied to the first section for 30 s and allowed to dry for 15 min. Two sterile 4 × 4-inch cotton gauze pads were moistened with 10 mL sterile saline and placed over the sites designed to receive a challenge for 30 s, then wiped once with light pressure to remove the gauze. This was repeated seven more times for a total of eight wipes. Challenges in prepped areas were completed sequentially for consistency in timing. After the challenges were completed, a 2-inch diameter sterile glass ring was placed in the centre of each test site. Pressing down to create a seal with the skin, 10 ml of 70% IPA was added into the ring and the area was scrubbed with a swab stick for 1 min. The solution was collected and analysed by high-performance liquid chromatography (HPLC) at 254 nm using a Waters XSelect Charged Surface Hybrid column at a flow rate of 2.0 mL/min and a gradient of 40 mM ammonium formate and acetonitrile.

Statistical analysis: The effect of preparation on CHG concentration was tested without and with challenge using a Mixed Model analysis of variance (ANOVA) with pigskin and pigskin*preparation interaction as random effects and preparation as a fixed effect. Testing was conducted at alpha=0.05. Three fewer samples for the investigational preparation (challenged sites, one from skin 2, two from skin 3) were submitted for analysis because of leakage during sample collection.

Pig skin study 2

This study was performed on six excised porcine abdominal skins. Each skin was immobilized and disinfected as described above. One side was designated for the investigational skin preparation, the other for the control skin preparation. Each

side was divided into three sections (preparation areas ~70 square inches each, approximate coverage area for 10.5-mL applicators). There were two test sites within each section: one unchallenged (control) site and one challenged site. In addition, three untreated sites (no CHG preparation) on each pig skin were used to collect baseline bacterial recovery samples. One preparation was applied to the first section for 30 s and allowed to dry for 15 min. The saline challenges were performed as described above for a total of eight wipes. After saline challenge, a 1-inch diameter glass ring was placed in the centre of each challenge site. Fifty microlitres from a suspension of tetracycline-resistant *S. aureus* (approximately 10^8 colony-forming units (cfu) per mL) was inoculated in the centre of the glass rings in droplets. After an exposure time of 30 min, a neutralizer (75 mM phosphate-buffered water -0.04% KH_2PO_4, 1.01% Na_2HPO_4- containing 0.1% Triton® X-100 with 1% Polysorbate 80, 0.3% lecithin and 1% Tamol; pH 7.9) was pipetted into the ring and the skin area scrubbed for 1 min for recovery of bacteria. The neutralization method was validated following ASTM E1054-08 [7] to ensure that the neutralizer was non-toxic to the bacteria and effective at inactivating CHG to stop bacterial kill beyond the set experimental exposure time. The scrub was repeated and the solutions were pooled (per reference method ASTM E1874-14) [8]. Recovery controls from the unprepped skin sites (three per skin) were inoculated and samples collected following the same method used for the saline/wiping challenged sites. Collected solutions were vortexed, diluted and plated for enumeration in Tryptic Soy Agar containing 4 μg/mL tetracycline to select for inoculated bacteria. Plates were incubated at 35°C for 24–48 h. Following incubation, bacterial counts were performed and data were transformed to $\log_{10}$ cfu/cm^2. The activity of CHG remaining on the skin after the saline challenge was assessed by calculating the bacterial recovery at each site.

Statistical analysis: The effect of preparation on bacterial log recovery was tested using a Mixed Model ANOVA with pigskin and pigskin*preparation interaction as random effects and preparation as a fixed effect. Testing was conducted at alpha=0.05.

Human volunteer study

Twenty-one healthy volunteers (18 years of age or older) participated in this prospective, randomized study. Overall, the mean age was 43 years, there were approximately 62% men and 38% women, and the races were approximately 52% Asian, 33% white, 10% black or African-American, and 5% Hispanic/Latino. All 21 subjects were enrolled, received treatments and completed the study. Twenty of the 21 subjects contributed data for analysis. Irritation was also scored (erythema, oedema, rash, dryness).

Each subject received both CHG-containing formulations topically applied to one of two 8-inch × 8-inch test areas on the back in a randomized fashion (Figure 1). The study products could not be blinded from the Investigator or study staff performing the product application, sample collection and skin assessment due to the obvious differences in applicator design and other physical characteristics. However, the study staff performing the HPLC analysis of CHG and the statistician performing the data analysis were blinded to the study products.

The four test sites in each area were randomized as no challenge or challenge (consisting of placing a saline-soaked gauze on the prepped site for 30 s, removing it by wiping with light pressure, and repeating for a total of eight times). Samples were obtained using a modified cup scrub method [9] and analysed for CHG content by the same method described under Pig skin study 1 (HPLC). The study endpoints were the amount of CHG (μg/cm^2) removed by the challenge and the amount of CHG (μg/cm^2) remaining after the challenge. In addition, skin irritation was rated pre- and post-product application and adverse events were collected.

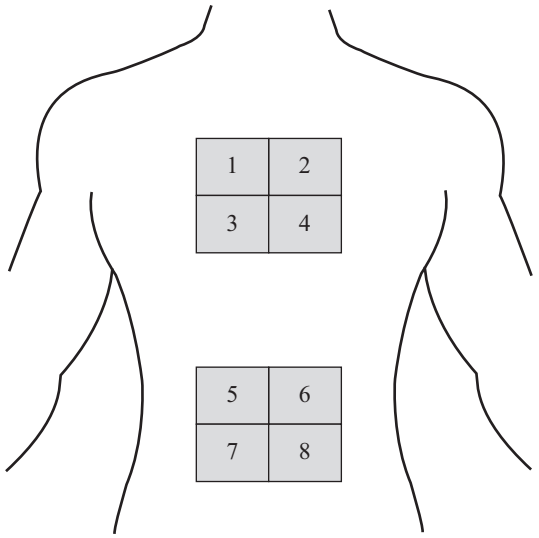

Figure 1. Layout of the test sites for the study in human volunteers.

Statistical analysis: The effect of preparation on CHG concentration was tested without and with challenge using a Mixed Model ANOVA with subject as a random effect and preparation as a fixed effect. The two CHG concentrations (without and with challenge) were averaged by subject and preparation. Testing was conducted at alpha=0.05. One subject was excluded from the analysis because the wrong sampling solution was inadvertently used.

Results

Ex vivo pig skin studies

In the first study, the CHG-containing products were applied to excised pig skin. The concentration of CHG on the skin was measured after application (no challenge, reflecting the concentration applied) and after a challenge of repeated soaking and wiping (concentration retained). These results are displayed in Figure 2.

Significantly more CHG was applied to the skin (72.4 vs 45.5 μg/cm^2, or a difference of 26.9 μg/cm^2; 95% confidence interval (CI): 20.1–33.8, $P<0.001$) and also retained on the skin after challenge (30.9 vs 8.7 μg/cm^2, or a difference of 22.2 μg/cm^2; 95% CI: 18.4–25.8; $P<0.001$) with the investigational formulation containing a film-forming copolymer than with the positive control, which has no film-forming component.

In the second study, the CHG-containing products were applied to excised pig skin. The activity of CHG on the skin was measured after a challenge of repeated soaking and wiping using a bacterial time kill end point with a strain of

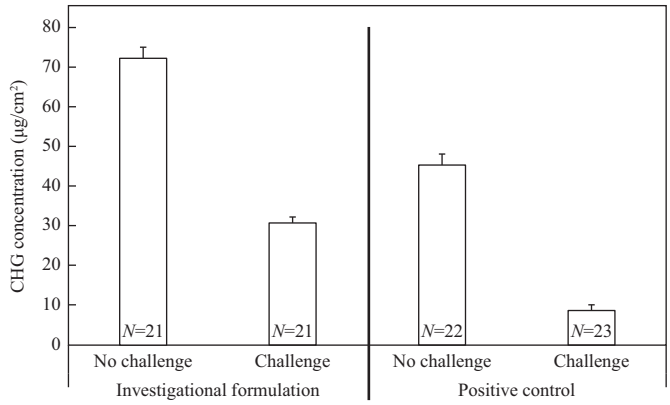

Figure 2. Mean chlorhexidine gluconate (CHG) concentration on ex vivo pig skin, before and after a challenge of repetitive soaking and wiping (with standard errors).

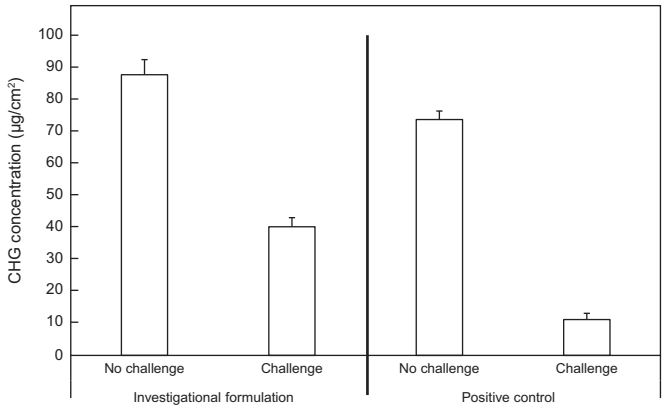

Figure 4. Mean chlorhexidine gluconate (CHG) concentration on the skin of human volunteers, before and after a challenge of repetitive soaking and wiping (N=20, with standard errors).

tetracycline-resistant *S. aureus*. These results are displayed in Figure 3.

There was significantly less bacterial inoculum remaining on the skin (lower recovery; 2.52 $\log_{10}$ cfu/cm^2) with the investigational formulation than with the positive control (3.08 $\log_{10}$ cfu/cm^2) after a challenge of repetitive soaking and wiping followed by bacterial inoculation. The difference in log recovery between the two skin preparations was 0.56 log (95% CI, 0.17–0.96 log; P=0.011).

In the excised pig skin model, skin treated with the film-forming CHG preparation had more CHG remaining and a lower recovery of inoculated bacteria than a CHG preparation without the film-forming copolymer after a challenge of irrigation and wiping.

Human study

The CHG-containing products were applied to the back of healthy human volunteers. The concentration of CHG on the skin was measured after application (no challenge, reflecting the concentration applied) and after a challenge of repeated soaking and wiping (concentration retained). These results are displayed in Figure 4. Of the 21 subjects enrolled, 20 contributed data for analysis.

Primary efficacy: Significantly less CHG was lost from the skin after the challenge (47.6 vs 62.6 μg/cm^2, or a difference of 15 μg/cm^2; P=0.012) with the investigational formulation containing a film-forming copolymer than with the positive control, which has no film-forming component.

Secondary outcomes: Significantly more CHG was applied to the skin (87.8 vs 73.8 μg/cm^2, or a difference of 14 μg/cm^2; P=0.001) and also retained on the skin after challenge (40.2 vs 11.2 μg/cm^2, or a difference of 29 μg/cm^2; P<0.0001) with the investigational formulation than with the positive control. This is similar to what was observed in the excised pig skin model (first study).

Safety results: No skin irritation or adverse events were reported.

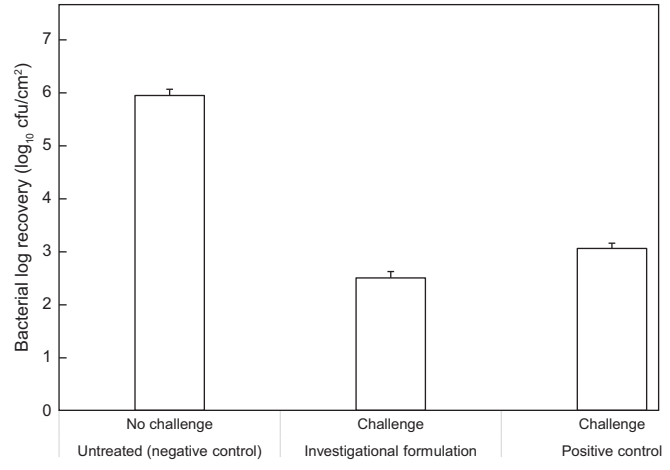

Figure 3. Mean bacterial log recovery on *ex vivo* pig skin treated with chlorhexidine gluconate (CHG) formulations after a challenge of repetitive soaking and wiping compared to untreated, unchallenged sites (N=18 for control and N=36 for each CHG formulation).

Discussion

This work used an *ex vivo* model of excised pig skin, and an *in vivo* model in human volunteers. The *ex vivo* model showed that significantly more CHG was applied to the skin when a formulation containing a film-forming copolymer was used than when a water-soluble formulation was used, even if both formulations contained the same concentration of CHG (2%). It was hypothesized that this is due to the higher viscosity of the investigational formulation containing a copolymer, which leads to a thicker film being deposited on the skin when the respective applicators are used as intended. In addition, significantly more CHG remained on the skin after a challenge of soaking and wiping, and this correlated with higher antimicrobial activity as seen from the significantly lower recovery of inoculated bacteria. The *in vivo* model in humans produced analogous CHG concentration data (no bacterial inoculation was used in this model). Because both preparations contain the same concentrations of CHG and IPA, it is reasonable to deduce that the film-forming copolymer played an important role in delivering a thicker film and therefore a larger amount of CHG, in improving the resistance to wash-off, and in the antimicrobial performance.

Other published studies measured CHG concentration on skin but they used different methods, making a comparison of results difficult. Edmiston *et al.* [10] compared different pre-operative showering/skin-cleansing protocols and measured CHG skin surface concentrations at different skin sites, and compared those concentrations to the minimal inhibitory concentration that inhibits 90% (MIC_{90}) of staphylococcal skin isolates. Their method was colorimetric and the results were expressed in parts per million (ppm), with a MIC determined to be 4.8 ppm. They found that the use of a 2% CHG-impregnated polyester cloth resulted in considerably higher skin concentrations than a shower with a 4% CHG soap (around 1000 ppm vs less than 125 ppm when considering the groups who had one treatment shortly before the measurement of the CHG concentration in order to choose the conditions closest to ours). They hypothesized that the CHG was diluted in the process of rinsing in the traditional shower, which is analogous to what might happen to the prepped skin exposed to irrigation fluids and wiping throughout surgery. Alserehi *et al.* [11] also compared bathing practices by measuring CHG skin concentration in intensive care unit (ICU) patients. As could be expected, they found lower skin concentrations of CHG when rinsing with water after a CHG bath compared with using a solution without rinse or using pre-impregnated CHG wipes (40–50 μg/mL after rinsing vs 400 μg/mL when not rinsing). They also measured CHG over time and found that some patients still had a significant amount of CHG present up to 23 h post-bath (up to 400 μg/mL in some cases). This article does not specify the surface area swabbed, so again a direct comparison with our results cannot be made. Popovitch *et al.* [12] measured CHG concentration on skin over time after skin cleansing in ICU patients to prevent infections, using a colorimetric method. They also determined the MIC of CHG against bacteria and yeast isolated from the skin of their patients (18.75 μg/mL); they found effective CHG concentrations (>MIC) for at least 24 h. These authors had previously published a study [13] reporting significantly lower central venous catheter-associated bloodstream infection and blood culture contamination rates after the introduction of CHG bathing in their ICU. Finally, Karki and Cheng [14] published a systematic review including 16 published studies and concluded that the use of non-rinse CHG application significantly reduces the risk of central line-associated bloodstream infection (CLABSI), surgical site infection (SSI), and colonization with vancomycin-resistant enterococci (VRE) or meticillin-resistant *S. aureus* (MRSA). These studies differ the present research in the type of product tested, because they look at skin bacterial load reduction either as a pre-operative step that the patient can perform at home, or to help prevent infections in ICUs, whereas this study tested a product intended for skin preparation immediately before surgery. Nevertheless, they also measured skin concentrations of CHG after application and over time, and demonstrated a reduction in infection rates with the bathing protocols that lead to higher CHG concentrations on the skin.

The concept of incorporating a film-forming copolymer in a surgical skin preparation has been used before in an iodine-based product. Iodine povacrylex (0.7% available iodine) in 74% IPA (3M™ DuraPrep™ Surgical Solution, 3M St. Paul, MN) contains a film-forming copolymer and has shown advantages over a standard povidone-iodine scrub. Birnbach *et al.* [15] compared both preparations for their ability to reduce skin flora and for the duration of their antimicrobial activity in women during labour receiving epidural analgesia. They found that the proportion of subjects with positive skin cultures immediately after skin disinfection differed significantly ($P=0.01$) between the povidone iodine group (30%) and the iodine povacrylex group (3%). The difference in mean reduction in bacterial burden (expressed as log cfu) between the two groups did not reach statistical significance: with both products, disinfection resulted in a greater than 2-log decrease in bacterial burden. In contrast, the percentage of subjects with positive skin cultures at the time of catheter removal was greater for the povidone iodine group than for the iodine povacrylex (97% vs 50%), and the mean bacterial burden was greater as well (1.93 ± 0.40 log cfu for povidone iodine and 0.90 ± 0.23 log cfu for iodine povacrylex; $P=0.0001$). In addition, six catheters from the povidone iodine group and none from the iodine povacrylex group yielded positive cultures. This difference was significant whether by the roll-plate method ($P=0.02$) or by inoculation in chopped meat glucose (CMG) broth ($P=0.002$), even though the catheter colonization did not result in any infections in this study. The authors concluded that the preparation with the copolymer led to a higher likelihood of negative cultures immediately after skin disinfection and was more effective at limiting regrowth of skin flora because it had a longer-lasting antimicrobial activity. A different study used a human volunteer model to compare the amount of active agent remaining after a saline-soaked gauze challenge when water-soluble CHG in alcohol and an iodine povacrylex in alcohol skin preparations were used. Their results showed that the CHG was removed by the challenge while the iodine povacrylex film remained intact under the same conditions [16]. Another study compared the same water-soluble CHG in alcohol and iodine povacrylex in alcohol skin preparations for their effect on incise drape adhesion, and found that the preparation with a film-forming copolymer provided significantly greater drape adhesion in healthy volunteers [17]. A previous study comparing the iodine povacrylex in alcohol skin preparation to aqueous iodophors also showed that the film-forming preparation significantly improved drape adhesion [18].

Given this information on the iodine-based preparation containing a film-forming copolymer, it was hypothesized that adding a film-forming copolymer to the new CHG preparation would also offer advantages over a water-soluble CHG preparation, which does not form a film. Our results presented here support this hypothesis. This study is one in a series of studies conducted to determine the safety and efficacy of this new formulation. Other manuscripts are in preparation to describe the other studies conducted: an *in vitro* time-kill study established that the tinted and colourless formulations had the same antibacterial activity; another *in vitro* study showed the lack of development of resistance; and two large safety and efficacy studies in human volunteers showed persistent antimicrobial activity for at least 6 h in the abdominal and inguinal areas. Extensive safety and efficacy studies have been conducted, in which no tolerability issues have been identified. Since the study described this article was performed, the investigative product described here has received US Food and Drug Administration approval.

This work has some limitations: the pig skin is a model, and the human study on healthy volunteers only looked at the CHG concentration, and not the activity. Nevertheless, the film-forming CHG preparation and the standard preparation

were subjected to the same simulated challenge under well-controlled conditions and the results were significantly different.

In conclusion, the addition of a film-forming copolymer to a CHG-containing formulation resulted in more CHG applied on the skin, and less CHG removed from the skin in a repetitive saline soak/wipe model mimicking a surgical challenge. It also resulted in a lower bacterial recovery in a seeded model, indicating better antimicrobial activity. Both formulations were well tolerated by the study population. Clinical studies will be needed to determine whether the new formulation can reduce surgical site infections.

Conflict of interest statement

M.H. Bashir and A. Hollingsworth are employees of Microbac Laboratories, Inc. The human study was performed by this laboratory under a contract with 3M. The *ex vivo* studies on pig skin were performed at 3M. D. Schwab, K.S. Prinsen, J. Paulson, D. Morse and S.F. Bernatchez are employees of 3M. The investigative product described here has received US Food and Drug Administration approval since the original submission of this manuscript and will be available under the brand name 3M™ SoluPrep™ Film-Forming Patient Prep.

Funding sources

This work was paid for by 3M. The human study design was performed in collaboration between 3M and Microbac Laboratories, Inc. Microbac Laboratories, Inc. performed the human study; 3M analysed the data and issued the final study report. 3M decided to submit the manuscript for publication and prepared the manuscript. All authors contributed to data interpretation and critical review of the manuscript for intellectual content.

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