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Commentary: Addressing the Challenges in Antisepsis: Focus on Povidone Iodine

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Introduction

Topical antimicrobials are essential in wound care as they aid the healing process by preventing and at the same time treating infections in wounds[1]. Broad spectrum antiseptics with high efficacy towards planktonic and sessile bacterial communities are preferred as wound healing can be delayed by the formation of biofilms often developed by antimicrobial resistant organisms[2]. Additionally, ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp), which are the leading causes of nosocomial infections across the world, are also becoming multidrug-resistant (MDR)[3]. The correct use of antiseptics can be tricky, and, in this commentary, an overview of key challenges in antisepsis, namely antimicrobial efficacy, antiseptic resistance, antibiotic and antiseptic cross-resistance, wound healing, cytotoxicity, and tolerability, focusing on povidone-iodine (PVP-I) in comparison with other commonly used antiseptics such as chlorhexidine gluconate (CHG), polyhexanide (PHMB) or octenidine (OCT) is provided.

Antimicrobial Efficacy of Antiseptics

Antimicrobial spectrum

PVP-I has a broader spectrum of antimicrobial activity compared with other commonly used antiseptics (PHMB, CHG and OCT), targeting a wider range of Gram-negative bacteria, fungi, and it also has similar and broad spectrum of activity against Gram-positive bacteria. Despite extensive clinical use of PVP-I over several decades, and rigorous testing of isolates, there have been no reports of resistance or increased bacterial tolerance to this antiseptic treatment[4,5]. The multiple mechanism of action seems to be also at the basis of the efficacy against a wide range of viruses, interacting with several viral proteins such as haemagglutinin, neuraminidase and sialidase[6], while antiseptics like CHG and PHMB have been found to primarily disrupt the viral envelope, having a limited efficacy against non-enveloped viruses[7].

Effect of organic material on antiseptic efficacy

The efficacy of antiseptics can be diminished by organic material, such as blood, which is typically present in wounds. A study by Schedler K, et al. showed that in presence of organic material, including blood, PVP-I had the shortest time to efficacy against *S. aureus*, *E. faecium* and *P. aeruginosa* compared to CHG, PHMB and OCT[8].

Efficacy against biofilms

A recent systematic review and meta-analysis found the prevalence of biofilms in chronic wounds to be 78.2%, suggesting that biofilms are present in the majority of chronic wounds[7]. Wounds infiltrated with biofilm, or "critically colonised" wounds are challenging to manage because biofilm microorganisms are particularly resistant to host defences and antimicrobial treatment[6]. Hence, there is a vital need for antiseptics that are effective against biofilms in the treatment of both acute and chronic wounds. Several studies have been conducted to assess the efficacy of commonly used antiseptics against biofilms, including PVP-I, CHG, PHMB, and OCT. Low-dose PVP-I (0.25% w/w) eradicated robust biofilms of MDR *S. aureus*, *K. pneumoniae*, *P. aeruginosa*, and *Candida albicans* in vitro[9]. Following dilution, PVP-I was more effective than other topical antimicrobials at removing biofilms of *P. aeruginosa* and multi-species biofilms of Methicillin-Resistant *Staphylococcus aureus* (MRSA), and *C. albicans*[5]. In addition, PVP-I completely eradicated both *S. aureus* and *P. aeruginosa* biofilms within 15 minutes of application, while CHG completely eradicated *S. aureus* biofilms only.

Antiseptic resistance

Resistance is one of the major challenges for antiseptic selection. Iodine contained in PVP-I complex has multiple modes of action, therefore no resistance or antibiotic cross-resistance has been reported. Unlike PVP-I, CHG has been found to act on one specific bacterial target: the bacterial cell wall[4]. Therefore, adaptations in this target can result in resistance to CHG, as demonstrated by the upregulation of major facilitator superfamily efflux pump genes and Qac (quaternary ammonium compounds) efflux proteins in *K. pneumoniae* and *Staphylococci*, respectively. Recent reports have suggested few cases of antimicrobial resistance for antiseptics like PHMB and OCT[10, 11].

Development of cross-resistance to last-line antibiotics

Cross-resistance can be defined as resistance to a particular antiseptic that results in concomitant resistance to antibiotics. Prolonged usage of antiseptics like CHG, PHMB and OCT have led to cross-resistance episodes. Serial exposure to sub-inhibitory concentrations of CHG selected for vancomycin-resistant *Enterococcus* (VRE) with reduced susceptibility to CHG and isolates with reduced susceptibility to daptomycin. Alongside the resistance issues observed with the use of CHG, prolonged in vitro exposure to low concentrations of PHMB selected for MRSA, with reduced susceptibility to PHMB and concomitant resistance to daptomycin generally characterized by an activity against most Gram-positive pathogens, including vancomycin-resistant enterococci and MRSA[12]. Exposing *P. aeruginosa* to increasing concentrations of OCT over several days lead to increased tolerance to OCT and CHG.

Wound healing and skin tolerability

Wound healing

Pre-clinical studies have shown that PVP-I increased wound healing via increased expression of transforming growth factor beta, neovascularisation, and re-epithelialisation. PVP-I has also been found to have haemostyptic (an astringent that stops bleeding) and anti-inflammatory effects in peri- apical surgery[13] and to reduce production of reactive oxygen species by human polymorphonuclear neutrophils[14]. Compared with controls, PVP-I significantly increased the healing rate of chronic leg ulcers with no apparent cytotoxicity towards dendrocytes, with the densities in micro vessels and dendrocytes higher in PVP-I-assigned lesions than in those receiving silver sulfadiazine or CHG.

Cytotoxicity

PVP-I is well tolerated by murine fibroblasts compared to CHG, PHMB and OCT as observed in cytotoxicity tests. PVP-I caused renewal of murine fibroblasts which was not observed with CHG, PHMB or OCT treatment[9]. Human fibroblasts did not lose complete cell viability when treated with PVP-I at the minimum bactericidal concentration (MBC) whereas PHMB, hydrogen peroxide, CHG and OCT were 100% cytotoxic at their MBC[15]. In the study by van Meurs et al.[15], the MBC was determined for the most resistant bacterial strain and then plotted on the cytotoxicity curve of that antiseptic. The MBC for different tested antiseptics were: PVP-I 1.32 g / L, OCT 0.033 g / L, CHG 0.78 g / L and hydrogen peroxide approx. 10 g / L (which is greater than its cytotoxic level). According to the authors, PHMB was completely cytotoxic at the undiluted concentration (0.4 g / L), which was hardly bactericidal and below the estimated MBC.[15]. Additional in vitro studies have indicated cytotoxic effects of PVP-I, PHMB and CHG[16-19].

Tolerability

An ideal antiseptic for wound care should promote healing and exhibit good local tolerability[13]. PVP-I was thought to be allergenic due to confusion between allergy and irritation. The prevalence of allergic contact dermatitis caused by PVP-I was estimated to be 0.4% when patients were tested for allergy using patch test[20]. PVP-I, OCT and PHMB rarely cause contract dermatitis whereas frequent reports are present for CHG[20]. Apart from contract dermatitis, urticarial and anaphylactic reactions have been reported for CHG, anaphylactic reactions for PHMB, and aseptic tissue necrosis for OCT[20-23]. Anaphylaxis caused by CHG has also been frequently reported in recent years. The World allergy organization anaphylaxis guidance 2020 included chlorhexidine among novel substances inducing anaphylaxis[24].

Summary

Choice of antiseptic in wound care is critical; several aspects need to be considered such as: antimicrobial spectrum and efficacy in the real-world setting; antiseptic resistance and antimicrobial cross-resistance; effect on wound healing; cytotoxicity and tolerability. When compared with other commonly used antiseptics, including CHG, PHMB and OCT, PVP-I showed several advantages.

PVP-I had a broad spectrum of antimicrobial activity against Gram-negative and Gram-positive bacteria, ESKAPE pathogens, fungi, and viruses. PVP-I was also highly effective at eliminating bacterial biofilms, which are difficult to remove and affect wound healing rate. PVP-I has been extensively used for decades for wound care but still there is no report of resistance or cross-resistance, which is in contrast with other antiseptics. Recent studies have shown that PVP-I has low allergenic properties, low cytotoxicity and can promote wound healing.

Based on all the features of PVP-I a practical guide to remove biofilm and manage critically colonized wounds using PVP-I has been proposed by Alves et. al[25]. It includes guidance on mechanical washing of the wound with soap or PVP-I scrub solution, debridement, disinfection with PVP-I dermic solution on gauze, and control of biofilm regrowth using PVP-I gel with or without PVP-I tulle with secondary dressings.

Healthcare facilities need to be mindful of the issues associated with antiseptics, in particular resistance/cross-resistance, to ensure that wounds are effectively treated without causing detrimental effects.

Conflict of Interest

SM declares that he has nothing to disclose. For this publication no fee has been paid to the author. Only medical writing assistance has been provided as expressed in the acknowledgments section.

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