The safety and efficacy of commonly used topical agents in the treatment of wound infections

M Davane¹, A Rao², B Nagoba¹
¹ Department of Microbiology, MIMSR Medical College, Latur, India
² Department of Orthopaedics, MIMSR Medical College, Latur, India
Correspondence to: dr_bsnagoba@yahoo.com, bsnagoba@gmail.com
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Abstract
Use of topical agents remained the primary mode of treatment of wound infections. The primary role of the use of topical agents in wounds is prevention and treatment of infections. Various topical agents are being used to treat wound infections. However, the safety and efficacy of many topical agents is a questionable issue. The commonly used topical agents are silver compounds, povidone-iodine, hydrogen peroxide, Dakin’s solution, chloroxylenol, polyhexamethylene biguanide, mafenide acetate, chlorhexidine, etc. The studies show that many topical agents in current use would not satisfy all the criteria of ideal topical agents and need to be evaluated in terms of safety and efficacy, which varies as every topical agent has a different spectrum of antimicrobial activity and adverse effects. In view of this, an attempt has been made to review the safety and efficacy of commonly used topical agents used for the treatment of wound infections. The literature review shows that almost all topical agents are inhibitory to bacteria and other microorganisms. However, many of them have been found to be toxic to cells involved in the wound-healing process, especially in in-vitro studies. Although found highly toxic in in-vitro studies, the majority of them have been shown to be safe clinically and not to influence the process of wound healing negatively.

Introduction
A number of experimental studies demonstrate that high levels of bacteria in wounds inhibit the normal wound-healing process by various mechanisms which in turn lead to failure of wound closure.¹ The management of wounds is a challenging task because of a risk of infection. The aim of wound management is primarily to treat the infection and ultimately to enhance wound healing. The opportunity to improve wound healing can be enhanced by creating unfavourable conditions to microorganisms and favourable for the host repair mechanism which is believed to be facilitated by the use of topical antimicrobial agents. Use of topical agents after thorough surgical debridement remains the primary mode of treatment of wound infection because it leads to easy sensitisation and better penetrability at the site of the wound.

The primary role of topical agents in wound care is prevention and treatment of infection, i.e. it is mainly concerned with the irreversible inactivation of microbes in wounds. A topical agent is expected to have multiple targets for its activity and a broad-spectrum biocidal activity (bacteria, spores, viruses and fungi). If it is not possible to eliminate microbes completely from the infection site, there must also be a substantial reduction in the number of organisms and biofilms. This is intended to halt the obstacles due to infection in the wound-healing process. The second most important role of topical agents is to enhance wound healing by causing favourable effects on cell proliferation and regeneration. The ideal topical agent should have wide-spectrum antimicrobial activity with efficacy against vegetative as well as spore-forming microorganisms, immediate onset of action, long-lasting activity, potency in the presence of blood and organic matters, activity against biofilms, safety to healthy as well as injured skin and tissue cells, good solubility in water and organic liquids, good stability, good tolerance without adverse effects, not to cause local irritation and allergic reactions, and double efficacy combining germicidal with cleansing effects.²

Methods
A literature search was performed using PubMed by using the keywords topical antiseptic agents and wound infections. A manual search was also conducted using references cited in original publications and relevant review articles. All the studies relating to topical antiseptic agents in the treatment of wound infections were included in the present review and repetitive types of studies with similar findings were excluded. A total of 70 articles were found, out of which the 55 most relevant articles were included in the present review. All studies included in the present review, were evaluated/analysed and all the relevant data were included.
Analysis and discussion

Using the above keywords, a total of 70 articles pertaining to topical antiseptics agents and wound infections were found. After reading the title and abstracts, 15 articles out of 70 were excluded because of repetitive/similar findings. The findings of 55 different studies were analysed/evaluated and the details of results of these studies are presented. These studies show that various topical agents are being used to treat wound infections. However, the safety and efficacy of many topical agents is a questionable issue. The commonly used topical agents are silver compounds, povidone-iodine, hydrogen peroxide, Dakin’s solution, chloroxylenol, chlorhexidine, etc. All presently available topical agents would not satisfy all the criteria of ideal topical agents. However, they should be evaluated in terms of safety and efficacy. Safety and efficacy of various topical agents varies as every topical agent has a different spectrum of antimicrobial activity and adverse effects. In view of the questionable safety and efficacy of topical agents, an attempt has been made to review the safety and efficacy of common topical agents used for the treatment of wound infections.

Silver compounds

In one form or another, silver and its compounds have been widely used as wound topical agents. Currently, silver sulfadiazine and silver nitrate are the most commonly used silver compounds. Silver sulfadiazine is the most relevant and commonly used topical agent in the treatment for prevention of infection of burn wounds. Silver is considered to act by attaching silver ions to the sulfhydril group of bacterial enzyme proteins thereby causing denaturation of proteins and deoxyribonucleic acids (DNA helix) leading to blocking of transcription of DNA.3-6 It is a broad-spectrum agent that shows strong activity against both Gram-positive and Gram-negative bacteria including antibiotic-resistant strains such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. It has also been reported to be effective against yeast and fungi. It has been found to minimise transmission of antibiotic-resistant organisms and help to fight against antimicrobial-resistant infections in wound care, reduce the need for antibiotics and may minimise the progression to systemic infection.30

Povidone-iodine (Betadine)

Povidone-iodine is a water-soluble complex formed by the interaction of iodine with the polymer polyvinyl pyrrolidone (an iodophore). It is available as solution, cream, ointment and scrub. It is the most commonly used topical agent. It has broad antibacterial activity against both Gram-positive and Gram-negative bacterial pathogens including Staphylococci, Pseudomonas species and Enterococci. It has also been claimed to have antmycobacterial, antifungal, antiprotozoal and antiviral activity. Betadine, on contact with the skin, releases iodine slowly from the povidone-iodine complex which exerts a mild antimicrobial activity. Although not clearly known, it seems most likely that iodine acts by oxidising the sulphhydril group of amino acid cystein. Its application in a concentration of 1–10 percent has been reported to be less irritating to skin and less allergenic than iodine.36,37,38 The available data shows that betadine is considered as the safest topical agent in terms of irritancy and allergic profile.38

In a concentration of 0.001%, it has been reported to be bactericidal to Staphylococcus aureus but non-cytotoxic to cultured fibroblasts.39 Although commonly used for pre- and perioperative skin cleansing in the treatment of superficial burns, incisions and other surgical wounds, most studies show that it impairs wound healing by its adverse effect on tensile strength and cytotoxicity.36,39 A study reported that multiple dilutions of povidone-iodine were found to be the most toxic of all agents tested on fibroblasts42 and it has been reported to have deleterious effect on wound epithelialization, especially when used in non-diluted concentration.42 It is also reported to possibly affect renal function when applied for a prolonged time, as it can be absorbed into circulation.43

Although iodine is an active topical agent when released from solution, povidone-iodine is readily inactivated by binding to serum proteins in exuding wounds.44 It is reported to be ineffective when applied to wounds colonised with greater than 10^6 organisms per gram of tissue.44 It has also been reported that the antibacterial action of betadine requires at least two minutes contact. It may cause stinging and erythema. Its effect may not persist and efficacy may be reduced in body fluids. Its prolonged use may cause metabolic acidosis, and staining of skin and clothing.45 Povidone-iodine absorption has been a concern in the treatment of lactating mothers because of the possibility of induced transient hypothyroidism.41 The results of these studies suggest that great care should be exercised in using betadine in the treatment of wounds/ulcers and it must be greatly diluted before use.

Hydrogen peroxide

Hydrogen peroxide is a clear colourless liquid widely used as topical agent, available in varying concentrations ranging from three to
fibroblasts in healthy healing tissue. It is widely considered to act as a mechanical cleansing agent and also as a non-selective debridling agent. It is primarily used for loosening dried exudates or debris including healthy regenerating tissue. Hydrogen peroxide has been reported to disrupt new capillaries in granulation tissue. It also oxidises wound debris and has been found toxic to fibroblasts, retards collagen synthesis and delays epithelialization. It may cause pain or lyse blood clots. It also inhibits 90% of neutrophil migration into wounds, thereby undermining the natural defence system of the body. Dakin’s solution contains sodium hypochlorite (dilute bleach), after being previously used for a long time, came into focus again in 1980s. It has a wide spectrum of anti-bacterial activity. However, it shows activity against some bacterial spores, fungi and viruses. It is commonly used for cleansing and reducing bacterial load in wounds. It is inexpensive and does not show systemic toxicity. Although acting as bactericidal against staphylococci, streptococci and pyocyanic microorganisms, it was found toxic to granulation tissue and fibroblasts, retards collagen synthesis and delays epithelialization. It may cause pain or lyse blood clots. It also inhibits 90% of neutrophil migration into wounds, thereby undermining the natural defence system of the body.

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Mafenide acetate (Sulfamylon)

Mafenide acetate (α-aminop-toluene sulfonamide acetate) was introduced in 1960 as a topical agent in the treatment of burns. It acts by competitive inhibition of p-aminobenzoate into dihydropteroic acid, the immediate precursor of folic acid. It is bactericidal in nature at higher concentrations, however a concentration of 5% in a water-soluble cream base is commonly used. It has broad antibacterial activity against Gram-negative bacterial pathogens, especially those pathogens associated with burns infections and Gram-positive bacteria including Clostridia, but less effective against oxacillin-resistant staphylococci. It has the ability to penetrate eschar. Its adverse effects include pain on application and inhibition of epithelialization. Pulmonary complications are frequent with continuous use in large burns. As it is rapidly absorbed, the risk of systemic toxicity increases with long-term use. Five percent of patients may experience maculopapular rash. Although the use of mafenide acetate has recently been decreased, it is used for short-term control of invasive infections because of its excellent eschar penetration.

Chloroxylenol

Chloroxylenol is a key halophenol widely used in antiseptic formulations (e.g. Dettol). It acts by disrupting the microbial cell wall and deactivating enzymes. It has mainly bactericidal activity. It shows good activity against Gram-positive bacteria but is less effective against Gram-negative bacteria, M. tuberculosis, fungi and viruses.

Polyhexamethylene biguanide (PHMB)

PHMB (also known as polyhexanide and polyaminopropyl biguanide) is one of the most frequently used topical agents nowadays. It has been reported to be a highly histocompatible and non-cytotoxic topical agent. It is used in a variety of products such as wound-care dressings, mouth wash, in ophthalmology as eye drops prior to cataract surgery and as a contact lens cleaning solution, perioperative cleansing agents and swimming pool cleaners.

The PHMB initially interacts on the surface and then enters into cytoplasmic membrane and cytoplasm. It has been shown that cationic PHMB has a little effect on neutral phospholipids within the bacterial membrane. The majority of effect was mainly on acidic negatively-charged species which later on aggregates leading to increased fluidity and permeability. This results in the release of lipopolysaccharides from the outer membrane, potassium ion efflux and finally death of the organism.

The literature review demonstrates in-vivo and in-vitro safety and effectiveness of PHMB in the treatment of wound infection, reducing the bioburden. Also, in contact lens disinfecting solution it was found to be effective against various microorganisms, including Acanthamoeba polyphaga, A. castellanii and A. hatchetti.

Polyhexanide was found to be clinically and histologically superior to povidone-iodine and silver nitrate in the treatment of second-degree burns. The re-epithelialization process was also not found to be inhibited by it. It has been found that the PHMB has detrimental effects on human endothelial cells and osteoblasts at a concentration with questionable antibacterial activity and has been shown to cause severe cell damage, raising some questions regarding its use in bone cement for the treatment of total arthroplasty infections and also in wound healing.

Chlorhexidine

It is a halogenated di-phenyl compound effective against Gram-positive and Gram-negative bacteria. It is mainly used as a skin antiseptic and bladder irrigant, and in the treatment of wounds. Studies suggest that it is highly bactericidal in nature and relatively safe with little effect on the wound-healing process. It has been reported to be toxic to tissue at higher concentration (0.05%). Hence, the lower concentrations (0.02%) are recommended for wound
irritation. In other studies, it has been reported to inhibit granulation and decrease the tensile strength of wounds. In view of controversial results seen in different studies, it is difficult to draw meaningful conclusions about its use as a topical agent for the treatment of wounds.

**Conclusion**

The literature review shows that almost all topical agents are inhibitory to bacteria and other microorganisms. The literature review also shows that the majority of topical agents are toxic to cells involved in the process of wound healing. Although most of them have been found to be highly toxic in in-vitro studies, the majority of them have been shown to be safe clinically and not to negatively influence the process of wound healing.

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**References**