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

M Davane[1], A Rao[2], B Nagoba[1]
[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
Keywords: topical agents, safety and efficacy, wound healing

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.

Wound Healing Southern Africa 2019;12(1):34-37

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 antiseptic 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 Gram-negative bacteria which are more commonly associated with chronic wounds. It has also been reported to have activity against more problematic antibiotic-resistant bacteria, fungi and viruses.[7] Although silver-based dressings have been reported to facilitate the early phase of wound healing,[8-11] promote re-epithelialization and accelerate the process of wound-healing,[12-15] silver compounds have been reported to have detrimental effects on wound healing in both in-vitro and in-vivo studies.[16,17] They have been found to be toxic to skin cells[17-19] and re-epithelialization.[17,20-22] In a study carried out on diabetic fibroblasts, silver dressings were found to reduce the viability of the diabetic fibroblast by 54–70% and collagen synthesis by 48–68%. They were found to produce significant change in the cell morphology and to decrease cell proliferation and collagen synthesis of diabetic fibroblasts.[23] Silver compounds have also been reported to cause allergic reaction and transient leucopenia.[24] In addition, they have been reported to be less penetrative into skin eschar and reported to cause staining of tissue.[25,26] Development of bacterial resistance to silver is another cause of concern.[27] These results of various earlier studies suggest that silver should be used with caution in treating wounds.

In recent studies, nanocrystalline silver has been reported to be potentially effective in the treatment of diabetic foot ulcers.[28] In a comprehensive systematic review and meta-analysis, the available evidence shows that nanocrystalline silver dressings significantly reduce the rates of infections as compared to silver sulphadiazine/silver nitrate and reduces the length of stay in hospital and reduces pain.[29] Nanocrystalline silver has been reported to be effective against 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 antimycobacterial, 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 sulfhydryl 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.[26,31,32] The available data shows that betadine is considered as the safest topical agent in terms of irritancy and allergic profile.[33]

In a concentration of 0.001% it has been reported to be bactericidal to *Staphylococcus aureus* but non-cytotoxic to cultured fibroblasts.[34] 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.[35,36] A study reported that multiple dilutions of povidone-iodine were found to be the most toxic of all agents tested on fibroblasts[37] and it has been reported to have deleterious effect on wound epithelialization, especially when used in non-diluted concentration.[32] It is also reported to possibly affect renal function when applied for a prolonged time, as it can be absorbed into circulation.[38]

Although iodine is an active topical agent when released from solution, povidone-iodine is readily inactivated by binding to serum proteins in exudating wounds.[39] It is reported to be ineffective when applied to wounds colonised with greater than 10^5 organisms per gram of tissue.[40] 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.[26] 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

90 percent.[3] It is used in a concentration of 1–3% solution or 1% cream (most commonly 3% solution is used for topical application to wounds). It is widely used as a biocide for disinfection, sterilisation and antisepsis. It is an oxidising agent active against many Gram-positive and Gram-negative bacteria but the presence of catalase in these bacteria makes it less effective in a concentration of 3%. It has broad-spectrum bactericidal activity. It is inexpensive and has not been reported to develop resistance.[26] This readily available oxidant is rapidly converted to highly active hydroxyl radical that damages cellular components. Hydrogen peroxide, because of its effervescent action, acts as a mechanical cleansing agent and also as a non-selective debriding agent.[40] It is primarily used for loosening dried exudates or debris including healthy regenerating tissue.[38] Hydrogen peroxide has been reported to disrupt new capillaries in granulation tissue. It also oxidises wound debris and has been found toxic to fibroblasts in healthy healing tissue.[40] It is widely considered innocuous and environmentally friendly. It is expensive and may cause some discomfort. It needs to be applied at relatively high concentration because of the significant catalase activity of several important bacteria.[3,4] Although commonly used, only few clinical studies have been reported so far on its use.[26]

Dakin's solution (Sodium hypochlorite)

Dakin's solution containing sodium hypochlorite (dilute bleach), after being previously used for a long time, came into focus again in 1980s. It has mainly wide spectrum antibacterial 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 pyocyaneous 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.[26,38,42-44]

Dakin's solution in a concentration of 0.025% and above has been found to have bactericidal activity and a concentration of 0.25% has been found to be toxic to tissues. Hence, a concentration of 0.025% is considered as an optimal concentration for human use.[45]

Mafenide acetate (Sulfamylon)

Mafenide acetate (a-amino-p-toluene sulfonamide acetate) was introduced in 1960 as a topical agent in the treatment of burns. It acts by competitive inhibition of p-amino benzoate 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.[20,31,46,47]

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.[3,41]

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.[48-50]

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.[49]

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*.[49]

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.[51] 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.[52]

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.[53,54] 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

irrigation. 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.[54,55]

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 human cells required for the wound healing process, especially the in-vitro studies show that many 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.

Conflict of Interest: None to declare

Source of Funding: Nil

References

1. Robson MC. Wound infection: a failure of wound healing caused by an imbalance of bacteria. Surg Clin N Am. 1997.77:637-650.
2. Daeschlein G. Antimicrobial and antiseptic strategies in wound management. Int Wound J. 2013.10:9-14.
3. Mc Donell G, Russell AD. Antiseptics and disinfectants: activity, action and resistance. Clin Microbiol Rev. 1999.12:147-179.
4. Thomas GW, Rael LT, Bar-Or R, et al. Mechanisms of delayed wound healing by commonly used antiseptics. J Trauma. 2009.66:82-91.
5. Steinstraesser L, Schubert C, Jacobsen F, Al-Benna S. Editorial: glycyrrhizin against multi-resistant bacteria? J Leukoc Biol. 2010.87:7-8.
6. McDougall IA. Burns and the use of silver sulphadiazine. Aust N Z J Surg. 1972.42:174-178.
7. Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother. 2010.65:i35-44.
8. Fong J, Wood F. Nanocrystalline silver dressings in wound management: a review. Int J Nanomedicine. 2006.1:441-449.
9. Lansdown AB. Metallothioneins: potential therapeutic aids for wound healing in the skin. Wound Repair Regen. 2002.10:130-132.
10. Mooney EK, Lippitt C, Friedman J. Silver dressings. Plast Reconstr Surg. 2006.117:666-669.
11. Wright B, Lam K, Buret A, Olsen ME, Burell RE. Early healing events in a porcine model of contaminated wounds: effects of nanocrystalline silver on matrix metalloproteinases, cell apoptosis, and healing. Wound Repair Regen. 2002.10:141-151.
12. Wilkinson LJ, White RJ, Chipman JK. Silver and nanoparticles of silver in wound dressings: a review of efficacy and safety. J Wound Care. 2011.20:543-549.
13. Demling RH, DeSanti L. The rate of re-epithelization across meshed skin grafts is increased with exposure to silver. Burns. 2002.28:264-266.
14. Lohsiriwat V, Chuangsuwanich A. Comparision of the ionic silver-containing Hydrofiber and paraffin gauze dressing on split-thickness skin graft donor sites. Ann Plast Surg. 2009.62:421-422.
15. Banos AM, Nogueras Flores I, Palomer Llatas F. Clinical evaluation of a silver dressing in the treatment of infected and colonized ulcers. Rev Enferm. 2008.1:42-48.
16. Weigand C, Heinze T, Hipler UC. Comparative in vitro study on cytotoxicity, antimicrobial activity, and binding capacity for patho-physiological factors in chronic wounds of alginate and silver-containing alginate. Wound Repair Regen. 2009.17:511-521.
17. Burd A, Kwok CH, Hung SC, et al. A comparative study of the cytotoxicity of silver-based dressings in monolayer cells, tissue explants, and animal models. Wound Repair Regen. 2007.15:94-104.
18. Paddle-Ledinek JE, Nasa Z, Cleland HJ. Effect of different wound dressings on cell viability and proliferation. Plast Reconstr Surg. 2006.117:110S-118S.
19. Poon VK, Burd A. In vitro cytotoxicity of silver: implication for clinical wound care. Burns. 2004.30:140-147.
20. Bollinger CG, Conway N. Effects of silver nitrate and sulfamylon on epithelial regeneration. Plast Reconstr Surg. 1970.45:582-585.
21. Scapicchio AP, Constable JD, Opiatz B. Comparative effects of silver nitrate and sulfamylon on epidermal regeneration. Plast Reconstr Surg. 1968.41:319-322.
22. Niedner R, Schopf E. Inhibition of wound healing by antiseptics. Br J Dermatol. 1986.115:41-44.
23. Zou SB, Yoon WY, Han SK, et al. Cytotoxicity of silver dressings on diabetic fibroblasts. Int Wound J. 2013.10:306-312.
24. Singer AD, Dagum AB, Current management of acute cutaneous wounds. N Eng J Med. 2008.350:1037-1046.
25. Ollstein RN, McDonald C. Topical and systemic antimicrobial agents in burns. Ann Plast Surg. 1980.5:386-392.
26. Lipsky DA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009.49:1541-1549.
27. Percival SL, Bowler PG, Russell D. Bacterial resistance to silver in wound care. J Hosp Infect. 2005.60:1-7.
28. Tsang K, Kwong EW, To TS, Chung JW, Wong TK. A pilot randomized, controlled study of nanocrystalline silver, manuka honey, and conventional dressing in healing diabetic foot ulcer. Evidence-Based Complementary Alternative Med.2017. https://doi.org/10.1155/2017/5294890.
29. Nherera LM, Trueman P, Roberts CD, Berg L. A systematic review and meta-analysis of clinical outcomes associated with nanocrystalline silver use compared to alternative silver delivery systems in the management of superficial and deep partial thickness burns. Burns. 2017.43(5):939-948.
30. Woodmansey EJ, Roberts CD. Appropriate use of dressings containing nanocrystalline silver to support antimicrobial stewardship in wounds. Int Wound J. 2018.15(6):1025-1032.
31. Mc Nultty C, Rodgers GL, Mortenson JE. An overview of the topical antimicrobial agents used in the treatment of burn wounds. Continuing Education Topics and Issues. 2004.74-78.
32. Miller JM, Creazzo J, Witt C. Wound healing: an introductory clinical approach. Contemporary Podiatric Physician. 1992.38-42.
33. Jean-Marie Lachapelle. A comparison of the irritant and allergenic properties of antiseptics. Eur J Dermatol. 2014.24:3-9.
34. Lineaweaver W, Howard R, Soucy D, et al. Topical antimicrobial toxicity. Arch Surg. 1985.120:267-270.
35. Kramer SA. Effect of povidone-iodine on wound healing: a review. J Vasc Nurse. 1999.17:17-23.
36. Rodeheaver G, Bellamy W, Kody M, Spatafora G, Fitton L, Leyden K, Edlich R. Bacterial activity and toxicity of iodine containing solutions in wounds. Arch Surg. 1982.117:181-186.
37. Cooper ML, Laer JA, Hansbrough. The cytotoxic effect of commonly used antimicrobial agents on human fibroblasts and keratinocytes. Trauma. 1991.31:775-784.
38. Frantz R. Wound care update 91. Nursing 91. 1991.21:47-48.
39. Kucan J, Robson MC, Heggers JP, Francis KO. Comparison of silver sulfadiazine, povidone-iodine and physiological saline in the treatment of chronic ulcers. J Am Ger Soc. 1981.29:232-235.
40. Kloth L, Mc Dulloch J, Feedar J. Wound healing: alternatives in management. F.A. Davis company, Philadelphia, 1990.
41. Jackson MM, Mahon Co. Topical antiseptics in healthcare. Posted on : Saturday, 30 July 2005.http://www.redorbit.com/news/science/191895/topical_antiseptics-in_healthcare/[accessed 5 June, 2018].
42. Dakins HD. The antiseptic action of hypochlorites: ancient history of new antiseptic. BMJ. 1995.2:809-810.
43. Kazol RA, Gillies C, Elgebaly SA. Effect of sodium hypochlorite (Dakin's solution) on the cells of wound module. Arch Surg. 1998.123:420-423.
44. Kjolseth D, Frank JM, Barkar JH, et al. Comparison of effects of commonly used wound agents on epithelization and neovascularization. J Am Coll Surg. 1994.179:305-312.
45. Barillo DJ. Topical antimicrobials in burn wound care: A recent history. Wounds. 2000.20:192-198.
46. Moncrief JA, Lindberg RB, Switzer WF, Pruitt Jr BA. Use of topical antibacterial therapy in the treatment of burn wound. Arch Surg. 1996.92:558-565.
47. McNulty C, Rodgers GL, Mortensen JE. An overview of topical antimicrobial agents used in the treatment of burn wounds. Continuing Education Topics and Issue 2004.273:74-78.
48. Atiyeh BS, Dibo SA, Hayek SN. Wound cleansing, topical antiseptics and wound healing. Int Wound J. 2009.6:420-430.
49. Mulder GD, Cavorsi JP, Lee DK. Polyhexamethylene Biguanide (PHMB): An Addendum to Current Topical Antimicrobials. Wounds. 2007.19:173-182.
50. Wehner F, Wehner HD, Schulz MM. Lethal intra-venous infusion of a wound antiseptic containing polyhexanide. Arch Kriminol. 2009.223:108-116.
51. Daeschlein G, Assadian O, Bruck JC, et al. Feasibility and clinical applicability of polyhexanide for treatment of second-degree burn wounds. Skin Pharmacol Physiol. 2007.20:292-296.
52. Ince A, Schutze N, Hendrich C, et al. Effect of polyhexanide and gentamycin on human osteoblasts and endothelial cells. Swiss Med Wkly. 2007.137:139-145.
53. Nagoba BS, Pichare AP. Medical Microbiology and Parasitology. 3rd ed. Elsevier, New Delhi, 2016.
54. Drosou A, Falabella A, Kirsner RS. Antiseptics on wounds: An area of controversy. Wounds. 2003. 15(5):149-166.
55. Severyns AM, Lejeune A, Rocoux G, Lejeune G. Non-toxic antiseptic irrigation with chlorhexidine in experimental revascularization in the rat. J Hosp Infect. 1991. 17:197-206.