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Povidone-iodine in wound healing and prevention of wound infections

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ABSTRACT: The wound infections caused by bacteria and fungi are a significant problem in healthcare. Therefore, an effective treatment and prevention seems to be essential. Povidone-iodine is one of the commercial antimicrobial agents used for skin disinfection, in surgery and for local anti-infective treatment. The broad activity spectrum of this compound includes numerous species of Gram-positive and Gram-negative bacteria, mycobacteria, fungi, protozoa and viruses. Povidone-iodine is recommended for acute wounds as well as lacerations, bruises and deep wounds due to its good tissue penetration.

Keywords: Povidone-iodine; PVP-I; Antiseptic; Antimicrobial; Wound infection.

1. INTRODUCTION

Bacteria are a part of the physiologic skin and mucous membranes flora and in that way wounds [1]. Additionally, non-pathogenic or potentially pathogenic microorganisms of transient flora reside the skin and mucous membranes for hours to weeks [2]. Exceeding the critical threshold of 10^5 bacteria (critical colonization) may cause an infection. Additionally, antibiotic-resistant strains can significantly impede wound healing [1].

Most chronic wounds comprise more than one bacterial species. Among them *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus agalactiae, Enterococcus faecalis, Corynebacterium spp., Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia, Acinetobacter baumannii, Escherichia coli, Proteus mirabilis, Serratia spp., Finegoldia magna, Propionibacterium acnes, Fusobacterium nucleatum, Prevotella spp.,* and *Bacteroides fragilis* are the most often. An increase in surgical site infections (SSIs) correlated with methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* were observed. Infections caused by fungi, such as *Candida albicans* and *C. glabrata* are also a significant problem. Moreover, *Pseudomonas aeruginosa, Staphylococcus epidermidis,* and *Staphylococcus aureus* are capable to form biofilms that contribute to antibiotic resistance [2-4].

To reduce the risk of infection, antiseptic agents are used. Antiseptics are naturally occurring or synthetic organic substances intended for local, topical use, that destroy or inhibit the growth of

microorganisms on skin, mucous membranes or damaged tissue [4]. One of the commercial antimicrobial agent is the polyvinylpyrrolidone–iodine (povidone-iodine, PVP-I).

PVP-I was introduced in 1956 [5] and its routinely used as a preparation for skin disinfection in combination with alcohol and intraoperatively as a dilute solution. Its efficacy against wide variety of Gram-positive and Gram-negative bacteria, fungi, protozoa, viruses, good tolerability and lack of resistance suggests the correctness of use PVP-I in wound healing and infection prevention [6-9].

2. CHEMICAL ASPECTS

Povidone-iodine is a yellowish-brown chemical complex of 1-ethenylpyrrolidin-2-one and molecular iodine with a slight characteristic odor. The iodine content is from 9.0 to 12.0% (calculated on a dry basis). The substance has a molecular formula $C_6H_9I_2NO$ and a molecular weight 364.95 g/mol [10]. Figure 1 shows the chemical structure of the compound.

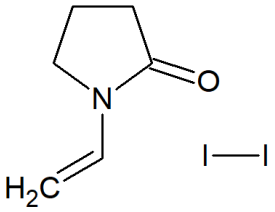

Figure 1. Chemical structure of povidone-iodine.

The solubility of PVP-I at water and alcohol is good and it is practically insoluble in acetone, chloroform, light petroleum or carbon tetrachloride. There are available different concentrations of PVP-I used depending on the purpose: as a 10%, 7.5%, 5%, 1.28%, 1% and also 0.45% formulation (as a throat spray) [10, 11].The 10% commercial formulation is composed of 90% water, 8.5% povidone and 1% iodine and iodide [12, 13].

Mixing povidone and iodine indicates a chemical reaction. It is considered that iodine is complexed by polyvinylpyrrolidone and iodide through a hydrogen bond between two pyrroles. As a result, povidone-iodine exists with a small amount of free iodine. It has been documented that exposure to organic substances like whole blood, pus or fat reduces a bactericidal activity of PVP-I. It is most likely caused by iodine complexing and chemical reactions, such as the reduction to iodide. Moreover, approximately 46 to 59 mg of iodine is bound by one gram of hemoglobin [6]. In addition, it is worth remembering that in chronic wounds, iodine compounds should not be combined with silver-containing dressings, also due to the precipitation of iodides [4].

3. MODE OF ACTION

The microbicidal activity of PVP-I is based on release the free iodine to the solution from the PVP-I complex. PVP provides iodine to cells membranes, but itself has no biocidal properties. There has been demonstrated the paradoxical behavior of substance; in contrast to other iodine preparations, the content of free iodine primitively increases with the increasing dilution, reaching a maximum value at about 0.1% formulation and decreasing on further dilution [14]. This translates into antimicrobial activity of compound [7].

The iodine effects on amino, thiol and phenolic hydroxyl groups of amino acids and nucleotides in biological structures. Additionally, iodine reacts with the double bonds of unsaturated fatty acids in the cell

wall and membranes of organelles [15]. This mode of action leads to disruption of pathogens metabolic pathways and irreversible damage of the cell membranes structural components. PVP-I also inhibits the production and secrete of bacterial exotoxins [3, 11, 16].

The virucidal mechanism of action is based on the inhibition of essential viral enzymes. The inactivation of neuraminidase prevents viral release from the host cell, making a further spread of the virus to uninfected cells impossible. Haemagglutinin is also inhibited by iodophor and attachment to host cell receptor is blocked [17].

4. ANTIMICROBIAL ACTIVITY

PVP-I has a broad spectrum of antimicrobial activity even after a short time of exposition [7]. It demonstrates efficacy against Gram-positive, Gram-negative, various spore-forming bacteria (*Clostridium* spp., *Bacillus* spp.), mycobacteria and also enveloped and non-enveloped viruses [8, 18]. Equally inactivation of antibiotic sensitive and resistant staphylococci and enterococci, such as methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*, by PVP-I was demonstrated [19-22]. Also Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Escherichia coli* presented sensitivity on PVP-I [17, 20, 23]. Minimal inhibitory concentrations (MIC) of PVP-I against some bacterial and fungal species are presented in Table 1.

Biofilms impede wound healing and increase resistance to antibiotics. Studies have shown the *in vitro* efficacious of PVP-I against *S. epidermidis*, *S. aureus* and *Candida albicans* growth, as well as the inhibition biofilm formation [8]. Moreover, the iodophor revealed fungicidal activity against *Candida auris* [24], *Aspergillus flavu*s and *Cryptococcus neoformans* [6].

Table 1. MICs (minimal inhibitory concentrations) of PVP-I against bacterial and fungal species.

Species	MIC (µg/mL)	References
Staphylococcus aureus	0.24-512	[3, 25, 26]
Methicillin-resistant *S. aureus* (MRSA)	7.81-5210	[9, 25, 27]
S. epidermidis	781-5000	[28, 29]
Streptococcus pyogenes	490-4688	[9, 27]
Escherichia coli	4-1024	[25, 26, 30]
Carbapenem-resistant *E. coli* (CREC)	4-128	[30]
Klebsiella pneumoniae	4-64	[30]
Carbapenem-resistant *K. pneumoniae* (CRKP)	8-128	[9, 30]
Pseudomonas aeruginosa	125-8330	[3, 27]
Chlamydia trachomatis	97-1562	[9, 31]
Bacteroides fragilis	3130-4688	[9, 27]
Candida albicans	256-5000	[25, 32, 33]
C. glabrata	10-5000	[32, 33]
Cryptococcus sp.	2500	[32]

Viruses and chlamydia play a meaningful role in infections. PVP solutions indicate high effective against *Herpes simplex* virus and excellent efficacy against the enveloped influenza A virus. Adenovirus type

8 proved to be sensitive to PVP-I, although, contrary to *Herpes simplex*, a longer time of exposure was necessary to inactivation. Enteroviruses and *Coxsackievirus* were resistant to povidone-iodine [7, 17].

5. APPLICATION

PVP-I has a wide range of applications. In 2014, European Chemicals Agency approved PVP-I as an existing active substance for use in biocidal products for types 1, 3, 4, and 22 (human hygiene, veterinary hygiene, food and feed area, and embalming and taxidermist fluids) [9]. Efficacy of wound infection treatment, prophylactic intraoperative wound irrigation, hand wash preparations, skin disinfection and topical antiseptic has been shown [13, 34-37]. Povidone-iodine is available in a pre- and postoperative skin desinfection [38, 39].

PVP-I as an antiseptic formulation is the first choice for stab, bite and gunshot wounds [3]. In difficult-to-heal wounds (including chronic wounds), it is not recommended due to its cytotoxicity, limitations of use, and the incompatibility between PVP-I and the silver-based dressings [40]. It is also useful in the care of surgical wounds, and in wounds such as the diabetic foot, as it can be used to rinse deep wounds with lack drainage [41-43]. The use of PVP-I as a vaginal antiseptic has also been demonstrated. Presurgical vaginal irrigation with PVP-I significantly reduces the risk of post-cesarean endometritis, wound infections and pyrexia in patients who underwent cesarean delivery [44, 45].

Some studies indicate that PVP-I formulations are effective in eradication pathogenic cultures of the external auditory canal after tympanoplasty [46], in intraocular injection, ophthalmic surgery, also as a cataract surgery [12], in treating the corneal ulcers [47] or preventing post-cystoscopy urinary tract infection (UTI) [48]. Moreover, PVP-I is used for mucosal antisepsis, in oral surgery and dental conditions [11]. Studies present the positive effects of PVP-I gargles/mouthwashes against *Bordetella pertussis*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae* strains [18, 49].

However, an equally important factor conditioning the proper healing process is the low cytotoxicity of the antiseptic. The Biocompatibility Index (BI) may be helpful in choosing the right preparation (Table 2).

Tabela 2. Biocompatibility index as a quotient of IC_{50} for L929 cells and the required MIC for a reduction factor of ≥3 log10 [40].

Compound	***Escherichia coli***	***Staphylococcus aureus***
Octenidine	1,7	2,1
PHMB	1,5	1,4
PVP-I (aqueous solution, referring on I_2)	0,9	1,0
Chlorhexidine	0,7	0,7
Triclosan	0,2	0,5
Ag-protein (referring on Ag+)	0,2	0,1
Ag(I)-sulfadiazine and silver nitrate	not measurable	

The BI value >1 indicates that a given product has a broad spectrum against microorganisms and a low level of cytotoxicity against fibroblasts or keratinocytes, and therefore its use does not adversely affect the healing process. It is also important that the antiseptic preparation has a high degree of penetration through biofilm structures, does not induce resistance build-up, and does not cause incompatibility with other substances contained in dressings and has the ability to prolonged operation (residua effect). Currently, in

clinical practice, the most frequently chosen antispetics for the prevention and treatment of chronic wounds are octenidine and iodine-containing agents (such as iodine povidone) [4, 40, 50].

Sometimes, sensitizations against PVP-I cross-reacts to iodinated contrast media. However, these can be detected by a simple skin test. In addition, PVP-I allergies are relatively rare [8]. Hypersensitivity to the povidone-iodine, hyperthyroidism, toxic nodular goiter, herpes dermatitis syndrome, radioactive iodine therapy and peritoneal lavage are contraindications to povidone-iodine usage. Application during pregnancy and breastfeeding, as well as in patients under 12 years old is not recommended [3, 51].

6. CONCLUSION

Povidone-iodine is a relatively inexpensive antimicrobial agent characterized by a broad spectrum of activity, efficacy against biofilms and no resistance. Additionally, rapid action and good tolerability confirm the appropriateness of using PVP-I formulations in the clinical treatment of surgical wounds and the prevention of infections. PVP-I may help reduce the wound healing period and shorten the hospitalization as well as reduce treatment costs.

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Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. Adv Ther. 2017; 34: 599-610.
2. Rahim K, Saleha S, Zhu X, Huo L, Basit A, Franco OL. Bacterial contribution in chronicity of wounds. Microb Ecol. 2017; 73: 710-721.
3. Karpiński TM. Zastosowanie antyseptyków w leczeniu ran. The use of antiseptics in the treatment of wounds. Chirurgia po Dyplomie. 2020 [in press].
4. Sopata M, Jawień A, Mrozikiewicz-Rakowska B, Augusewicz Z, Bakowska M, Samson I, et al. Wytyczne postępowania miejscowego w ranach niezakażonych, zagrożonych infekcją oraz zakażonych – przegląd dostępnych substancji przeciwdrobnoustrojowych stosowanych w leczeniu ran. Zalecenia Polskiego Towarzystwa Leczenia Ran. Leczenie Ran. 2020; 17: 1-21.
5. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev. 1999; 12: 147-179.
6. Zamora JL. Chemical and microbiologic characteristics and toxicity of povidone-iodine solutions. Am J Surg. 1986; 151: 400-406.
7. Reimer K, Wichelhaus TA, Schäfer V, Rudolph P, Kramer A, Wutzler P, Ganzer D, Fleischer W. Antimicrobial effectiveness of povidone-iodine and consequences for new application areas. Dermatology. 2002; 204: 114-120.
8. Bigliardi PL, Alsagoff SAL, El-Kafrawi HY, Pyon J-K, Wa CTC, Villa MA. Povidone iodine in wound healing: A review of current concepts and practices. Int J Surg. 2017; 44: 260-268.
9. Kampf G. Antiseptic stewardship: biocide resistance and clinical implications. Springer International Publishing, 2018.

10. National Center for Biotechnology Information. PubChem Database. Povidone iodine, CID=410087, https://pubchem.ncbi.nlm.nih.gov/compound/Povidone-iodine (accessed on May 13, 2020)
11. Kanagalingam J, Feliciano R, Hah JH, Labib H, Le TA, Lin J-C. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. Int J Clin Pract. 2015; 69: 1247-1256.
12. Koerner JC, George MJ, Meyer DR, Rosco MG, Habib MM. Povidone-iodine concentration and dosing in cataract surgery. Surv Ophthalmol. 2018; 63: 862-868.
13. Burks RI. Povidone-iodine solution in wound treatment. Phys Ther. 1998; 78: 212-218.
14. Rackur H. New aspects of mechanism of action of povidone-iodine. J Hosp Infect. 1985; 6: 13-23.
15. Schreier H, Erdos G, Reimer K, König B, König W, Fleischer W. Molecular effects of povidone-iodine on relevant microorganisms: an electron-microscopic and biochemical study. DRM. 1997; 195: 111-116.
16. König B, Reimer K, Fleischer W, König W. Effects of betaisodona on parameters of host defense. Dermatology. 1997; 195: 42-48.
17. Eggers M. Infectious disease management and control with povidone iodine. Infect Dis Ther. 2019; 8: 581-593.
18. Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In vitro bactericidal and virucidal efficacy of povidone-iodine gargle/mouthwash against respiratory and oral tract pathogens. Infect Dis Ther. 2018; 7: 249-259.
19. Block C, Robenshtok E, Simhon A, Shapiro M. Evaluation of chlorhexidine and povidone iodine activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* using a surface test. J Hosp Infect. 2000; 46: 147-152.
20. Kunisada T, Yamada K, Oda S, Hara O. Investigation on the efficacy of povidone-iodine against antiseptic-resistant species. Dermatology. 1997; 195: 14-18.
21. Wichelhaus TA, Schäfer V, Hunfeld KP, Reimer K, Fleischer W, Brade V. Antibacterial effectiveness of povidone-iodine (Betaisodona) against highly resistance gram positive organisms. Zentralbl Hyg Umweltmed. 1998; 200: 435-442.
22. Ghaddara HA, Kumar JA, Cadnum JL, Ng-Wong YK, Donskey CJ. Efficacy of a povidone iodine preparation in reducing nasal methicillin-resistant *Staphylococcus aureus* in colonized patients. Am J Infect Control. 2020; 48: 456-459.
23. Tsuda S, Soutome S, Hayashida S, Funahara M, Yanamoto S, Umeda M. Topical povidone iodine inhibits bacterial growth in the oral cavity of patients on mechanical ventilation: a randomized controlled study. BMC Oral Health. 2020; 20: 62.
24. Kean R, McKloud E, Townsend EM, Sherry L, Delaney C, Jones BL, et al. The comparative efficacy of antiseptics against *Candida auris* biofilms. Int J Antimicrob Agents. 2018; 52: 673-677.
25. Koburger T, Hubner N-O, Braun M, Siebert J, Kramer A. Standardized comparison of antiseptic efficacy of triclosan, PVP-iodine, octenidine dihydrochloride, polyhexanide and chlorhexidine digluconate. J Antimicrob Chemother. 2010; 65: 1712-1719.
26. Lacey RW. Antibacterial activity of povidone iodine towards non-sporing bacteria. J Appl Bacteriol. 1979; 46: 443-449.
27. Oates A, Lindsay S, Mistry H, Ortega F, McBain AJ. Modelling antisepsis using defined populations of facultative and anaerobic wound pathogens grown in a basally perfused biofilm model. Biofouling. 2018; 34: 507-518.

28. Reynolds MM, Greenwood-Quaintance KE, Patel R, Pulido JS. Selected antimicrobial activity of topical ophthalmic anesthetics. Transl Vis Sci Technol. 2016; 5(4): 2.
29. Herruzo-Cabrera R, Garcia-Torres V, Rey-Calero J, Vizcaino-Alcaide MJ. Evaluation of the penetration strength, bactericidal efficacy and spectrum of action of several antimicrobial creams against isolated microorganisms in a burn centre. Burns. 1992; 18: 39-44.
30. Chen Y, Liao K, Huang Y,Guo P, Huang H, Wu Z, Liu M. Determining the susceptibility of carbapenem resistant *Klebsiella pneumoniae* and *Escherichia coli* strains against common disinfectants at a tertiary hospital in China. BMC Infect Dis. 2020; 20: 88.
31. Párducz L, Eszik I, Wagner G, Burián K, Endrész V, Virok DP. Impact of antiseptics on *Chlamydia trachomatis* growth. Lett Appl Microbiol. 2016; 63: 260-267.
32. Kondo S, Tabe Y, Yamada T, Misawa S, Oguri T, Ohsaka A, Miida T. Comparison of antifungal activities of gentian violet and povidone-iodine against clinical isolates of *Candida* species and other yeasts: a framework to establish topical disinfectant activities. Mycopathologia. 2012; 173: 21-25.
33. Traboulsi RS, Mukherjee PK, Ghannoum MA. In vitro activity of inexpensive topical alternatives against *Candida* spp. isolated from the oral cavity of HIV-infected patients. Int J Antimicrob Agents. 2008; 31: 272-276.
34. Goswami K, Austin MS. Intraoperative povidone-iodine irrigation for infection prevention. Arthroplast Today. 2019; 5: 306-308.
35. Eggers M, Koburger-Janssen T, Ward LS, Newby C, Müller S. Bactericidal and virucidal activity of povidone-iodine and chlorhexidine gluconate cleansers in an in vivo hand hygiene clinical simulation study. Infect Dis Ther. 2018; 7: 235-247.
36. Durani P, Leaper D. Povidone–iodine: use in hand disinfection, skin preparation and antiseptic irrigation. Int Wound J. 2008; 5(3): 376-387.
37. Kambara Y, Hiramatsu K, Kato T, Sibata Y, Yoshihara M, Aoba T, et al. Randomized clinical trial of single skin sterilization with a povidone–iodine applicator versus conventional skin sterilization in abdominal surgery. BJS Open. 2019; 3: 282-287.
38. Chen S, Chen JW, Guo B, Xu CC. Preoperative antisepsis with chlorhexidine versus povidone-iodine for the prevention of surgical site infection: a systematic review and meta-analysis. World J Surg. 2020; 44: 1412-1424.
39. Ghobrial GM, Wang MY, Green BA, Levene HB, Manzano G, Vanni S, et al. Preoperative skin antisepsis with chlorhexidine gluconate versus povidone-iodine: a prospective analysis of 6959 consecutive spinal surgery patients. J Neurosurg Spine. 2018; 28: 209-214.
40. Kramer A, Dissemond J, Kim S, Willy C, Mayer D, Papke R, et al. Consensus on wound antisepsis: update 2018. Skin Pharmacol Physiol. 2018; 31(1): 28-58.
41. Daróczy J. Quality control in chronic wound management: the role of local povidone-iodine (Betadine®) therapy. Dermatology. 2006; 212: 82-87.
42. Gwak HC, Han SH, Lee J, et al. Efficacy of a povidone-iodine foam dressing (Betafoam) on diabetic foot ulcer. Int Wound J. 2020; 17: 91-99.
43. Ritter B, Herlyn PKE, Mittlmeier T, Herlyn A. Preoperative skin antisepsis using chlorhexidine may reduce surgical wound infections in lower limb trauma surgery when compared to povidone-iodine - a prospective randomized trial. Am J Infect Control. 2020; 48: 167-172.

44. Roeckner JT, Sanchez-Ramos L, Mitta M, Kovacs A, Kaunitz AM. Povidone-iodine 1% is the most effective vaginal antiseptic for preventing post-cesarean endometritis: A systematic review and network meta-analysis. Am J Obstet Gynecol. 2019; 221: 261.e1-261.e20.
45. Haas DM, Morgan S, Contreras K, Enders S. Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections. Cochrane Database Syst Rev. 2018; 7: CD007892.
46. Arslan IB, Genc S, Kayhan BC, Gumussoy M, Ozel G, Cukurova I. Bacterial change in external auditory canal upon antisepsis with povidone-iodine during tympanoplasty. Eur Arch Otorhinolaryngol. 2015; 272: 551-555.
47. Bordin P. Corneal ulcer treated with 0.66% nanoemulsion povidone-iodine: a case report. Am J Case Rep. 2020; 21: e919822-1–e919822-6.
48. Nayyar R, Dadhwal R, Kapil A, Pandey RM, Dogra P. Urethral instillation of povidone-iodine reduces post-cystoscopy urinary tract infection in males: a randomized controlled trial. Sci Rep. 2020; 10: 3585.
49. Suzuki T, Kataoka H, Ida T, Mikuniya T, Suzuki T, Kamachi K. Bactericidal activity of topical antiseptics and their gargles against *Bordetella pertussis*. J Infect Chemother. 2012; 18: 272-275.
50. Karpiński TM. Efficacy of octenidine against *Pseudomonas aeruginosa* strains. Eur J Biol Res. 2019; 9: 135-140.
51. Nobukuni K, Hayakawa N, Namba R, Ihara Y. The influence of long-term treatment with povidone-iodine on thyroid function. Dermatology. 1997; 195: 69-72.