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An Asian Perspective on Povidone Iodine in Wound Healing

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Abstract
Antiseptics, with a broader spectrum of antimicrobial efficacy, lower risk of antibiotic resistance development, and minimal collateral damage to host tissues, are important alternatives to control the bioburden in wounds. Povidone iodine (PVP-I), in use for several decades, has the broadest spectrum of activity, a persistent antimicrobial effect, an ability to penetrate biofilms, and a lack of acquired or cross-resistance. It demonstrates good skin tolerance and low cytotoxicity. However, some reports on PVP-I have raised concerns over allergy, ineffective penetration, and toxic effects on host cells. The majority of these concerns are based on in vitro or rodent wound studies with diverse study designs and outcomes; these results may not be directly applicable in the clinical reality in humans. In this paper, we discuss the efficacy and safety of PVP-I and outline its place in wound healing in Asia, based on an appraisal of recent literature and clinical practice across the region.

Introduction

Antiseptics are defined as agents used to inhibit or kill microorganisms present within a wound or on intact skin [1, 2] and have long been used on wounds to prevent or treat infections. Despite this, and in the absence of standardized practice and clinical study guidelines, there continues to be a great deal of debate and controversy on the appropriate use of antiseptics.

Iodine has been used as an antiseptic in the treatment of wounds for more than a century [3], yet questions are raised about the place of iodine-based agents in the man-

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agement of wounds. With povidone iodine (PVP-I), there have been concerns about allergy, ineffective penetration, and toxic effects on host cells [4–7], but how justified are these concerns? There are reports which indicate that these concerns may be based on inappropriately performed in vitro cellular or in vivo animal studies with sometimes limited applicability to the clinical reality [3, 8, 9]. The objective of this paper is to discuss the efficacy and safety of PVP-I and to outline its place in wound care management based on an appraisal of the literature as well as clinical practice, particularly in an Asian context.

Methods

The Asian Working Group (AWG) on wound management includes 5 advisors from Asia (Singapore, the Philippines, Thailand, Korea, and Malaysia) and an advisor from Germany (to provide a global perspective). All advisors are recognized experts with vast experience in wound management in their respective countries.

The AWG convened in April 2016 to assess the available published evidence for PVP-I in conjunction with their own clinical experience of its use in the wound care environment in a research/clinical setting, and to develop consensus statements for PVP-I to support clinicians in Asia in making informed decisions. The topics for discussion included the current perceptions and clinical practice with regard to the role of antiseptics (PVP-I in particular) in the wound care setting in Asia, and the evidence available for PVP-I. Consensus was reached after discussions within the group.

Prior to the meeting, a search strategy was developed for identifying relevant literature for PVP-I. A PubMed search, using the keywords "wound" AND ("povidone iodine" OR "Betadine") AND ("efficacy" OR "safety" OR "cytotoxicity") was conducted, and the results were limited to those in the English language. The resulting papers were qualitatively assessed, and only those papers relevant to wound management and with the primary objective of comparing the different antiseptics including PVP-I were selected for discussion at the meeting.

Results

Profile of an Ideal Antimicrobial

Antiseptics act on multiple targets and have a broader spectrum of activity against different classes of viruses, fungi and bacteria, including multiresistant organisms, compared to antibiotics [1, 10, 11]. Furthermore, antibiotic use is associated with a high risk of resistance and cross-resistance [11, 12] as well as allergies. In this context, antiseptics are important alternatives in the clinical setting to control the bioburden in wounds.

The properties of an ideal antimicrobial agent have been described in detail in several publications [1, 11, 13–16]. The efficacy profile of an ideal antimicrobial agent for wound care should include a broad antimicrobial effect (antibacterial [Gram-positive and Gram-negative bacteria], antimycotic, and antiviral), good local penetration, stability in the presence of body fluids and wound exudates, and a low potential for acquired resistance. From a safety viewpoint, an ideal antiseptic should also have good local and systemic tolerability and low systemic absorption, be nonsensitizing/hypoallergenic, and cause no delay in the wound healing process [11, 13, 14, 16].

Additionally, in the experience of the AWG, an ideal formulation of antiseptic should not penetrate the corneal layer of intact surrounding skin of the wound, but should have optimal activity on the wound where the skin barrier is lost, and should also easily penetrate into microbial biofilms. If the antiseptic penetrates into the granulation tissue, which is typically highly vascularized, it may cause systemic toxicity. Further, the AWG notes that antiseptics should act continuously over a long period of time, rather than be fast-acting. This ensures a constant and high enough concentration for antimicrobial efficacy and allows for infrequent dosing, providing patient comfort and contributing to cost savings in terms of the reduced nursing care required.

Low cost and acceptable cosmetic and esthetic qualities are believed to be important attributes of antiseptics [16]. The Asia-Pacific region comprises several countries, and given the diversity in the economic and health care systems, the AWG notes that the cost-efficacy balance of an ideal antiseptic should be optimized. Furthermore, cultural practices, beliefs, and perceptions vary in the different countries in Asia – while some patients find antiseptic staining of the wound and surrounding tissues concerning, others associate it with increased efficacy. The AWG also believes that the concentration and formulation of the active ingredient are important factors contributing to the efficacy of antiseptics. There is a lack of evidence around the concentration and formulation of antiseptics to be used in different kinds of wounds, especially in relation to locally made, readily available formulations. Local and country-specific guidelines could potentially address this issue, while offering guidance to the clinicians.

Several antiseptic preparations are available for the prevention and treatment of infection in wound care, such as the iodophors polyvinylpyrrolidone-iodine and cadexomer-iodine, the biguanides chlorhexidine, octenidine, and polyhexanide, the bisphenols triclosan and hexachlorophene, silver compounds, benzalkonium chloride, and hydrogen peroxide.

Povidone Iodine

Iodine has been extensively used for decades as an antiseptic. PVP-I, the most well-established iodophor, is a combination of molecular iodine and a polyvinylpyrrolidone surfactant/iodine complex which acts as a reservoir of free iodine [17, 18]. The bactericidal component of PVP-I is the free iodine, the levels of which are dependent on the concentration of the PVP-I solution.

The polyvinylpyrrolidone component of PVP-I delivers the iodine directly to the microorganism cell surface; the free iodine penetrates into the cell wall and targets proteins, nucleotides, and fatty acids, resulting in cell death [3, 18, 19]. The free iodine concentration increases with increasing dilutions of PVP-I: dilution weakens the iodine linkage to the carrier, resulting in an increase in free iodine in the solution [19]. It is believed that the concentration of free iodine contributes to the bactericidal activity of PVP-I; this is thought to explain the paradoxical increase in the antibacterial action of PVP-I with increasing degree of dilution (0.1–1% solutions were reported to be *more rapidly* bactericidal than the 10% solution) [19].

Efficacy: In vitro Studies

Spectrum of Activity

PVP-I has demonstrated a broad spectrum of activity against Gram-positive (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and Gram-negative bacteria, fungi, viruses, protozoa, and bacterial spores in several studies [11, 17, 18, 20, 21]. PVP-I has also shown high bactericidal activity against test strains comprising causative organisms of nosocomial infections (MRSA, *Serratia marcescens, Pseudomonas aeruginosa, Burkholderia cepacia*) after 30 s of exposure [22]. In addition, PVP-I proved to be the only antiseptic without the development of cross-resistance. A similar study confirmed the efficacy of PVP-I against two Gram-negative bacteria (*Xanthomonas maltophilia* and *S. marcescens*), including resistant strains of both species; both sensitive and resistant strains of both species were killed within 20 s of exposure to PVP-I [23].

Efficacy against Biofilms

Wound biofilms – bacterial communities living within a protective extracellular matrix – are often resistant to conventional treatment with antimicrobials and delay the wound healing process [20, 24]. The sustained efficacy of PVP-I in wound healing in the presence of biofilms has been described in several studies [20, 24, 25]. Hill et al. [25] used an in vitro biofilm model closely mimicking chronic wound biofilms and demonstrated the complete eradication of an established 7-day mixed *Pseudomonas* and *Staphylococcus* biofilm by using iodine-based dressings. Furthermore, Hoekstra et al. [24] recently demonstrated the efficacy of PVP-I in the presence of biofilms grown in a mixed culture of MRSA and *Candida albicans*, even when diluted. However, these are studies conducted in an in vitro environment and do not conclusively prove the efficacy of PVP-I on biofilms.

Resistance

Increasing bacterial resistance to antibiotics is a major clinical and public health problem worldwide [9, 11, 26], and Asia is no exception [12, 27].

Bacterial resistance to topical antimicrobial agents, such as vancomycin, mupirocin, fusidic acid, and gentamicin, has been widely reported [11, 28, 29]. Bacterial resistance to chlorhexidine, quaternary ammonium salts, triclosan, and silver has also been reported [11, 22, 23]. Furthermore, cross-resistance to other antibiotics and antiseptics has been documented with chlorhexidine and triclosan [30]. However, despite widespread and extensive use, no acquired or cross-resistance has ever been reported for iodine [11, 22, 23, 30].

Efficacy: In vivo Studies

In vitro studies with PVP-I have reported contradictory results [6, 7, 31, 32]. The role of PVP-I in wound healing has also been investigated in animal studies, with varying results [17, 33]. Most of these animal studies were published at least 2 decades ago, were conducted in beagles, rats, rabbits, and guinea pigs, and demonstrated that concentrations of up to 10% of PVP-I did not cause any inhibition in the granulation and epithelialization process [33]. Increased microcirculation is an important feature of the wound healing process. In experiments performed on wounds in male SKH1-hr hairless mice, PVP-I products (PVP-I liposomal hydrogel) showed a positive effect on dermal wound healing and wound microcirculation [34]. In full thickness wounds in mice, Kjolseth et al. [35] also demonstrated earlier and complete neovascularization with PVP-I versus other antiseptics.

Some human studies conducted in varying settings have established the efficacy of PVP-I in reducing the bacterial load in both acute and chronic wounds [8, 9, 17, 36–42]. Gravett et al. [36] and Stringer et al. [37] reported that PVP-I in patients prior to suturing lacerations reduces the incidence of wound infection. Similarly, postoperative irrigation of surgical wounds with PVP-I resulted in a decrease in wound infection rates in another study [38]. Further, in a study of 294 pediatric surgical

wounds, PVP-I did not impair wound healing rates [39]. PVP-I has also been demonstrated to be effective in reducing wound infection in pressure ulcers [40, 41]. Fumal et al. [41] also demonstrated faster healing rates and a positive reduction in bioburden in venous ulcers with PVP-I. Daróczy [42] also showed similar results in chronic wounds.

Studies of PVP-I in patients with diabetic foot ulcers and patients with burns have also established its efficacy. In one study, 29% of the wounds achieved full closure and 45% achieved partial closure within 6 months of regular topical PVP-I application [43]. In another study evaluating PVP-I in patients with partial thickness burns, treatment with PVP-I dressing was associated with reduced treatment times, lower need for analgesia, fewer hospital visits, and less time off work; less pain and bleeding on the removal of the dressing was also observed [44]. In similar settings, faster healing times and a favorable cosmetic result was demonstrated by PVP-I [45]. Studies evaluating a PVP-I preparation in hydrogel (containing iodine in a 3% concentration) in patients receiving meshed skin grafts after burns or reconstructive procedures have also reported significantly improved epithelialization, decreased transplant loss, and improved healing [46, 47].

Table 1 details some of the key studies investigating PVP-I in a variety of settings, including in vitro and human studies (burns, ulcers, skin trauma and lacerations, and pre- and postoperative antisepsis) [6, 7, 31, 32, 36, 38, 39–45, 48–61].

Safety, Toxicity, and Allergenic Activity

There have been concerns about perceived cytotoxicity with PVP-I, and the potential detrimental effect of PVP-I on wound healing has been widely argued, with several in vitro studies demonstrating the dose-dependent cytotoxicity of PVP-I on cultures of granulocytes, monocytes, keratinocytes, and fibroblasts [6, 62, 63]. At the same time, questions have been raised on the clinical relevance and application of these in vitro reports of topical toxicity or impact on wound healing [30, 33, 62]. In vitro cell toxicity and toxicity in rodents with thinner skins could potentially be more marked than those seen in a human wound [30, 33]. Isolated cells in cell cultures have no supportive matrix or vascular network, making them very susceptible to the slightest disturbances, in contrast to multiple layers of intact skin [33]. Experimental conditions also have a distinct impact on results, and as such the choice of experimental conditions for the assessment of cytotoxicity of antiseptics in cell culture has varied to a great extent [64]. The additives in the products being used or the formulation itself may produce variable degrees of toxicity in cell culture [33].

Whereas several in vitro studies report cytotoxicity, some in vivo human studies have demonstrated that PVP-I does not have a negative impact on wound healing [11, 33, 41, 62, 65]. As mentioned previously, Fumal et al. [41] described an increased healing rate and reduced time to healing by 2–9 weeks with PVP-I versus chlorhexidine in venous ulcers. Faster healing times with PVP-I have also been demonstrated in patients with burns [44, 45]. Niedner [33] reviewed the cytotoxicity of PVP-I and reported that the course of wound healing is not influenced negatively by PVP-I. More standardized human studies are needed to address these disparities in evidence seen in in vitro and in vivo animal studies.

There is much debate among dermatologists about the allergenic and irritant potential of PVP-I. All antiseptics have irritant properties when misused, particularly in skin conditions with a damaged skin barrier (e.g., eczematous skin), under inadequate occlusion, and at very high concentrations [66]. However, the sensitizing potential of PVP-I is very low and it is considered a weak allergen with a prevalence of allergenicity of 0.4% [67]. Furthermore, there appears to be no link between iodine-associated allergies (particularly allergic contact dermatitis) and anaphylactic, allergic, or intolerance reactions or delayed-type hypersensitivity against radiologic iodine-containing contrast media [11, 68]. There are some rare case reports of immediate or delayed allergic reactions to PVP-I, with povidone or nonoxynol as the most likely sensitizing agents [69, 70]. However, a more complete investigation into the allergenic potential of PVP-I is needed to evaluate the clinical relevance. Until there is irrefutable evidence for the nonallergenicity of PVP-I, the AWG advises caution in the use of PVP-I in patients who report a previous reaction to iodine products. It is important that toxic reactions to the inappropriate use of PVP-I should be clearly separated from real allergic reactions. In the case of toxic effects of PVP-I, it can still be used, with a change in the concentration and method of application. If there is a real allergic reaction to PVP-I or its additives, proven by prick tests if immediate or patch tests if delayed type, the PVP-I or the offending additives have to be avoided under all circumstances. In addition, PVP-I is contraindicated in patients with hyperthyroidism/thyroid cancer; it should be used with caution in pregnant and lactating women and infants.

Systemic toxicity does not seem to be a common occurrence with PVP-I. However, systemic absorption from large surface area wounds may be a concern. There have

Table 1. Key human and in vitro studies using povidone iodine (PVP-I)

First author, year	Wound type	Study parameters	Result
Daróczy 2002 [42]	Chronic ulcers	25 patients with chronic lymphedematous ulcers; cleansing the ulcer with PVP-I solution and PVP-I ointment placed in the cavity of the ulcer	Reduction in the number of bacterial colonies within 4 weeks; infection, satellite ulcers, erythema, and edema were significantly improved after 6 weeks
de Jonge 2017 [56]	Surgical site infections	Systematic review which included randomized controlled trials comparing either prophylactic intraoperative wound irrigation (pIOWI) with no pIOWI or with pIOWI using different solutions and techniques	A significant benefit for incisional wound irrigation with an aqueous PVP-I solution in clean and clean contaminated wounds was reported
DeKock 1986 [49]	Burns	60 patients with burns; 10% PVP-I ointment mixed with a proteolytic agent, 5% PVP-I cream alone and in combination with the same proteolytic agent	Shorter healing times in burns treated with PVP-I cream; the addition of a proteolytic agent to the cream made no difference to the results; fewer positive cultures for *Staphylococcus aureus* and *Pseudomonas aeruginosa* in the groups treated with the cream
Eming 2006 [50]	In vitro	Difference concentrations of PVP-I on fluid collected from venous leg ulcers incubated with a range of PVP-I concentrations	At higher PVP-I concentrations, elastase and plasmin activity was reduced significantly, suggesting the suitability of PVP-I for nonhealing wounds
Fumal 2002 [41]	Chronic leg ulcers	17 patients with similar chronic leg ulcers treated with PVP-I, silver sulfadiazine, or chlorhexidine digluconate	PVP-I significantly increased the healing rate, and the time to healing was reduced by 2–9 weeks
Georgiade 1973 [51]	Burns	50 patients with burns treated with PVP-I ointment	77% of wound cultures did not have bacterial growth after 4 times daily application vs. 42% and 33% twice/thrice daily and once daily/every other day application, respectively
Gravett 1987 [36]	Lacerations	500 consecutive emergency department patients with traumatic lacerations requiring sutures; topical 1% PVP-I and scrubbing vs. wound management by irrigation with normal saline without scrubbing (control group)	11 wounds became infected in the treatment group vs. 30 in the control group ($p < 0.01$)
Han 1989 [44]	Burns	213 patients with <10% partial thickness burns; treatment with chlorhexidine or PVP-I dressing	PVP-I caused less bleeding on dressing removal, required less analgesia, reduced treatment time, and smaller number of hospital visits
Homann 2007 [45]	Partial thickness burns	43 patients; PVP-I in a liposome hydrogel vs. silver sulfadiazine cream	PVP-I hydrogel group has a significantly faster complete healing with an improved cosmetic result
Hussain 2010 [48]	Surgical wound	41 patients with surgical wounds; 10% solution of PVP-I vs. 1.25–2.5% chloroxylenol solution wash, pre- and postoperatively	No bacterial growth and no infection in patients treated with PVP-I
Lammers 1990 [52]	Acute, traumatic wounds	29 patients (33 wounds); 10-min soaking in either PVP-I or saline, and controls were covered with gauze during this period	No difference between PVP-I and control groups in wound infection; increased bacterial counts in the normal saline group
Lee 1979 [40]	Stasis ulcers	18 chronic wounds treated with PVP-I (10%)	67% wounds cured, 33% showed improvements
Lineaweaver 1985 [6]	In vitro	3 topical antibiotics and 4 antiseptic agents (1% PVP-I, 0.25% acetic acid, 3% hydrogen peroxide, and 0.5% sodium hypochlorite) to assess their cytotoxicity to cultured human fibroblasts	All 4 antiseptics were found to be cytotoxic
Lineaweaver 1985 [53]	In vitro	1% PVP-I , 0.5% sodium hypochlorite, 0.25% acetic acid, and 3% hydrogen peroxide on human cells and bacteria	All 4 antiseptics were toxic at full strength
Liu 2017 [57]	In vitro	Human primary osteoblasts, fibroblasts, and myoblasts were expanded in cell culture and subjected to various concentrations of PVP-I (0%, 0.001%, 0.01%, 0.1%, 0.35%, 1%) for 3 min, followed by a scratch assay to assess the effect of PVP-I on cell migration	Clinically used concentration of PVP-I (0.35%) was found to be cytotoxic to osteoblasts, fibroblasts, and myoblasts in vitro
McKenna 1991 [31]	In vitro	0.005% sodium hypochlorite, 0.001% PVP-I, 0.0025% acetic acid, and 0.003% hydrogen peroxide for effectiveness against common wound isolates without compromising fibroblasts and leukocyte function	Bactericidal activity of all agents with the exception of 0.005% sodium hypochlorite was compromised at reduced levels that maintained fibroblast activity

Table 1 (continued)

First author, year	Wound type	Study parameters	Result
McLure 1992 [32]	In vitro	PVP-I and chlorhexidine against 33 clinical isolates of MRSA	PVP-I demonstrated a superior killing effect whether measured by rate of kill or final logarithmic reduction factors (LRF) achieved; the mean LRF (measure of bactericidal potency) achieved over all dilutions, times, and strains were higher for PVP-I vs. chlorhexidine
Norman 2016 [58]	Pressure ulcers	Systematic review which included randomized controlled trials enrolling patients with pressure ulcers assessing PVP-I, cadexomer iodine, gentian violet, lysozyme, silver dressings, honey, pine resin, polyhexanide, silver sulfadiazine, and nitrofurazone with ethoxy-diaminoacridine	Some moderate- and low-quality evidence that fewer ulcers may heal in the short term when treated with PVP-I vs. nonantimicrobial alternatives
O'Meara 2014 [59]	Venous ulcers	Systematic review which included randomized controlled trials enrolling patients with venous leg ulcers, evaluating at least one systemic antibiotic, topical antibiotic, or topical antiseptic that reported an objective assessment of wound healing	No between-group differences in complete healing were found when PVP-I was compared with hydrocolloid, moist or foam dressings according to wound status, and growth factor
Piérard-Franchimont 2002 [54]	Venous ulcers	15 patients (2 venous ulcers per patient); treatment with hydrocolloid dressing alone or in combination with PVP-I	Increase in wound healing rates in the hydrocolloid + PVP-I group
Privitera 2017 [60]	Surgical site infections	Systematic review of preoperative antisepsis with the primary end point of incidence of surgical site infection and secondary skin bacterial colonization; chlorhexidine vs. iodine	Moderate-quality evidence supporting the use of chlorhexidine for preoperative skin antisepsis and high-quality evidence that the use of chlorhexidine is associated with fewer positive skin cultures, compared with PVP-I
Rodeheaver 1982 [7]	In vitro	Comparison of bactericidal activity of aqueous iodine, PVP-I solution, PVP-I surgical scrub, and normal saline (control)	The bactericidal activity of PVP-I solution and scrub was inferior to that of aqueous iodine
Sindelar 1979 [38]	Surgical wounds	Surgical wounds irrigated with PVP-I (242 wounds) or saline (258 wounds)	Wound infection rates decreased in the PVP-I group
Shukrimi 2008 [61]	Diabetic foot ulcer	30 patients with diabetic foot ulcers; honey dressing vs. controlled dressing group (PVP-I followed by normal saline)	Ulcer healing was not significantly different in both study groups
Vehmeyer-Heeman 2005 [55]	Freshly grafted burn wounds	PVP-I vs. Vaseline gauze	PVP-I did not prolong the healing time; bacterial colonization of PVP-I group was lower than the control group
Viljanto 1980 [39]	Surgical wounds	294 pediatric surgical wounds; treatment with 5% PVP-I, 1% PVP-I, or saline (control)	Wound healing unaffected in all groups; decrease in infection (2.6%) with 1% PVP-I vs. 8.5% of control; increase in infection (19%) with 5% PVP-I vs. 8% of control
Woo 2014 [43]	Chronic wounds (diabetic/venous/arterial/pressure ulcers)	Chart review; 33 patients	29% of the wounds achieved full closure and 45% achieved partial closure within 6 months of regular topical PVP-I application; results indicate that PVP-I is appropriate for routine management of nonhealable and maintenance wounds

been reports of patients developing systemic iodine toxicity from wounds dressed with gauze soaked in PVP-I or when PVP-I solution was used as a continuous wound irrigant [62]. The use of PVP-I in children with a higher skin surface area per body weight and less developed skin barrier could also lead to increased penetration and systemic absorption.

Another concern with PVP-I appears to be the reduced activity reported in the presence of certain proteins in wound exudates or body fluids [71]. It is postulated that this could be due to the masking and inactivation of the iodine in the presence of organic matter in the wounds. This could potentially be a limiting factor in the activity of PVP-I. However, further studies to evaluate this in greater detail are required.

Discussion

Role of PVP-I in Wound Management in Asia

In Asia, PVP-I is widely used and the perception of PVP-I in health care practitioners centers on its effica-

Table 2. Uses of povidone iodine (PVP-I) in Asia

Type of wound	Concentration and formulation of PVP-I	Remarks
Diabetic ulcer – dry	10% ointment or solution	
Diabetic ulcer – moist	10% spray or solution	
Venous ulcers		
Pre- and postoperative skin cleansing	10% solution	
Coating fixtures or pins protruding from surgical surfaces	10% solution	
Candida growth in between toenails	10% solution	
Small surface area burns	10% solution	Bath and rinse-off
Large surface area burns	7.5% scrub	Rinse-off after application
Skin trauma, abrasions, and lacerations	7.5% antiseptic wash or 10% solution	

cy, ease of use, and availability is good. PVP-I has been available in the region for several decades, but is still used primarily for acute wounds and not very commonly for chronic wounds. There is a need for a formulation of PVP-I that would last for a longer time for use in chronic wounds. Some members of the AWG report good results with PVP-I in chronic wounds, with daily dressing changes.

Studies reporting toxicity of PVP-I remain at the back of the minds of health care practitioners. While there is no doubt regarding the efficacy of PVP-I, the concentration required for different types of wounds and the recommended contact time with the tissue continue to remain contentious. Given the conflicting reports about cytotoxicity with PVP-I, the AWG reiterates that the only aspects of toxicity that may be of concern are systemic effects due to absorption and local tissue toxicity. It is generally believed that absorption from large surface area wounds may lead to systemic toxicity. According to the AWG, this concern can be addressed by limiting the contact time of PVP-I on large surface area wounds, such as large burns. Furthermore, in the clinical experience of the AWG, PVP-I causes no problems when used in a concentration appropriate for the type of wound. There is a need to educate clinicians on the different formulations of PVP-I, such as ointments and solutions, which are diluted to concentrations appropriate for antisepsis without being cytotoxic.

In Asia, as in the rest of the world, antibiotic resistance is showing a rising trend [12, 27]. The AWG notes that antibiotic overuse is rampant in the region and contributes to the development of resistant strains. In this scenario, PVP-I, which has been in use for a long time without the development of resistance, becomes an important measure for antisepsis.

PVP-I is available in a range of antiseptic formulations – the most commonly used in the Asian region is the 10% aqueous/alcoholic solution. PVP-I is also available as a 7.5% surgical scrub, a 2.5% dry powder spray, and a 10% ointment. Some of the common clinical uses of PVP-I in Asia, as discussed by the AWG, are listed in Table 2.

PVP-I in Wound Care Management in Asia: A Consensus

The members of the AWG considered the literature available for PVP-I, in conjunction with their own clinical experience of using PVP-I in the management of wounds, to postulate consensus statements to guide the use of PVP-I in an Asian context.

The AWG believes and reiterates that there are no questions about the efficacy of PVP-I. It is fairly well accepted in the Asia-Pacific region that PVP-I is efficacious, with a broad spectrum of activity and demonstrated activity against biofilms, with no risk of resistance. However, concerns of cytotoxicity have yet to be addressed adequately. It is noteworthy that the pronounced cytotoxicity demonstrated in certain in vitro studies has not been confirmed in human studies, where PVP-I has been found to be safe in appropriate concentrations. The concentration and formulation of PVP-I has to be tailored and personalized according to the area and location (skin, mucus membranes) of application, skin condition, indication of use, and microbial load. It is important to know and understand the various formulations and concentrations of PVP-I and to adapt them to the scope of application. This necessitates access to updated information and regular training.

Table 3. Elements for designing studies evaluating the toxicology of antiseptics

Studies should compare various antiseptics with regard to their toxicology in relation to the antimicrobial efficacy; toxicology and efficacy tests should be performed at comparable concentrations of the antiseptics and with comparable additives (e.g., with or without alcohol)
For discussing the toxicology of antiseptics, in vivo studies are more relevant compared with in vitro studies
In an in vitro environment, studies in 3-dimensional cultures are more valuable than those in 2-dimensional cultures In vitro absorption and distribution of the compounds in the wound models should be evaluated with greater resolution Composition and formulations of the study compounds should be taken into account while making comparisons between antiseptics The methodology used for dilution of antiseptics should be defined and standardized, and equivalent concentration of the study compounds should be used
All parameters measuring cytotoxicity of antiseptics must be clearly defined – robust markers of cell survival should be used, rather than surrogate markers
In vitro and in vivo study results should be cross-validated with the results seen in a clinical environment

Table 4. Consensus statements for PVP-I

(E, CP) The concentration of the active ingredient as well as formulation is important for the efficacy of antiseptics There is a lack of evidence around the concentration and formulation of antiseptics to be used in different kinds of wounds, especially in relation to locally made, readily available formulations
(E) PVP-I is an effective antimicrobial with a broad spectrum of activity with no known resistance; (E) PVP-I shows efficacy against biofilms, particularly in prevention
(E, CP) Systemic absorption of PVP-I is low, but caution should be used when using on large surface area wounds
(E, CP) PVP-I activity may be reduced in the presence of certain proteins in wound exudate/body fluids; application may need to be more frequent in these situations
(CP) The color/staining is not always an issue for the patients, families, or physicians
(E, CP) PVP-I is well tolerated with no reported allergy and rare adverse drug reactions If a patient reports iodine allergy/intolerance, then it should be avoided or an allergy test to PVP-I performed (E) PVP-I is contraindicated in patients with a proven allergy and in those with hyperthyroidism/thyroid cancer; it should be used with caution in pregnant and lactating women and infants
(E) There are contradictory observations on the cytotoxicity of PVP-I in clinical practice and experimental studies (animal and cellular models)
New standardized and clinically relevant studies using in vitro and in vivo models, and novel noninvasive measurements, comparing antimicrobial efficacy and toxicology are required Studies investigating the long-term efficacy of PVP-I will be useful for the clinic Education around the use of iodine-based antimicrobial agents can be improved with more recent evidence
E, evidence; CP, clinical practice.

In an era of growing issues with antibiotic resistance, antiseptics (including PVP-I) are important viable alternatives; they do not lead to the development of drug-resistant bacteria and have a broader antimicrobial spectrum. Additionally, to combat the growing menace of antimicrobial resistance, the AWG recommends a more aggressive and methodical adoption of Antibiotic Stewardship Programs (ASPs) in the Asian region. The inter-

ventions in an ASP are targeted towards improving and monitoring appropriate antimicrobial use [72, 73].

Given the wide disparity in the experimental settings evaluating the efficacy and safety of antiseptics as well as the conflicting results observed over the years, the AWG believes that new standardized and clinically relevant studies, using in vitro and in vivo models, along with novel noninvasive measurement systems, to compare antimicrobial efficacy and toxicology are the need of the day. Some tools to study in vitro and in vivo absorption and distribution of various compounds in wounds, which are currently being investigated, include in vitro skin-on-a-chip microfluidics and in vivo Raman spectroscopy and photoacoustics [74]. The differences in the study parameters under evaluation – assessment times, antiseptic concentrations and formulations, and the wound models – impact the results of the studies and should be carefully considered when arriving at conclusions. While in vivo studies are more relevant than in vitro studies, overall the research should be focused at comparing various antiseptics with regard to their toxicology in relation to the antimicrobial efficacy. Some of the elements that should be considered in designing toxicology research are listed in Table 3.

The AWG has developed consensus statements for PVP-I based on the evidence reviewed and their discussions (Table 4). These consensus statements are based on a critical appraisal of evidence for PVP-I available in the literature, albeit from in vitro and in vivo animal research, as well as the experience and opinion of the members of AWG of using PVP-I and other antiseptics in their clinical practice. These statements will not only support clinicians in Asia in making decisions for wound management, but could potentially guide future research in the field of antiseptics.

Conclusion

The use of PVP-I as an effective and safe antiseptic to prevent and address the bioburden in wounds is supported by several in vitro and in vivo studies. It has a broad spectrum of activity, the ability to penetrate biofilms, and a lack of development of bacterial resistance. Although PVP-I is used globally, questions about allergy and cytotoxicity are often raised based on data from in vitro cellular or in vivo animal studies. Furthermore, evidence from research investigating the comparative efficacy of antiseptics is limited by the disparity in elements such as the study design, the wound model, and the formulation and concentration of the antiseptics evaluated. Additional well-designed clinical studies in human wounds could potentially provide further evidence for the efficacy and safety of PVP-I.

Key Message

The Asian Working Group presents consensus statements for povidone iodine based on evidence and their experience.

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Disclosure Statement

Paul Bigliardi has given presentations for Mundipharma GmbH and has received some support for an investigator-initiated clinical trial comparing a Mundipharma iodine product with silver dressing. Stefan Langer has given presentations for Mundipharma GmbH, Germany, and has received support for preclinical studies with Mundipharma research products. Jose Joven Cruz, Sang Wha Kim, Harikrishna Nair, and Gulapar Srisawasdi report no conflicts of interest.

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