WHAM Evidence summary: Wound infection: Iodophors

Wound Healing and Management Collaborative, 2014

CLINICAL QUESTIONS

What is the best available evidence on the effectiveness of iodophors in the management of wounds?

KEYWORDS

Povidone iodine, PVP-I, cadexomer iodine, iodophor

SUMMARY

Iodine preparations (iodophors) are a low cost option for providing topical antimicrobial treatment to superficial and shallow-depth wounds. Although there is conflicting evidence on their effectiveness, the majority of findings indicate that they play a favorable role in reducing wound bio-burden (particularly *S. aureus*) and there is some evidence that iodine enhances angiogenesis and modulates white cell activity.[1-3] Although iodophors are not appropriate for all patients their appropriate use is not associated with a significant increase in adverse reactions in clinical trials.[3]

CLINICAL PRACTICE RECOMMENDATIONS

All recommendations should be applied with consideration to the wound, the person, the health professional and the clinical context:

Cadexomer iodine is an effective topical agent for promoting wound healing and reducing bio-burden in individuals over the age of 12 with no contra-indications for the use of iodine (Grade A).

Povidone iodine could be used for promoting wound healing and reducing bio-burden, particularly when due to *S. aureus,* in adults and children over the age of six months with no contra-indications for the use of iodine. (Grade B)

SOURCES OF EVIDENCE

This summary was conducted using methods published by the Joanna Briggs Institute.[4-7] This evidence summary is based on a structured database search using variations of search terms related to wound management and iodophors. Searches were conducted in EMBASE, Medline, AMED and the Cochrane Library for evidence from 1990 to August 2014 in English. Levels of evidence for intervention studies are reported in the table below.

BACKGROUND

Iodophors are complexes of elemental iodine with a surfactant and they are used to decrease wound surface bacteria. A surfactant is a solubilizing agent that reduces surface tension of a liquid (in this case, iodine). Iodine delivered within an iodophor has increased solubility which allows it to be released to the wound bed in a slow, sustained and controlled manner.[8-10] In addition to stabilizing elemental iodine, iodophors retain iodine's antimicrobial properties while reducing its side effects (e.g. allergic reactions,

Table 1: Sources of evidence and the level

Level 1 Evidence	Level 2 Evidence	Level 3 Evidence	Level 4 Evidence	Level 5 Evidence
Experimental Designs	**Quasi-experimental Designs**	**Observational – Analytic Designs**	**Observational – Descriptive Studies**	**Expert Opinion/ Bench Research**
1.a Systematic review of RCTs[1-3, 11] 1.c RCT[12-15]	2.c Quasi-experimental prospectively controlled study[16]	3.e Observational study without a control group	4.c Case series	5.c Expert opinion[8-10, 17-20] 5.c Bench research[16, 21-26]

pain upon application to open wounds and irritation to tissue).[8-10] The two iodophors most commonly used in wound management are povidone iodine (PVP-I) and cadexomer iodine.

CLINICAL EVIDENCE: POVIDONE IODINE

Povidone iodine is available as a solution (alcohol or water based), cream, ointment, spray and impregnated in dressing products.[9, 10] It is used as both a cleanser/irrigant and as a topical dressing agent.[2]

Povidone iodine needs to be re-applied at regular intervals to ensure that a consistent supply of iodine is available to the wound bed. The re-application rate of PVP-I will depend upon a number of factors related to the patient, wound characteristics and the environment[10] (*Level 5*).

Types of wounds treated in the research

The application of PVP-I is usually considered for:[10] (*Level 5)*

- clinically infected wounds;
- chronic wounds with suspected biofilm; and
- an infection prevention measure when there is a risk of infection such as: minor burns and in superficial skin-loss wounds (e.g., graft sites, injuries).

Toxicity profile of povidone iodine

In-vitro studies[17, 23] have shown PVP-I concentrations above 0.05% are toxic to granulocytes and concentrations above 1% are completely toxic (*Level 5*). Histological examination of chronic leg ulcers treated with 10% PVP-I showed decrease in micro vessels, neutrophils, fibroblasts and dedrocytes[15] (*Level 1*). Despite this, animal and clinical studies have shown no reduction in healing rates for wounds treated with up to 10% PVP-I compared with normal saline,[15-17] suggesting that the toxicity observed in-vitro may not be of clinical relevance with topical application[9, 17] (*Levels 1, 2 and 5*).

Effectiveness in promoting healing

It is reported that PVP-I enhances angiogenesis [21, 26]and contributes to wound healing through activating monocyte, T-lymphocyte and macrophage activity.[25] Relevant evidence on the effectiveness of PVP-I in promoting wound healing is summarised below.

One systematic review[3] including 19 randomised controlled trials (RCTs) in which PVP-I preparations were generally superior to controls (paraffin gauze, hydrocolloid dressings, other antibacterial preparations) for a variety of measures of wound healing[3] (*Level 1*).

Another systematic review[2] concluded that further good quality research is required before definitive conclusions can be drawn about the effectiveness of povidone-iodine in healing venous leg ulcers[2] (*Level 1*).

A small trial[16] (n = 40) in which there was no significant difference in mean time to complete healing between graft sites treated with 10% PVP-I and saline (9.3 days versus 9.5 days), and also no difference compared with acetic acid or hydrogen peroxide[16] (*Level 2*).

A small split-body RCT[15] (n = 17) in which there was a significant ($p < 0.01$) reduction in mean time to complete healing between chronic leg ulcers treated with 10% PVP-I (11 weeks; 95% confidence interval [CI] 9 to 17) and those treated with normal saline (18 weeks, 95% CI 11 to 24)[15] (*Level 1*).

Small animal and clinical studies reported to have shown no reduction in wound healing rates associated with up to 10% PVP-I compared with saline, silver sulfadiazine or no topical agent[14, 17, 19] (*Levels 1and 5*).

Effectiveness of povidone iodine in reducing bacterial contamination

The evidence on effectiveness of PVP-I in reducing bacterial contamination of wounds is mixed and likely relates to the concentration of preparations, condition of wounds and frequency of PVP-I application. The evidence is summarised below.

One descriptive systematic review[3] reported mixed findings in 19 RCTs regarding the efficacy of PVP-I preparations for reducing bacterial load or preventing infection in leg ulcers, pressure injuries, acute surgical wounds, burns and skin graft sites[3] (*Level 1*).

At low concentrations, PVP-I was ineffective in significantly reducing colonies of *E. coli*,[24] *Acinetobacter* spp,[22] *Klebsiella* spp[17] or *P. aeruginosa*[22] in laboratory conditions (*Level 5*). Other *in-vitro* studies are reported to have found PVP-I was active against gram negative rods; however, PVP-I concentrations were not reported[18] (*Level 5*). Other *in-vitro* studies have shown PVP-I is active against *S. aureus* at concentrations of 0.001%[22, 24] and 0.005%[17] (*Level 5*).

Pooled results[11] from two RCTs (n = 71) comparing clinical infection rates in contaminated wounds cleansed with 1% PVP-I to those cleansed with saline found a

small but significant effect for PVP-I (odds ratio 0.15, 95% CI 0.05 to 0.43, p=0.0004)[11] (*Level 1*).

In two clinical studies in which PVP-I (applied 6 hourly) was compared to saline for reducing infection rates in pressure injuries and acute wounds, there was no significant differences in rate of clinical infection.[17]

CLINICAL EVIDENCE: CADEXOMER IODINE

Cadexomer iodine is a polysaccharide and iodine complex which slows and sustains the release of iodine and is reportedly less toxic to fibroblasts. Cadexomer iodine is also reported to increase wound epithelialization and reduce symptoms associated with infection (including inflammation, exudate and pain). It is available as a powder, paste or dressing.[10]

Types of wounds treated in the research

The majority of research on the effectiveness of cadexomer iodine has been conducted in venous leg ulcers (VLUs).[1, 2, 13] It is often considered for use in cavity wounds.[10]

Effectiveness of cadexomer iodine in reducing bacterial contamination

One RCT found a significant reduction in colonization with *S aureus* in VLUs treated with compression and cadexomer iodine compared with compression alone (RR 31.31, 95% CI 1.95 to 503.29, p=0.015).[2] There was also a reduction in *P. aeruginosa* colonies (*Level 1*).

Another review[1] reported an RCT reported no significant difference in bacterial burden in wounds treated with cadexomer iodine, or that healing rates appeared unrelated to elimination of bacteria[1] (*Level 1*).

Effectiveness of cadexomer iodine in promoting healing

Pooled results[2] from two RCTs (n = 132) showed cadexomer iodine and compression was superior to compression alone in achieving complete healing in VLUs (RR 6.72, 95% CI 1.56 to 28.95)[2] (*Level 1*).

In four RCTs comparing cadexomer iodine with standard care for treating VLUs, three reported statistically significant improved healing ($p < 0.05$) for cadexomer iodine across a variety of wound healing measures[1, 2] (*Level 1*).

One large (n = 281) non-blinded RCT[12, 13] found a significant difference in wound healing associated with the use of nanocrystalline silver as compared with cadexomer iodine in the first 2 weeks of treatment when nil or low levels of leukocytes, gram positive bacilli, gram positive cocci or gram negative cocci were reported[12, 13] (*Level 1*).

CONSIDERATIONS FOR USE

Adverse effects and risk management for iodophors

One systematic review reporting 27 RCTs found no substantial difference in adverse reactions between iodine and other methods of local care. No major adverse events were reported[3] (*Level 1*) .

Although its use is not recommended for patients with a history of thyroid disorders, some clinical trials have included monitoring of participants' thyroid functioning and reported no changes[10] (*Level 3*).

Iodine should not be used with patients who have the following conditions[9, 10] (*Level 5*):

- known or suspected sensitivity to iodine;
- impaired renal function;
- in the presence of thyroid disorders unless reviewed and approved by a medical practitioner;
- pregnancy or breast-feeding;
- povidone iodine should not be used in newborns and infants less than 6 months of age and cadexomer iodine not recommended in children under 12 years of age;[20]
- extensive burns to the body; or
- before and after treatment with radio-iodine until permanent healing has been achieved.

Other considerations

In two trials in which cost effectiveness was an outcome measure, a course of treatment with PVP-I cost substantially less than other standard treatments. Cadexomer iodine was more expensive[3] (*Level 1*).

CONFLICTS OF INTEREST

The author declares no conflicts of interest in accordance with International Committee of Medical Journal Editors (ICMJE) standards.

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ABOUT WHAM EVIDENCE SUMMARIES

WHAM evidence summaries are consistent with methodology published in

Munn Z, Lockwood C, Moola S. The development and use of evidence summaries for point of care information systems: A streamlined rapid review approach, Worldviews Evid Based Nurs. 2015;12(3):131-8.

Methods are provided in detail in resources published by the Joanna Briggs Institute as cited in this evidence summary. WHAM evidence summaries undergo peer-review by an international review panel. More information is available on the WHAM website: https://www.whamwounds.com/ .

WHAM evidence summaries provide a summary of the best available evidence on specific topics and make suggestions that can be used to inform clinical practice. Evidence contained within this summary should be evaluated by appropriately trained professionals with expertise in wound prevention and management, and the evidence should be considered in the context of the individual, the professional, the clinical setting and other relevant clinical information.

PUBLICATION

This evidence summary has been published in Wound Practice and Research:

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