Evidence Summary: Wound Infection: Iodophors

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Author
Wound Healing and Management Node Group

QUESTION

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

CLINICAL BOTTOM LINE

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 favourable 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 (see Risk Management section) their appropriate use is not associated with a significant increase in adverse reactions in clinical trials.[1]

BACKGROUND

Iodophors are complexes of elemental iodine with a surfactant and they are used to decrease wound surface bacteria. A surfactant is a solubilising 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.[4-6] In addition to stabilising elemental iodine, iodophors retain iodine's antimicrobial properties while reducing its side effects (e.g. allergic reactions, pain upon application to open wounds and irritation to tissue).[4-6] The two iodophors commonly used in wound management are povidone iodine (PVP-I) and cadexomer iodine.

POVIDONE IODINE

Povidone iodine is available as a solution (alcohol or water based), cream, ointment, spray and impregnated in dressing products.[4,5] It is used as both a cleanser/irrigant and as a topical dressing agent.[3]

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[5] (Level IV).

Types of wounds

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

- 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

- In-vitro studies have shown PVP-I concentrations above 0.05% are toxic to granulocytes and concentrations above 1% are completely toxic.[7,8] (Level II and IV)
- Histological examination of chronic leg ulcers treated with 10% PVP-I showed decrease in micro vessels, neutrophils, fibroblasts and dedrocytes.[9] (Level II)
- 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,[7,9 13] suggesting that the toxicity observed in-vitro may not be of clinical relevance with topical application.[4, 7] (Level III and IV)

Effectiveness in promoting healing

It is reported that PVP-I enhances angiogenesis[10,11] and contributes to wound healing through activating monocyte, T-lymphocyte and macrophage activity.[12] Relevant evidence on the effectiveness of PVP-I in promoting wound healing includes:

- One systematic review 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.[1] (Level I)
- A small trial (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.[13] (Level III)
- A small split-body RCT (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).[9] (Level II)

- 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.[7,14, 15] (Level II and IV)

Effectiveness 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 includes:

- One descriptive systematic review 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.[1] (Level I)
- At low concentrations PVP-I was ineffective in significantly reducing colonies of *E. coli*,[16] *Acinetobacter spp*,[17] *Klebsiella spp*[17] or *P. aeruginosa*[17] in laboratory conditions. (Level III)
- 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 IV)
- In-vitro studies have shown PVP-I is active against *S. aureus* at concentrations of 0.001% and[16,17] and 0.005%.[7] (Level III and IV)
- Pooled results 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).[19] (Level I)
- In two 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 difference in rate of clinical infection.[7] (Level IV)
- A systematic review 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.[3]

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 epithelialisation and reduce symptoms associated with infection (including inflammation, exudate and pain). It is available as a powder, paste or dressing.[5]

Types of wounds

The majority of research on the effectiveness of cadexomer iodine was conducted in venous leg ulcers (VLUs).[2,3, 20] It is often considered for use in cavity wounds.[5]

Effectiveness in reducing bacterial contamination

- One RCT found a significant reduction in colonisation 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).[3] There was also a reduction in P. aeruginosa colonies.[2] (Level I)
- Other RCTs have reported no significant difference in bacterial burden in wounds treated with cadexomer iodine, or that healing rates appeared unrelated to elimination of bacteria.[2] (Level I)

Effectiveness in promoting healing

- Pooled results from 2 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).[3] (Level I)
- In 4 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.[2,3] (Level I)
- One large (n=281) non-blinded RCT 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.[20, 21] (Level II)

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.[1] (Level I)

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.[5] (Level IV)

Iodine should not be used with patients who have the following conditions:[4,5] (Level IV)

- known or suspected sensitivity to iodine;
- impaired renal function;
- 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;[22]
- 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.[1] (Level I)

CHARACTERISTICS OF THE EVIDENCE

This evidence summary is based on a structured literature and database search combining search terms that describe wound management and iodophors. The evidence in this summary comes from:

- Four systematic reviews of RCTs,[1,2,3, 19] including one in which review of harmful effects of iodine was a specific goal[1] (Level I)
- Small non-blinded RCTs[9,15,20, 21] (Level II)
- In-vitro micro culture, sensitivity (MC&S) and tissue toxicity studies[8,13,16,17] (Level III)
- Discussion papers providing non-systematic reviews of evi dence[4,5,6,7,10,11,12,14,18,22] (Level IV)

BEST PRACTICE RECOMMENDATIONS

- Cadexomer iodine is an effective topical agent for promoting wound healing and reducing bio-burden. (Grade A)
- Povidone iodine could be considered for promoting wound healing and reducing bio-burden, particularly when due to *S. aureus*. (Grade B)

NB: RELATED TOPICS:

JBI Evidence Summary ID7020 Wound infection: biofilms defined and described.

JBI Evidence Summary ID 7369 Wound infection: biofilms and iodophors

JBI Evidence Summary ID7368 Wound infection: silver products and biofilms

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KEYWORDS

Povidone iodine; PVP-I; cadexomer iodine; iodine; iodophor