Clinicians have used numerous strategies to combat wound infections, including topical and systemic administration of antibiotics, and various antiseptic agents such as hypochlorite (bleach) and hydrogen peroxide have been placed on wounds to kill bacteria or inhibit their growth. A commonly used antimicrobial agent is povidone-iodine (Betadine®), a complex of iodine, the bactericidal component, with polyvinylpyrrolidone (povidone), a synthetic polymer. The most common commercial form is a 10% solution in water yielding 1% available iodine. Povidone-iodine is available as a surgical scrub or skin cleanser with a detergent base (0.75% available iodine) or in other forms.

Decisions regarding choice of wound treatment involve two basic considerations: (1) how safe is the treatment, and (2) how effective is the treatment. The safety of a wound care treatment may be determined by whether the treatment retards the progress of the wound through the stages of healing (inflammatory, proliferative/reepithelializing, and remodeling). The efficacy of a wound care treatment (eg, povidone-iodine) can be judged in vitro by its ability to kill microorganisms and in vivo by whether it decreases the rate or severity of wound infection. The task of evaluating the choice of povidone-iodine solution for treatment of wounds, especially the chronic wounds most often seen in physical therapy practice, is made complex by two factors. First, although there is a large body of research into various aspects of povidone-iodine use in wound care, the results are not always germane to the types of wound treatment most often provided by physical therapists. The relevance of in vitro studies regarding safety and effectiveness to in vivo use with patients may be limited. Much of the published research on wound healing uses animal wound models; however, the applicability of findings in animal studies to human wounds has been questioned.


**Key Words:** Povidone-iodine, Topical disinfectants, Wound care.

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The second factor complicating decisions about using povidone-iodine is that it may be used in a variety of ways. Wounds may be irrigated or soaked once or repeatedly with povidone-iodine solution. Povidone-iodine solution also can be applied for longer periods as part of the dressing. There are no studies comparing the effects of these methods. Povidone-iodine solution also may be used full strength (10%) or diluted to any desired concentration prior to use. Research results should be interpreted based on the specifics of the application used.

Recent positions taken by two federal agencies—the Food and Drug Administration (FDA) and the Agency for Health Care Policy and Research (AHCPR)—have implications for the use of povidone-iodine solution in wound treatment. The FDA has approved povidone-iodine for use in nonprescription first-aid antiseptic products.* Use of the term “first aid” implies that povidone-iodine can be used for short-term treatment (approximately 1 week) and on relatively superficial and acute wounds. In assessing the evidence regarding use of povidone-iodine, the FDA report states:

Controlled studies on wound healing were conducted in animals and humans and involved various types of dermal wounds. Both superficial and deeper wounds were studied with a contralateral control. Results showed that there were no statistically significant differences in mean healing times between any of the treatment groups and their controls. In addition, microscopic analysis showed no differences in wound healing in the groups studied. These pathological and histological studies did not indicate any deleterious effect of povidone-iodine on wound healing. However, there was also no evidence demonstrating that povidone-iodine might aid wound healing.2

The AHCPR has published guidelines for treatment of pressure ulcers.3 These guidelines state, “Do not clean ulcer wounds with skin cleansers or antiseptic agents (eg, povidone-iodine, iodophor, sodium hypochlorite solution [Dakin's solution], hydrogen peroxide, acetic acid).” Due to the stature of the AHCPR, as well as the strong proscriptive wording, the guidelines may be used in future liability actions where pressure ulcers were treated with povidone-iodine. Murphy argues that clinicians will be held accountable to the guidelines as “the most effective and appropriate standard of care based on current and exhaustive scientific research and available evidence.”4(p30) Murphy believes that if treatment is not in accordance with the guidelines, clinicians must document why. The implication here is that use of povidone-iodine, as well as other antiseptic agents, can no longer be considered a customary treatment for pressure ulcers. Although the guidelines are directly applicable only to pressure ulcers, the evidence on which they are based appears to be applicable to all wound treatments involving povidone-iodine. This update will examine the research evidence regarding the safety and efficacy of povidone-iodine solutions in preventing infections and in promoting wound healing.

Two basic considerations guide decisions regarding choice of wound treatment: safety and effectiveness. The FDA has issued no position statement on povidone-iodine use for prolonged periods or in treating chronic wounds.

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Safety

Wound healing is a complex process involving many physiological events. Immunological resources are recruited to fight infection and debride damaged tissue. Blood supply in the healing area is reestablished (angiogenesis). Regeneration of tissue (cell proliferation, fibroplasia) follows, replacing damaged or destroyed tissue. The area to be healed is decreased via wound contraction. Closure of the wound is achieved through epithelial cell migration. Finally, remodeling of scar tissue occurs to approximate prior appearance and function. A safe treatment should promote, or at least not impair, this process.

In Vitro Studies

Researchers have examined the effect of povidone-iodine on several of the cellular components of the wound healing mechanism. Van Den Broek and coworkers found povidone-iodine solution at concentrations greater than 0.05% to be toxic to granulocytes; monocytes showed some effects of toxicity at concentrations above 0.05% and complete toxicity at concentrations above 1%. Tatnall and colleagues found concentrations of povidone-iodine greater than 0.004% to be 100% toxic to keratinocytes. Lineaweaver et al identified 0.05% as a safe concentration of povidone-iodine for fibroblasts; higher concentrations (including the 10% concentration that is commonly used in clinical practice) were 100% cytotoxic. These studies show that in vitro povidone-iodine, unless it is diluted to a far lower concentration than that commonly used in clinical settings, is toxic to all of the cell types that are essential to the healing process.

In Vivo Studies

Lineaweaver et al irrigated surgically induced wounds in rats with several solutions, including saline and 1% povidone-iodine, three times daily. At 4 days postsurgery, tensile strength in the wounds treated with povidone-iodine was only 21% that of the wounds treated with saline. There were no differences at 8, 12, or 16 days postsurgery, despite continued irrigation. Epithelialization was found to be delayed in the wounds treated with povidone-iodine at 4 and 8 days postsurgery, but not thereafter.

Bränemark et al used a microwound in the cheek pouch of a hamster as a model to investigate the effects of povidone-iodine on microcirculation. Exposure for 60 minutes to 1% povidone-iodine solution resulted in cessation of blood flow in surface capillaries. Circulation did not resume within 1 hour. No alteration in blood flow was found with exposure to 1% povidone-iodine solution for 5 minutes, nor was any alteration of blood flow in capillaries covered with epithelial tissue found with exposure to 1% povidone-iodine solution for 60 minutes. No circulatory changes were seen in the cheek pouches of control hamsters in which the wounds were treated with saline. Brennan and Leaper created wounds in rabbit ears. The wounds were enclosed in a plastic chamber. When the wounds were fully granulated, they were “flooded” with saline or one of several antiseptic solutions, including 5% and 1% povidone-iodine. Brennan and Leaper did not clearly state how long the solution remained in contact with the wound. They inspected the wounds microscopically to examine the effects of the test solutions on the microcirculation in the granulation tissue. Saline had “little or no effect” on the blood flow. The 1% povidone-iodine solution gave similar results. With the 5% povidone-iodine solution, however, there was cessation of blood flow in the granulation tissue, which did not fully recover for 72 hours. Bränemark and colleagues examined the effects of disinfectants on microcirculation in wounds to connective, synovial, and nerve tissue in mice, hamsters, and rabbits as well as dermal tissue in humans. The findings, based on qualitative evaluation using vital micrography, electron micrography, and vital angiography showed “a very slight reaction” in wound microcirculation when exposed to a 1% solution of povidone-iodine. Bränemark and colleagues commented that other disinfectants produced a much greater reaction.

Hughes-Papsidero and Levine exposed the carotid artery and vagus nerve in wound beds of rabbits. Wounds were kept open until the arteries were 100% covered with granulation tissue. One group of rabbits received daily topical application of saline, and a second group of rabbits received daily topical application of 10% povidone-iodine. The wounds in both groups were treated identically except for the topical agent that was used. No differences in rate of healing were found between the groups, nor was any damage to arterial tissue identified.

Kjolseth and coworkers compared the effects of bacitracin (500 U/g), silver nitrate (0.5%), silver sulfadiazine (1%), mafenide acetate (8.5%), and povidone-iodine (10%) on two measures of healing in full-thickness wounds in mouse ears. The test substances were applied once daily to the wounds and covered with a dressing. Wounds treated with povidone-iodine required more time to epithelialize (11.8 ± 0.55 days) than did controls (7.2 ± 0.7 days) or wounds treated with silver sulfadiazine (7.1 ± 0.3 days) or mafenide acetate (7.3 ± 0.3 days). Interestingly, the wounds treated with povidone-iodine showed complete neovascularization in less time (15.0 ± 0.4 days) than the wounds treated with the other topical agents (range: 15.3 ± 0.7 to 18.4 ± 0.56 days).

Gruber et al compared times to complete wound epithelialization in both partial-thickness and full-thickness wounds.
wounds in rats. Wounds were treated by applying hydrogen peroxide (3%), povidone-iodine, acetic acid (0.25%), or saline (control) to the surface of the wound four times daily. Healing times for the wounds treated with povidone-iodine or saline were not different. In an additional experiment, split-thickness skin graft donor sites in humans were treated with the same antiseptics or saline by application with cotton blotters four times daily. Again, no differences in the time to epithelialization (pink surface free of scabs) was found between wounds treated with saline or povidone-iodine. Gruber et al did not specify the concentration of povidone-iodine used in their study; it is identified as “Betadine” and therefore is probably the commercially available 10% stock solution.

Despite the cytotoxicity documented in in vitro studies, the results of in vivo studies seem to suggest that povidone-iodine does not interfere with healing, especially if it is used at concentrations of 1% or lower. Povidone-iodine may temporarily decrease blood flow in the wound bed at higher concentrations, as shown by Brennan and Leaper, but concentrations of 1% or less do not appear to have this effect. The effects of repeated use of povidone-iodine solution on microcirculation have not been investigated. All of the above studies used healthy animal or human subjects with acute, surgically induced wounds.

Systemic Toxicity
Patients have developed systemic iodine toxicity as a result of iodine absorption from wounds dressed with gauze soaked in povidone-iodine or when povidone-iodine solution was used as a wound irrigant. Patients developed decreased renal function or renal failure following 10 hours of continuous irrigation of their wounds with povidone-iodine or 17 days to 5 weeks of wound dressing with gauze soaked in povidone-iodine. The four patients described in these reports, aged 50 to 83 years, had multiple health problems, including preexisting renal insufficiency (n=3), diabetes (n=2), and congestive heart failure (n=1). The wounds involved were pressure ulcers or debrided septic hip wounds. Systemic toxicity does not appear to be a common occurrence. No toxicity has been reported with povidone-iodine used as a brief rinse or soak.

Efficacy

In Vitro Studies
In the laboratory, povidone-iodine has been demonstrated to be effective at killing a broad range of the pathogens generally associated with wound infection. Berkelman et al found that povidone-iodine solutions diluted to concentrations of 0.1% to 5% were more effective in killing common wound contaminants than was the 10% stock solution. Even the 10% solution was completely effective within 4 minutes of exposure. Van Den Broek and coworkers found povidone-iodine to be effective against Staphylococcus aureus at concentrations of 0.005% or higher, but they questioned whether this effectiveness would be true in vivo. Lineaweaver and associates found povidone-iodine to be an effective bactericide at a concentration of 0.001%.

Povidone-iodine is not always effective at killing common bacteria. Anderson discussed two reports of povidone-iodine stock solution (10%) contaminated with Pseudomonas sp. The contamination apparently occurred during production of the povidone-iodine solution. The bacteria remained viable for several weeks and were eventually involved in patient infections. Why povidone-iodine failed to kill these bacteria is not known. These isolated incidents are inconsistent with other in vitro findings and cannot be explained by the concentration of povidone-iodine solution involved.

In Vivo Studies
There are a small number of studies in which the ability of povidone-iodine to control infection in dermal wounds was examined. Dire and Welsh studied wounds treated in a hospital emergency department. No differences were found in infection rates between wounds irrigated with povidone-iodine and those irrigated with normal saline. Rodeheaver et al inoculated experimental wounds in guinea pigs with 102 to 107 organisms of S aureus. Ten minutes later, the wounds were irrigated with either povidone-iodine solution (10%) or normal saline. Four days after treatment, the authors found no difference between the two groups in the number of viable bacteria present in the wounds or in the number of wounds with visible purulent exudate. When the same experiment was conducted using povidone-iodine surgical scrub, the wounds treated with povidone-iodine had higher rates of infection than those treated with saline. Wounds contaminated with 103 organisms showed 60% infection when treated with povidone-iodine versus 0% with saline. Inoculation with 104 organisms produced 90% infection when treated with povidone-iodine versus 0% with saline. With 105 organisms, wounds treated with povidone-iodine were 100% infected versus 15% for saline controls.

Edlich and coworkers also created wounds in guinea pigs, which they inoculated with S aureus. Five minutes later, the wounds were irrigated with either a povidone-iodine solution (10%) or saline. After 4 days, wound infection as shown by visible purulent exudate was lower for the wounds treated with povidone-iodine than for the saline-treated wounds. There were no differences in percentage of positive cultures and area of induration.

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The findings of this study regarding visible purulent exudate appear to be contradictory to the results of the study by Rodeheaver et al.\(^2\)\(^8\)

Kucan and associates\(^2\)\(^5\) examined infection rates in pressure ulcers under various treatment conditions. The threshold for infection was defined as 105 bacteria per gram of tissue on biopsy. Wounds were treated with gauze dressing saturated with either saline or povidone-iodine (10%). Treatment was given for 3 weeks. At the end of that time, 78.6% of the saline-treated wounds had bacteria counts below the infection threshold, compared to with 63.6% of the wounds treated with povidone-iodine. No statistical analysis of this difference was reported. The saline dressings were changed every 4 hours, whereas the povidone-iodine dressings were changed every 6 hours. No explanation was given for this difference in procedure.

Other researchers have investigated the antibacterial properties of povidone-iodine for use in surgery. Amstey and Jones\(^2\)\(^0\) found povidone-iodine to be no more effective than normal saline for preventing infection when used as a vaginal irritant before vaginal hysterectomy. Sindelar and Mason\(^2\)\(^7\) found that superficial infections of surgical wounds irrigated with 10% povidone-iodine solution prior to closure had an overall infection rate of 2.9%. Wounds irrigated with saline had a 15.1% infection rate.

Viljanto\(^2\)\(^8\) found that irrigation of appendectomy wounds with 1% povidone-iodine before closure resulted in a reduction in wound infection when infection before surgery was isolated to the appendix (2.6% infection rate versus 8.6% for saline controls). If infection had spread beyond the appendix before surgery, however, there was no difference in infection rates between wounds irrigated with povidone-iodine and saline-irrigated controls.

In several of the studies discussed, wounds treated with povidone-iodine solution were compared with wounds treated with saline to assess impairment of healing. If povidone-iodine is helpful in promoting wound healing by decreasing infection rates, healing rates would be expected to be faster in wounds treated with povidone-iodine. Some researchers,\(^9,13,15\) however, found no difference in healing rates between wounds treated with povidone-iodine and saline-treated controls. This finding suggests that the antibacterial effects of the povidone-iodine either did not promote healing or were offset by some other effect such as cytotoxicity.

Although povidone-iodine clearly is an efficient bactericide in vitro, the benefits in treating actual wounds appear to be inconsistent at best. Several studies demonstrated no difference in infection rates between wounds treated with povidone-iodine solution and wounds treated with other topical agents. In the only study involving chronic wounds, povidone-iodine treatment seemed to be inferior to treatment with saline.\(^2\)\(^5\)

### Summary and Clinical Considerations

Most in vivo research on the use of povidone-iodine was conducted on experimentally or surgically induced acute wounds. The applicability of these findings to the chronic wounds typically seen by physical therapists has not been demonstrated. Apparently, some people assume that chronic wounds, especially those containing necrotic tissue, have a greater risk of infection and therefore a greater need for treatment to decrease the number of surface bacteria. Moreover, many patients with chronic wounds have generally compromised health status and may be less able to produce an effective immune response to bacterial invasion. These patients, therefore, may need more assistance to prevent infection than patients with acute wounds and fewer systemic complications.

Conversely, patients with compromised health status may be more susceptible to the cytotoxic character of povidone-iodine. In light of the findings of Berkelman et al\(^2\)\(^0\) that povidone-iodine was more effective when diluted to a concentration of 0.1% to 5%, use of a less concentrated solution than the 10% stock solution may be prudent if povidone-iodine is the treatment of choice. Limited evidence\(^2\)\(^3\) suggests that povidone-iodine surgical scrub may increase infection rates when used in open wounds.

Edlich and associates\(^2\)\(^9\) examined the decrease in effectiveness of antibiotic therapy when the amount of time that a wound was left open before closure increased. They found that bacteria became coated with a "fibrin" coagulum" derived from the wound drainage, which served to protect them from antibiotic action. Howell et al\(^3\)\(^0\) suggest that the effectiveness of povidone-iodine in wounds might also be decreased through this mechanism. This suggestion may explain the finding by Kucan and colleagues\(^2\)\(^5\) that povidone-iodine did not reduce bacteria counts in pressure ulcers. Further investigation with chronic wounds is necessary to establish the benefit, if any, of using povidone-iodine as an adjunct to wound treatment.

The optimal method of application of povidone-iodine has not been clearly established. Brief contact, such as wound irrigation, especially if followed by a saline rinse, or use of diluted solutions might minimize the risk of cytotoxicity. Prolonged contact such as packing the wound with gauze saturated with povidone-iodine, however, might enhance the bactericidal effects. The safety
and efficacy of these alternatives have not been compared in either acute or chronic wounds.

The use of povidone-iodine for wound packing requires particular scrutiny. This treatment option precludes the use of occlusive or semiocclusive dressings. A thorough discussion of the benefits of these “moist environment” dressings is beyond the scope of this update; however, these dressings have been shown to decrease wound infection rates.\(^1\) Saydak\(^2\) reported the results of a pilot study comparing wound healing rates in pressure ulcers dressed with either an unsaturated, amorphous hydrogel absorption dressing (Hydra-Gran\(^3\)) (moist healing environment) or povidone-iodine solution cleansing followed by normal saline rinse and dry gauze dressing. Wounds treated with the absorption dressing healed more quickly. The percentage of decrease in the length of the longest axis of the wound was more than double, and the percentage of decrease in depth was more than nine times that of wounds treated with povidone-iodine and dry gauze. No data were reported regarding infection rates. Although this study did not isolate the effect of povidone-iodine from that of dry dressings, it suggests that moist environment dressings may be a viable, possibly safer, alternative to povidone-iodine.

Wound packing with gauze soaked with povidone-iodine also presents a small danger of systemic toxicity. Andrews\(^3\) discusses these concerns in patients receiving povidone-iodine dressings for prolonged periods. The author recommends that such patients be observed for systemic effects of povidone-iodine compounds, phagocytic cells, and microorganisms. Antimicrob Agents Chemother. 1982;22:593–597.

Povidone-iodine solution appears to be a relatively safe treatment for small acute wounds. Its safety for treatment of patients with extensive or chronic wounds has not been adequately investigated. The evidence regarding efficacy of povidone-iodine solution in treating patients with acute wounds is inconclusive. There is insufficient evidence to demonstrate effectiveness in treating chronic wounds. Better alternative treatments may be available, including the use of moist environment dressings. Clinically and legally adequate reasons to use povidone-iodine solution for managing wounds do not currently exist.

Acknowledgment

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2. 56 Federal Register 33644 at 33662.

\(^1\) Baxter Healthcare Corp, One Baxter Pkwy, Deerfield, IL 60015.


