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Comparison of Chlorhexidine and Povidone-Iodine for Preoperative Skin Preparation in Orthopedic Surgery: A Literature Review

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Abstract

Chlorhexidine gluconate (CHG) and povidone-iodine (PI) are two of the most used antiseptics for preoperative skin preparation. Understanding and identifying advantages and limitations between them ensures a methodical approach to antiseptic selection in orthopedic procedures, especially considering fracture versus non-fracture, elective surgeries. CHG, commonly used in orthopedic surgery, has been shown to provide long-lasting antimicrobial protection, especially against anaerobic pathogens. However, there are concerns regarding the application of CHG near mucosal surfaces or areas of compromised skin. In contrast, PI has shown to be more effective than CHG at minute-interval periods primarily against aerobic pathogens and has a wider microbial coverage due to its mechanism of action. However, PI may be associated with higher risks of skin irritation and thyroid complications due to its iodine content. Regarding cost, PI is more affordable, but CHG may offer better value considering risk of postoperative infection in some cases. Furthermore, combined use has shown promise in antimicrobial efficacy, suggesting a potential synergistic effect in their use that should be investigated further. This literature review analyzes CHG compared to PI for orthopedic surgeries regarding considerations for use of either antiseptic agent and subsequent surgical outcomes. Ultimately, CHG and PI both have risks and benefits without one demonstrating superiority, but there are considerations for the utilization of both in different types of orthopedic surgeries.

Keywords: chlorhexidine, povidone-iodine, betadine, preoperative skin preparation, orthopedic surgery, surgical site infection, surgical antisepsis

Introduction

Although surgical site infections (SSIs) are generally low risk in elective orthopedic surgeries, SSIs can be a significant complication if they occur. This is in comparison to open fractures that often have a higher risk of SSIs due to the nature of the injury. Surgical site infection (SSI) lifelong incidence rate averages 1% for primary hip and knee arthroplasties and up to 2-5% for other elective orthopedic cases [1]. SSI outcomes can cause increased morbidity to patients, increased healthcare costs, postoperative discomfort, additional treatments, and prolonged hospital stays [1-4]. The skin is a natural reservoir for microorganisms, so the skin can never truly be sterile. Preoperative skin antiseptic agents, amongst other important preoperative practices, help reduce the incidence of SSIs, largely attributed to reducing skin microorganisms temporarily [5-7]. Utilization of skin antiseptic agents, such as chlorhexidine gluconate (CHG) and povidone-iodine (PI), plays an important role in reducing the risk of SSIs.

CHG and PI are common antiseptics used for surgical site preparation prior to an incision being made in orthopedic surgery. Despite the widespread use of both antiseptics, there remains debate regarding their effectiveness in the reduction of postoperative SSI rates, and which may be more appropriate for elective, non-fracture orthopedic surgery. While both solutions are proven to be effective in SSI reduction, the present literature demonstrates conflicting views, with some suggesting superiority of CHG, and others discussing potential greater efficacy with PI [8]. This review outlines CHG and PI's antimicrobial effectiveness, their mechanisms of action, current literature recommendations of their application and use, healthcare costs, suitability and tolerance for specific populations and cases, and any nonspecific advantages or disadvantages noted for both antiseptic agents. This review highlights that choosing the most appropriate antiseptic agent requires a multifactorial approach to positively impact patient outcomes.

Overview of Chlorhexidine and Povidone-Iodine for Preoperative Skin Preparation

One of the most devastating complications following elective orthopedic surgery are surgical site infections (SSIs), resulting in delayed recovery, excessive economic burden, prolonged hospital stays, possible need for revision surgery, and increased risk of mortality [9, 10]. The Centers for Disease Control and Prevention (CDC) defines SSIs as infections occurring within 30 days postoperatively near the surgical site, or within 90 days if hardware is implanted. SSIs are further classified as superficial or deep incisional infections. [11].

Preoperative skin preparation serves an instrumental role in reducing the risk of SSIs. Proper skin preparation is the pillar of infection prevention, necessitating an antiseptic agent. However, recommendations for chlorhexidine gluconate (CHG) and povidone-iodine (PI) vary in the orthopedic literature particularly regarding treatment of open versus closed fractures. However, the utilization of CHG and PI in elective, non-fracture orthopedic surgeries are often facility and surgeon dependent. The use of antiseptic agents has gained attention with respect to its utility in uncomplicated carpal tunnel release and closed reduction with percutaneous pinning. SSIs can impose a financial and health burden on the affected patients [12]. Evaluating the rate of SSIs may help illuminate the underlying procedures and antiseptic agents at play to achieve favorable outcomes. Preoperative skin antiseptic preparation is the gold standard of SSI prevention, with antiseptics categorized under aqueous-based or alcohol-based disinfectants, such as PI and CHG, respectively [13]. Table 1 organizes the various properties of PI and CHG, comparing the mechanism of action, microbial coverage, commercial name, application/drying time, and duration of action. Price points were excluded, as this often varies depending on manufacturers and local supplier consultations. This review assesses the methodology of preoperative skin preparation by comparing the indications and molecular mechanisms of action for CHG and PI in elective, non-fracture orthopedic surgeries.

Table 1: Comparative Chart Evaluating Various Properties of Povidone-Iodine and Chlorhexidine Gluconate.

	Povidone-Iodine (PI)	**Chlorhexidine Gluconate (CHG)**
Mechanism of Action	Alcohol denatures protein, releases free iodine. Aqueous penetrates cell membranes and oxidizes key proteins and nucleosides resulting in cell death.	Alcohol dissolves lipid membranes and disrupts cell membranes resulting in protein denaturation and cell death. Aqueous binds to cell walls and disrupts integrity resulting in leakage of intracellular content and cell death.
Microbial Coverage	Alcohol has improved gram negative bacteria coverage and for *Mycobacterium tuberculosis*. Aqueous has coverage for gram positive/negative bacteria, fungi, and viruses.	Alcohol has improved gram negative bacteria, fungi, and *Mycobacterium tuberculosis* coverage. Aqueous has coverage for gram positive/negative bacteria, fungi, and viruses, but poor *Mycobacterium tuberculosis* coverage.
Different Commercial Types	Alcohol: DuraPrep Aqueous: Betadine	Alcohol: ChloraPrep Aqueous: Hibiclens
Application / Drying time	Alcohol: 40 sec/180 sec Aqueous: 4 min/4-8 min	Alcohol: 30 sec/30 sec Aqueous: 4 min/4-8 min
Duration of Action	Alcohol: 48 hours Aqueous: 2 hours	Alcohol: 48 hours Aqueous: 6 hours

Chlorhexidine Gluconate & Povidone-Iodine Overview

Chlorhexidine gluconate (CHG) is a positively-charged biguanide at physiologic pH, which adheres to the negatively-charged cell wall of bacteria, imposing a disruption to the bacteria's structural integrity and releasing its cellular contents [14]. When administered at low concentrations, CHG is bacteriostatic, while at higher concentrations it maintains bactericidal activity, as well as antifungal and *Mycobacterium tuberculosis* activity [14]. In general, CHG offers benefits, such as resistance to neutralization by blood or organic matter in surgical wounds [15]. However, its activity can be neutralized by pH secondary to non-ionic surfactants, inorganic anions, and other organic anions [15]. CHG's contraindication lies within surgical fields involving the ears, meninges, and eyes. As a result, iodine-based antiseptic formulations are recommended for ophthalmic or head and neck surgeries because they are better tolerated [13]. Hemani et al. compared antiseptic agents for prevention of surgical site infections (SSIs). They report DuraPrep, Iodine Povacrylex and Isopropyl Alcohol, which is similar to povidone-iodine (PI), should be applied in one step [16]. PI-related products have a dry time of three minutes on hairless skin, leaves a water-insoluble film on the skin, and demonstrates antimicrobial activity for up to 48 hours [16]. Current CDC guidelines recommend against chlorhexidine-impregnated dressings on patients younger than 18 years of age due to risk of serious adverse skin reactions [17].

Magalini et al. performed a double observational study on 50 surgical procedures that utilized Betadine, a commercial form of povidone-iodine (PI), and 50 procedures that employed ChloraPrep, a form of CHG [18]. The study found that ChloraPrep kits of 26 mL and 10 mL were commonly utilized but are more expensive than PI [18]. The study recommends a more effective disinfectant, since the cost is marginal to the risk

and cost of SSIs [18]. Darouiche et al. conducted prospective randomized clinical trials between 2004-2008, evaluating the efficacy outcomes for patients who underwent preoperative skin antisepsis with ChloraPrep, which is 2% chlorhexidine gluconate and 70% isopropyl alcohol [19]. They report the relative risk of any SSI and superior incisional infections was lower among the CHG cohort [19]. These findings, which favor SSI mitigation, illuminate the mechanism of action underlying CHG's antimicrobial properties.

Further illuminating the biochemical profile of these antiseptic agents, iodophors are iodine compounds with a carrier that retains iodine and the concentration of free iodine contributes to its bactericidal effect [13]. The chemical composition reveals a complex of povidone, hydrogen iodide, and elemental iodine, primarily acting on bacteria by iodination to oxidize the lipids of the cell membrane, which form salts with microbial proteins [14]. PI, commercially known as Betadine, is an antiseptic solution consisting of polyvinylpyrrolidone with water, iodine, and 1% available iodine [20]. It retains broad coverage against gram-positive and gram-negative bacteria, as well as spores, fungi, viruses, protozoa, and *Mycobacterium tuberculosis* [14]. Chou et al. conducted an experimental study that fixated primary human corneal fibroblasts and human corneal epithelial cells in a solution of PI, performing enzyme-linked immunosorbent assay (ELISA) to measure interleukin secretions [21]. The ELISA testing helped quantify PI's cytotoxic profile [21]. They report PI has effectiveness against chlorhexidine-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Burkholderia cepacia*, proposing an indication for iodophor solutions over CHG [21]. Limitations to PI utility in surgery is that it is rapidly neutralized in the presence of organic materials, such as blood or sputum [22]. Additionally, Durani et al. report a slower onset of action and extended amount of time needed to reach maximal antimicrobial activity, secondary to the release of free iodine, despite its aqueous properties which prolong drying time and activity [23]. In essence, once the iodophor contacts the skin during antiseptic preoperative preparation, the free iodine activity quickly depletes while the solution dries, restricting its efficacy. A limitation to the utility of PI is that neonates meet exclusion criteria, because percutaneous absorption can induce hypothyroidism in newborn infants, predisposing them to chronic conditions [22]. In a meta-analysis by Mastrocola et al., reviewing the prevalence of SSI in clean and clean-contaminated surgery, the team's primary finding was that the surgical skin preparation with CHG is more effective than povidone-iodine in reducing bacterial load on the skin, but this does not directly translate to a reduction in SSI, since that is a multifactorial complication [7].

Chlorhexidine Gluconate and Povidone-Iodine Utilization in Orthopedic Surgery

Chlorhexidine gluconate (CHG) has become a mainstay of preoperative skin preparation in elective, non-fracture orthopedic surgeries. It has strong bactericidal and bacteriostatic activity, rapid action, minimal adverse effects, persistent antimicrobial effect, and reliability in reducing skin flora [2]. Alcohol-based formulations are typically preferred to aqueous-based formulations of CHG due to superior antiseptic performance and faster action [7], and common formulations include a solution of 2% CHG in 70% isopropyl alcohol (ChloraPrep) and an alternative solution consisting of 0.5% CHG in 79% ethanol [2, 8, 19, 24]. A standardized application method for these formulations is the "scrub-and-paint" method, which prioritizes mechanical microbial removal and solution penetration, as well as adequate and thorough coverage. In this method, the field is actively scrubbed with solution, starting at the surgical site and moving outward in a centripetal motion, for approximately 30 seconds for smaller surgical sites (e.g. hand surgeries) to two minutes for larger surgical sites (e.g. hip surgeries) [2, 24, 25]. Complete air-drying following application, which usually requires about three minutes, is essential for ensuring maximal antiseptic efficacy, and reducing the risk of alcohol-induced fire during surgery [2, 24, 25]. Additionally, elective orthopedic surgical patients frequently undergo preoperative CHG bathing or cleansing using 2% CHG-impregnated wipes typically both the night before and morning of surgery to further reduce baseline skin microbial colonization before surgery [2, 8, 24].

Despite the widespread adoption of CHG, povidone-iodine (PI) remains an extensively utilized antiseptic for orthopedic surgical site preparation, and it is available in traditional aqueous solutions and alcohol-based solutions like CHG. Unlike CHG, which is most commonly applied as an alcohol-based formulation, PI is most applied applied as an aqueous formulation [7]. Traditional application of aqueous PI, similar to CHG formulations, is the "scrub-and-paint" method, involving an initial scrubbing phase with a detergent-based 7.5% PI solution, followed by painting the surgical field with a 10% PI solution, which typically requires at least three to five minutes of combined antiseptic contact time to ensure effective microbial eradication prior to draping [2, 24, 26]. However, newer solutions, such as iodine povacrylex (0.7% iodine in 74% isopropyl alcohol), now marketed as DuraPrep, allow for single-step application and provide combined rapid microbial killing from alcohol as well as long-lasting, broad-spectrum antimicrobial coverage from iodine. These newer alcohol-based PI solutions dry quickly, typically in three minutes, to form a persistent polymer film that provides an effective antiseptic field that maintains continuous protection against bacterial re-colonization throughout the procedure. Importantly, just as with alcohol-based CHG solutions, complete drying of alcohol-based PI solutions is critical for patient safety and antiseptic activity [2, 8, 24, 25].

CHG is a first-line antiseptic for elective, non-fracture orthopedic procedures performed on intact skin surfaces. It is widely relied upon for procedures involving the introduction of prosthetic materials or hardware, such as spinal surgery, total joint arthroplasty, and various orthopedic sports medicine surgeries. The broad-spectrum antimicrobial efficacy, rapid-onset microbial killing, and persistent antimicrobial activity of CHG formulations make them ideal for surgeries where prolonged operative times may permit skin flora regrowth or contamination [2, 8, 24, 25]. Though, despite its diverse application, CHG must be avoided in certain anatomical areas, including surgeries close to or involving mucosal surfaces (e.g. procedures near genitalia, mouth, nose, eyes, or inner ears), and procedures involving breached skin or open wounds, due to potentially irritating or toxic effects. In addition, hypersensitivity to chlorhexidine, although relatively uncommon, is an absolute contraindication to CHG, and these patients, thus, require alternative antiseptic preparations [2, 24, 26].

Though also regarded as a first-line antiseptic, PI is typically indicated for non-fracture orthopedic surgery in situations where CHG is unsuitable, contraindicated, or carries increased risk, such as in patients with CHG hypersensitivity, in pediatric, neonatal, and infant populations, and in patients with delicate skin conditions that may be irritated by CHG solutions. In addition, surgeries involving the aforementioned anatomical areas on which CHG are not recommended for, including mucosal surfaces, ocular, or auditory areas, will often be preferentially prepared with PI solutions [2, 24, 26]. Furthermore, some elective protocols use PI solutions as part of a combined antiseptic strategy particularly in high-risk cases, such as revision arthroplasty surgeries or shoulder surgeries with higher rates of *Cutibacterium acnes* colonization. In such procedures, sequential application of both CHG and PI is utilized to achieve broad antimicrobial coverage and utilize complementary properties of each agent, which enhances overall microbial reduction before incision [2, 8, 24, 25]. Finally, iodine's inherent safety on open wound surfaces makes it uniquely appropriate in certain complex orthopedic cases involving compromised skin integrity.

General Considerations

Several published studies have shown that preoperative antisepsis with chlorhexidine gluconate (CHG) is superior to the standard of care for elective orthopedic surgery [27, 28]. This becomes clinically relevant when considering patients who may be allergic to povidone-iodine (PI). Das et al. noted five patients (without a known history of allergy) showed an allergic reaction to PI, but no such hypersensitivity was reported with CHG [29]. Peel et al. had two patients with allergic skin reactions to PI [8]. Allergic reaction to PI seems to be more common, so CHG may be used as an alternative without an increased risk of infection. Although rare, excessive and long-term exposure to iodine sources, such as topical PI, may result in hyperthyroidism or hyperthyroidism [30]. In these cases, CHG can also be used as a safe alternative. Many orthopedic elective cases have even incorporated the use of CHG washcloths as an additional antiseptic to use the night before and day of surgery. Johnson et al. conducted two randomized studies evaluating infection rates in total knee and total hip arthroplasty following CHG washcloth antisepsis compared to standard of care, iodine solution in alcohol [10,31]. Both studies showed reduced superficial and deep infection rates [10, 31]. These two studies demonstrate that at-home CHG washcloths are an effective and easy method to reduce the risk of surgical site infections (SSIs) and exposure of excessive iodine in at-risk patients. A smaller scale randomized-control trial, Das et al., favored 4% CHG over 7.5% PI, given the decreased rate of SSI, 6.66% and 12.3%, respectively ($p = 0.008$) [29]. The participants of this study did not use any antiseptic the night before or morning of their elective orthopedic surgery besides the skin preparation noted in the study. The study also controlled for antibiotic prophylaxis, draping, and hair removal [29]. Both treatment groups were of the same size [29]. All these considerations reduce the chance of the findings being secondary to confounding factors, making this a reliable study as well. While randomized trials have been conducted to determine which antisepsis is more effective, the answer remains inconclusive. Further evaluation with large-scale studies should be conducted to assess whether there is a significant difference in infection rate between using CHG or PI for elective orthopedic surgeries.

Some studies have even explored the benefits of sequential application, prepping with CHG followed by PI or vice-versa in patients with no adverse reaction to PI. Patrick et al. studied the application of 10% PI in 95% denatured alcohol, followed by 2% CHG in 70% isopropyl alcohol, for five minutes each [32]. They found that the number of viable bacteria detected was lower in the intervention group, suggesting that with more effective elimination of skin flora, infection rates may be reduced [32]. Bebko et al. explored infection rates after following a specific antisepsis procedure involving both CHG and PI. They found a significant decrease in overall SSIs among orthopedic patients after the implementation of a decontamination protocol consisting of the following: application of both CHG washcloths and oral rinse, along with an intranasal PI solution [33]. Although there have been no large-scale randomized trials assessing the outcomes following this sequential application procedure, the outcomes of these studies pave the way for a potentially effective new antisepsis method to be explored. Das et al. also found no significant difference in cost for either antiseptic [29]. This suggests that two five-minute applications of CHG and PI could possibly prevent even more surgical site infections without costing more time or money than either alone.

Elective Arthroplasty Surgery Considerations

Prosthetic joint infections (PJIs) are a severe complication that can ultimately leave a joint dysfunctional. 92% of PJIs are a result of gram-positive organisms with the majority due to *Staphylococcus aureus* [28]. *Propionibacterium acnes* is another significant cause of these infections with its ability to form biofilms can make this skin flora especially difficult to eliminate [32]. The most common source of wound contamination tends to be from the operating room and the patient's own skin flora, making these infections less likely with interventions like surgical skin preparation [27, 28].

Peel et al. conducted a blinded randomized-control trial comparing surgical site preparation the day of hip and knee arthroplasty. Using an intention-to-treat analysis, there was a statistically significant difference in favor of 1% iodine in 70% alcohol compared to 0.5% chlorhexidine gluconate in 70% alcohol to prevent deep surgical site infection, including PJIs [8]. However, no statistically significant difference in the rates of superficial skin infections [8]. All participants were instructed to use 2% chlorhexidine body wash the night prior to their surgery, with no data on compliance, which may have influenced the outcome of SSIs [8]. There was an equal number of participants in both treatment groups, with the majority of participants administered cefazolin and no statistically significant difference in antibiotic prophylaxis between treatment groups [8]. Overall, this is a well-organized large-scale study comparing the two of the most used antiseptics in hip and knee arthroplasty.

Elective Pediatric Surgery Considerations

The pediatric skin microbiome is on average more diverse when compared to adults [34]. This was a retrospective study with a greater number of participants in the povidone-iodine (PI) group [31]. They found no statistically significant difference in infection rate for chlorhexidine gluconate (CHG) with 2% CHG in 70% isopropyl alcohol versus PI subjects when comparing all procedures [34]. Beber et al. compared the use of both antiseptics in elective pediatric orthopedic surgeries [35]. Looking at the results from elective orthopedic procedures, in sports and upper extremity cases, PI resulted in 29 fewer

infections per 1000 cases than CHG ($p = 0.005$) and equivalent infection rates in lower extremity cases, but the number needed to treat is not specified [35]. Given the retrospective nature of data collection, there remain many questions about coherent application and use of the antiseptics, reliance on accurate documentation, and confounding antibiotic prophylaxis. Both studies do not demonstrate superiority in either the use of CHG or PI.

Fracture-related Surgery Considerations

Studies on open and closed fractures provide meaningful insight regarding the future direction for antiseptic selection. Sprague et al. conducted a trial that emphasized the relevance of tissue integrity and environmental exposure when operating on open versus closed fractures [36]. In a randomized, multi-hospital, large sample size trial, the comparison was made between a 0.7% iodine povacrylex in 74% isopropyl alcohol group or 2% chlorhexidine gluconate in 70% isopropyl alcohol group, with separate populations of patients with either open or closed fractures. The results demonstrated that surgical site infections in patients with closed fractures were significantly reduced in the iodine povacrylex group, but no statistical difference was noted in patients with open fractures [36]. This opens debate to wound integrity and early contamination in orthopedic fracture management. Iodine povacrylex, which differs from povidone-iodine (PI), consists of a povacrylex polymer, which is believed to provide sustained protection in closed fracture orthopedic cases, likely due to its insolubility to fluids and blood and its improved adhesion to surgical drapes, protecting any mitigation of flora during incision [37, 38]. In open fractures, there are several reasons mentioned that may have caused the insignificant comparison. It is likely that through the extensive wound irrigation and the early and prolonged exposure to bacteria, the choice of antiseptic management may not have any considerable effect [36]. Within the scope of this review, this allows for further understanding of how certain factors may play a considerable role in the prevention of surgical site infection rates. In non-fracture orthopedic cases, the skin is generally intact and the procedure is performed in a sterile environment, inviting discussion as to how iodine povacrylex, an iodophor, may demonstrate potential superiority in these types of procedures. However, the debate and lack of consensus remains, as there are not enough trials to demonstrate this comparison in elective cases, where other factors may have to be considered. This well-run study has emphasized the importance of the consideration between antiseptic choice, and has highlighted importance not only based on antimicrobial efficacy of each antiseptic, but more on case-specific factors, such as surgical environment and wound classification.

Challenges and Limitations

The choice of what antiseptics to use in the cases of preventing hospital-acquired infections, especially those from vascular catheters and bacteremia, is important. The disc diffusion method was used in order to test the efficacy of different antiseptics against some pathogens, which is similar to testing antibiotic sensitivity, where the size of the zone of inhibition corresponds to the efficacy of antiseptics [39]. The bigger the diameter, the more efficacious the antiseptic against the bacteria and/or fungi. While the disc diffusion method was prominent for Guzek et al., European Standards (EN) were developed by the European Committee for Standardization (CEN), Technical Committee 216 (CEN/TC 216) to test if a disinfectant or antiseptic has appropriate bactericidal, fungicidal, sporicidal, activity and more [40]. These present with laboratory methods for testing certain antiseptics and disinfectants to support claims that they cover certain antimicrobial activity for their intended purposes. The American Society for Testing and Materials (ASTM) has also developed many standards covering procedures for testing and classifying materials of different types. However, it is not used in European countries due to them having their very own standard [40].

In a narrative study by Tyski et al., they found that many others have tested antiseptics from different suspensions and applied them topically to see how well they perform, measuring bactericidal activity [40]. When it came to forefoot surgery, Ostrander et al. used different pre-surgical preps to determine how effective they were at decreasing bacteria formation on the skin [41]. Cultures were taken from three different sites on the forefoot and efficacy would be measured by the percentage of positive cultures to come from the different preps used [41]. The ChloraPrep (2% chlorhexidine gluconate and 70% isopropyl alcohol) group showed the most promise as the positive culture rate on the hallux site was significantly lower than the DuraPrep (0.7% iodine and 74% isopropyl alcohol) and Techni-Care (3.0% chloroxylenol) groups [41]. The ChloraPrep group was also significantly lower for the positive culture rate in the toe site, as well as the control site compared to the Techni-Care group [41].

All in all, disc diffusion methods have been a common practice to test the efficacy of antiseptics, and even antibiotics, by measuring the zone of inhibition to prove how efficacious an antiseptic can be. Many other organizations and committees have been made in order to determine if antiseptics have the correct level of antimicrobial activity as well. Lastly, cultures taken straight from surgical sites have been used to measure the level of positive culture rates from different antiseptics.

Limitations of Chlorhexidine as Preoperative Antiseptic Solution

While chlorhexidine gluconate (CHG) has been shown to be effective when it comes to antisepsis material, especially with Guzek et al. [39], showing that it is generally well-tolerated by the skin and easily absorbed by the epidermis, it does have its limitations. One of the limitations that is associated with CHG, especially with the use of intranasal mupirocin, is the adherence with the protocol [33]. As low adherence can decrease success rates, it has been associated with increased antibiotic resistance. When it comes to the residual activity of CHG, it has been reported to be capable of eliminating transient microorganisms long after it has been applied to the skin [42]. Yet, some of these studies don't have real world simulation within their methods, making the data somewhat unsuitable. Rutter et al. found that the use of CHG prior to being contaminated on a dry surface showed no such reduction in bacteria [42]. However, it did show reduction almost immediately when applied with a bacterial suspension [42]. This shows that CHG is very useful when it comes into contact with a wet solution rather than a dry surface, meaning certain areas of the body may be of better use for CHG, such as the axilla, groin, and foot, which can help us better understand the clinical situations and implications that CHG can be used best in.

Limitations of Povidone-iodine as Preoperative Antiseptic Solution

Povidone-iodine (PI) has demonstrated efficacy as a preoperative antiseptic solution. Some limitations include skin irritability, such as itching, redness, or burns [43]. When it came to aerobic skin flora, PI was significantly more effective than chlorhexidine gluconate (CHG) when applied 2.5 minutes afterwards, but that was not the case when sampling got to 30 minutes and 3 hours [44]. PI demonstrates efficacy when eradicating the anaerobic skin flora, as it had better result at 2.5 and 30 minutes compared to CHG, but not at the 3-hour interval. This shows that while PI is effective at eradicating microbial activity of skin flora, it may not necessarily have longer-lasting effects compared to CHG. It is good to note as well, that PI inhibited microbial activity in a dilution of 0.33%, which is far less than what is used in hospital settings [45]. Yet, it is ill-advised to use a minimal dilution, as it can lead to not eradicating all potential biofilm production within, and lead to potential antibiotic resistance.

Adverse Effects of Chlorhexidine Gluconate and Povidone-Iodine

Both chlorhexidine gluconate (CHG) and povidone-iodine (PI) are effective antiseptics valued for their ability to reduce the risk of infections. However, their potent antimicrobial effects do not come without drawbacks, including the disruption of natural skin flora. There are two main local skin reactions that can be seen with both agents: irritant contact dermatitis and allergic contact dermatitis [14]. These adverse reactions can lead to further unwanted complications.

Irritant contact dermatitis can occur from repeated or prolonged exposure to these antiseptics. This often results in localized erythema and pruritus. The exact incidence of CHG allergic reactions and associated morbidity or mortality are unknown, however, patch testing has revealed reactions in 2% of patients tested [46]. More severe symptoms from PI, such as blistering and skin necrosis, have been reported, although this is more common in outdated products [47]. In general, PI, due to the iodine content, is considered more irritating to the skin than CHG. Irritant contact dermatitis from PI is seen in about 51% of patients with a skin reaction [48]. Irritant contact dermatitis results in a damaged skin barrier, potentially making the skin more vulnerable to infections.

Allergic contact dermatitis is a delayed hypersensitivity reaction that can initially present like eczema. In allergic contact dermatitis, the patient's immune system is activated and reacts to the antiseptic. This type of reaction may precede the development of anaphylaxis through IgE sensitization, so it is important to avoid further use of the offending agent in these patients [49]. Immediate hypersensitivity or anaphylaxis is a rare, but possible, adverse effect of PI and CHG. Anaphylaxis is particularly seen when these antiseptics are applied near damaged skin or mucosal areas leading to systemic absorption. Iodine alone is a harsh irritant, but the formulation of PI is widely used as it seems to be less irritating while still being an effective antiseptic [50].

Iodine is absorbed to some extent when applied to the skin, although the numeric amount is not known for humans, there is data suggesting that it is absorbed across the skin of animals [51]. Accidental systemic absorption of iodine has also been associated with thyroid dysfunction. In patients with an unknown history of thyroid dysfunction, iodine exposure can lead to hypothyroidism and hyperthyroidism [30]. In a case study by Vercammen et al., a 13-year-old boy who had a bilateral lower leg fasciotomy after he became septic from a small bowel obstruction procedure [52]. The lower leg fasciotomy had to stay open for a while, so povidone-iodine (PI) antiseptic was used daily from ICU day 12 onward [52]. The boy had started to develop acute pancreatitis and it was found that he had developed hypothyroidism, exhibiting a severely elevated TSH of 16.8 mU/L, a T4 of 4.0 mg/L, and a T3 of 64 ng/dL, with the latter two being severely decreased [52]. The patient also had dangerously high levels of urinary iodide, showing that it had been absorbed [52]. PVP-I was formally stopped at day 23 in the ICU and eventually returned to normal [52]. Another study by Tomoda et al., demonstrated transcutaneous absorption of povidone-iodine disinfectant in patients undergoing total thyroidectomy for treating thyroid cancer [53]. They measured the levels of urinary iodine excretion in order to see how much absorption was taking place [53]. Urinary iodine levels were up to seven times higher compared to the preoperative levels of 47 patients that had povidone-iodine as their disinfectant for surgery [53]. Although, urinary iodine levels did go back to normal levels by about the third to fifth day post-operation [53]. This suggests that PI disinfectant could cause more than just thyroid problems, such as altering scintigraphy or radioactive iodine treatment. It could also cause thyroid disinfection in susceptible patients. Anaphylaxis and thyrotoxicosis are both life threatening adverse effects that should be avoided whenever possible. Out of the 50 published case reports of CHG-related anaphylaxis from 2005 to 2015, 15 occurred during surgery [49]. This underscores the importance of careful observation during preoperative skin preparation with both CHG and PI. Patch testing has been proposed to prevent these adverse effects [50]. This method should be incorporated prior to surgery to avoid a preventable life-threatening complication.

Cost and Accessibility

According to many studies, chlorhexidine gluconate (CHG) and povidone-iodine (PI) are safe and effective to use across patient populations in elective orthopedic surgeries. Guzek et al. discussed that their results confirmed guidelines that skin should be decontaminated with alcohol solutions of CHG with a concentration above 0.5% [39]. According to Moskven et al., intranasal photodynamic disinfection therapy and CHG body wipes (nPDT-CHG) when used as a combination antiseptic in spine surgery, was on average $45-$55 per patient in Canadian currency [54]. It was also shown that the annual cost for nPDT-CHG would be about $1,350-$1,650 to prevent one additional spine surgical site infection [54]. As CHG solutions have shown greater promise, it is something that is widely used more to prevent any surgical site infection. Lee et al. calculated the cost of 2% chlorhexidine gluconate/70% isopropyl alcohol (CHG-IPA) to be $6.0 per 26 mL single-use applicator, $1.6 per 113-g bottle of 4% chlorhexidine, and $1.4 per 118 mL of surgical scrub with 7.5% povidone-iodine [55]. Paradoxically, as PI seems cheaper, with the greater efficacy of CHG solutions and decreased rates of surgical site infections, switching to CHG saves approximately $16-$26 per surgical case when considering the number needed to treat several studies.

Future Directions

The American Academy of Orthopaedic Surgeons (AAOS) guidelines to prevent surgical site infection (SSI) are primarily focused on the methods used for fractured orthopedic surgeries due to higher incidences [56]. In comparison, non-fracture

orthopedic surgeries pose a lower risk as evidenced by studies conducted by Zuo et al. and Gajda et al., where the incidence after clean incision orthopedic surgery was 0.48% and after primary total hip arthroplasty SSI incidence was found to be 0.92% and 0.95% for primary total knee arthroplasty [57, 58]. Despite low incidence rates, the efficacy of preoperative skin preparations in elective non-fracture orthopedic surgeries remains an important area of study in the prevention of SSI due to antimicrobial resistance.

Chlorhexidine (CHG) and povidone-iodine (PI) have demonstrated effectiveness against antimicrobial resistance, including biofilms, that contribute to postoperative superficial and deep incisional surgical site infections (SSIs) [27, 28]. In a study by Coles et al., in-vitro growth and biofilm formation of bacteria including *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans* were measured at different concentrations of CHG or PI [45]. At concentrations of 0.0004% and 0.33% as well as lower, inhibition of growth and biofilm formation occurred [45]. However, highly diluted CHG and PI increased biofilm formation [45]. CHG was effective against biofilm formation for bacteria that cause infections in prosthetic joints, but there was an increase in bacterial resistance activity such as the efflux pump [45]. The outcome of this study suggests the need to consider the concentrations of antiseptic in the prevention of biofilm formations that significantly contributed to SSIs [45].

In a study of patients undergoing shoulder surgery that was conducted by Dorfel et al., the efficacy against biofilms with the use of CHG combined with alcohol vs. PI combined with alcohol after immediate sampling, and after prolonged 3-hour sampling, determined that the PI-alcohol combination was more effective in reducing SSIs in elective shoulder surgery [44]. Aerobic skin flora, coagulase-negative staphylococci, and anaerobic flora had a reduced reduction factor 2.55 ± 0.75 vs. 1.94 ± 0.91, $p = 0.04$, RF 3.96 ± 1.46 vs. 1.74 ± 1.24, $p < 0.0$, RF 3.14 ± 1.20 vs. 1.38 ± 1.16, $p < 0.01$, respectively. Despite a minimal reduction factor in aerobic skin flora compared to other common bacteria present in shoulder surgery after prolonged exposure at 3 hours, there was a substantial increase in reduction factor after sampling for bacteria immediately after application of PI-alcohol combination. Anaerobic immediate sampling demonstrated PI-alcohol was more effective than at 3 hours sampling [44]. The differences demonstrated in this study suggest a benefit in combination of antiseptics that specifically target bacteria commonly found on closed orthopedic surgical sites. Another study by Chao et al. examined efficacy of 10% PI, 10% PI and 3% hydrogen peroxide, diluted PI, 0.05% chlorhexidine gluconate in sterile water, and a formulation of water with ethanol, acetic acid sodium acetate, benzalkonium chloride [59]. Each antiseptic solution was tested on discs containing *S. aureus* and *E. Coli* and that resembled total knee arthroplasty implants, each consisting of either polymethylmethacrylate (PMMA), cobalt-chromium (CC), or oxidized zirconium (OxZr) [59]. According to the United States Food and Drug Administration, the commonly accepted standard of an antiseptic that is considered clinically effective must reach the threshold of 3-log or 1,000-fold reduction in colony forming units (CFU) [60]. Antiseptic containing 10% povidone-iodine with hydrogen peroxide was found to be clinically effective on PMMA and eliminated all *S. aureus* at both 24 hours and 72 hours of biofilm formation ($p=0.002$). In comparison, 10% PI effectively eradicated all bacteria on OxZr and CC ($p=0.04$). The efficacy against bacterial resistance, including biofilm formation, is dependent on the timing to reach the 1,000-fold reduction of CFU, the most common bacteria found at the surgical site, and the materials being used for implants or prosthetics in non-fracture orthopedic surgery.

Another study by Dudek in the International Journal of Molecular Sciences, assessed antiseptic properties and cytotoxicity of polyhexanide, PI, low-concentrated hypochlorite, and lavage solutions, including saline [61]. Polyhexanide was the most effective in comparison to PI and also exhibited decreased cytotoxicity [61]. Dudek's research presents a future area of study on antiseptics used in non-fracture orthopedic surgeries that focuses on their cytotoxicity. Further research may provide valuable clinical application in understanding how cytotoxicity can affect the viability of keratinocytes and fibroblast cells involved in wound healing, and affect the ability of antiseptics to reduce the risk of SSI [62]. These studies highlight the importance of considering multifactorial susceptibility to SSI when making clinical decisions about the most appropriate antiseptic to use in non-fracture orthopedic surgery.

Given the susceptibility for developing resistance and biofilms that contribute to SSI postoperative non-fractured orthopedic surgery, further research is warranted. Larger scale studies would increase statistical power of studies that contain a small sample size. In-vivo studies would help further understand the efficacy of these antiseptics at surgical sites and a potential role in the process of recovery from non-fracture surgeries. One area understudied is the efficacy of antiseptics in immunocompromised patients undergoing non-fracture orthopedic surgery. To conclude, continued research on perioperative antiseptic use in non-fracture orthopedic surgeries is key to improving surgical outcomes and reducing risks of SSI.

Conclusion

Despite low rates of surgical site infections (SSIs) in orthopedic surgery for elective and closed fracture management, the use of antiseptics perioperatively has played a crucial role in reducing the risk of SSI after surgery. While chlorhexidine gluconate (CHG) and povidone-iodine (PI) are some of the most used agents, studies comparing the efficacy of each of these antiseptics have varying results and lack consensus. Given its widespread and standardized use in surgical settings, it became of interest to review the current literature on CHG and PI. In this literature review, the antimicrobial efficacy of antiseptics is evaluated to determine if there is a difference between the two agents when used in the surgical setting. The mechanisms of action, clinical applications in the general population and for specific populations, and cost-effectiveness are also discussed in the comparison.

Studies included in this literature review suggest that CHG and PI are both effective in reducing SSI as previously thought. CHG, and more so alcohol-based agents, offers rapid and ongoing antimicrobial activity for longer periods of time postoperatively. Yet, it is contraindicated near the eyes, ears, mucosal surfaces, and in pediatric patients. On the other hand, PI was found to be effective against broad spectrum pathogens but had a slower onset and was at risk of being neutralized by blood or body fluids. PI had higher risks of causing allergic reactions and complications that

were associated with thyroid dysfunction in pediatric populations.

Additional studies demonstrated that CHG was found to have remaining antimicrobial effectiveness postoperatively for pathogens, such as Staphylococcus aureus and Pseudomonas aeruginosa. On the other hand, PI was the most effective in surgeries that involved anaerobic bacteria or biofilms. CHG's mechanism of action involves disrupting the bacterial cell wall, while PI oxidizes microbial proteins. CHG requires two to three minutes of drying time, while PI requires a longer contact time. Lastly, studies noted PI has a lower cost. However, when considering long-term costs, CHG may reduce this as it is more likely to prevent SSI.

Current literature gaps that present opportunity for future research include a need for more highly powered randomized trials comparing CHG to PI for surgical site preparation in different orthopedic surgeries. In addition, certain surgical site infection prevention methods have been inherently difficult to study due to reliance on patient application, such as the use of chlorhexidine wipes the night before surgery. Research studying surgical site preparation in immuno-compromised populations is also limited. Our review demonstrates that while both CHG and PI can be effective for a broad range of applications and may even exhibit synergistic effects when combined, the use of each should be tailored and optimized based on factors including procedure type and location, contraindications, and patient allergies. Additionally, the review supports the patient-focused use of chlorhexidine wipes and oral rinse, and that CHG may demonstrate cost savings versus PI.

This study overall highlighted current literature on the comparison of two commonly utilized antiseptics in procedures that have a lower risk of SSIs, and it continues to be of importance to further understand how antiseptics can address bacterial resistance and biofilm formations in orthopedic surgeries.

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