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Preoperative Intranasal Decolonization with Topical Povidone-Iodine Antiseptic and the Incidence of Surgical Site Infection: A Review

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Surgical site infection (SSI) occurs at the incisional site of a surgical procedure and usually involves the skin. The use of antibacterial courses to manage SSIs is still very challenging in clinical settings. When not used appropriately, antibacterial agents can lead to increased rates of adverse events. However, various antibacterial agents that can destroy the growth of bacteria are now available. This article aims to discuss the role of preoperative intranasal decolonization with topical povidone-iodine antiseptic in the incidence of SSI based on a review of the literature.

Topical bactericidal agents can be administered intranasally before surgery to eliminate potentially harmful bacteria, including antibiotic-resistant strains of bacteria. Therefore, a few studies have recommended the use of intranasal povidone-iodine solution in the clinical setting; however, it also appears to be a promising antiseptic regimen for preoperative decontamination in patients planned to undergo surgery. Povidone-iodine is a commonly used medical antiseptic agent that is used by surgeons to promote wound healing and prevent postoperative bacterial infections. Chlorhexidine gluconate is both an antiseptic and a disinfectant, which is used to clean the skin and surgical instruments. Our review of the literature on studies on the effectiveness of intranasal povidone-iodine in the reduction of intranasal bacterial colonization and the prevention of SSI identified only 5 controlled clinical studies. One study, however, showed increased effectiveness in preventing SSI when topical intranasal povidone-iodine was combined with the use of chlorhexidine gluconate washcloths. Further large-scale controlled clinical studies are needed before proper guidelines can be made.

MeSH Keywords: Administration, Intranasal • Oral Surgical Procedures • Povidone-Iodine

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Background

Surgical site infections (SSIs) are defined as infections that occur after surgery through the incisional surgical site and sometimes can involve the skin, soft tissues, or implanted material [1–3]. SSIs are complicated conditions for patients and surgeons and are associated with increased morbidity and mortality [3,4]. The term surgical site infection was introduced by the Surgical Wound Infection Task Force in 1992, when Horan et al. defined it as an infection affecting the wound and occurring within 30 days of surgery [5]. In 2013, the Centers for Disease Control and Prevention (CDC) modified the surveillance period to 30 days for superficial SSIs and 90 days for deep incisional or organ/space SSIs [6]. SSI is a common problem in the hospital setting. In 2009, the World Health Organization (WHO) reported that 23% of surgical patients worldwide developed an SSI [7]. Recently, the WHO reported that SSI is the most surveyed and common type of healthcare-associated infection in low-income and middle-income countries, affecting up to one-third of patients who have undergone a surgical procedure [8]. The impact of healthcare-associated infection is multifactorial and includes extended hospital stays, increased resistance of microorganisms to antimicrobials, and high healthcare system costs [9]. The prevention of SSI has become more important as the number of surgical procedures performed worldwide continues to grow. It is well known that there is an increasing need for evidence-based regimens for the prevention of SSI. Darouiche et al. suggested that since a patient's skin is a reservoir of pathogens, improving skin antisepsis would reduce SSIs [1]. Antiseptics are chemical agents used to decrease the number of bacteria on the skin surface and surgical instruments [10]. However, the control of SSI remains challenging in the clinical setting. Notwithstanding the improvements that have been made in infection control systems, SSI continues to influence the quality and cost of health care [11].

According to the surveillance of SSI in the National Health Service hospitals in the United Kingdom, *Staphylococcus aureus* was the predominant isolate bacteria in the orthopedic setting, accounting for isolates in 33% of hip prosthesis surgeries (83/254), 26% of isolates in knee prosthesis surgeries (63/238), and 33% of isolates in neck femur repairs (87/263) [12]. It was reported that methicillin-resistant *S. aureus* (MRSA) is an avirulent and resistant type of *S. aureus* found on the skin and in the nasal cavity of up to 25% of healthy people and animals [12,13]. These bacteria are usually not harmful, but they can sometimes cause serious infections. Accordingly, the skin surface is a possible source of contamination. Approximately 15% of patients who had MRSA before surgery developed a MRSA infection, and the risk of infection in patients with colonization was significant in the peri-hospitalization period [13]. Many clinical investigations have revealed that cleansing with antiseptic agents the night and morning before a planned surgery can minimize the incidence of postoperative SSIs [14]. According to the WHO's process for guideline development, their recommendations for the prevention of SSIs in the preoperative, intraoperative, and postoperative periods are reviewed and updated following the identification of new evidence at least every 5 years. In the review by Allegranzi et al., which summarized the WHO global guidelines for the prevention of SSI, the authors suggested irrigating incisional wounds with an aqueous povidone-iodine solution before closure to prevent SSI, especially in clean and clean-contaminated wounds [8]. In 2018, the WHO suggested that either plain or antimicrobial soap may be used for decreasing the incidence of SSIs in surgical patients, but the panel decided not to formulate a recommendation on the use of chlorhexidine gluconate-impregnated cloths to reduce infections, owing to the very low quality of available evidence. For surgical site preparation, the WHO recommended the use of alcohol-based antiseptic solutions containing chlorohexidine gluconate [15].

Antiseptic agents are classified into 3 levels, high, intermediate, and low, depending on the spectrum of microbicidal activity. High-level antiseptic agents are capable of killing all types of microorganisms, but their use is limited to disinfecting instruments. Povidone-iodine, which belongs to the intermediate-level, can be used for preoperative disinfection of the skin. Chlorohexidine gluconate, which is a low-level antibacterial agent, has a more limited microbicidal effect compared to povidone-iodine. Povidone-iodine and chlorohexidine gluconate are used worldwide because of their wide-spectrum antimicrobial activity and because bacteria resistance against these agents is rare. However, most staph infections (*S. Aureus*) can be managed with antibiotics, although some strains have developed antibiotic resistance.

In the past 20 years, mupirocin has been the most used regimen for preoperative decolonization. Perl et al. found that the risk of resistance to mupirocin, when mupirocin is used for preoperative decolonization, was low, at 0.6% [16]. However, mupirocin regimens are more expensive than intranasal povidone-iodine regimens. Povidone-iodine is a broad-spectrum antiseptic for topical application in the management and prevention of wound infection. It has long-lasting antiseptic effects, which are due to its slow absorption through soft tissue, making it the choice for longer operations [17]. Studies have shown that chlorhexidine gluconate provides superior prevention of SSI [18,19]. We believe that if the data support the relevant clinical effectiveness of a povidone-iodine strategy for SSI, this should be acknowledged. As highlighted by Liu et al., intranasal decolonization using antimicrobials or antiseptics is done to minimize the risk of SSI by preventing pathogens from the nasal cavity being transferred to the skin where a surgical incision will be performed [20]. They have also pointed out that the potential effectiveness of intranasal

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Table 1. Clinical characteristics of a decontamination protocol on surgical site infection in patients undergoing surgery from included studies.

Fisrt author	Participants	Study design	Intervention	*P* value
Bebko SP [21], 2015	365	Prospective clinical study	Chlorhexidine washcloths 2% (one time the night before and the morning of the operation day) Oral rinse 0.12% (one time the night before and the morning of the operation day) Intranasal povidone-iodine solution 5% (one time the morning of the operation day)	.02
Phillips M [22], 2016	842	Randomized open label trial	Intranasal povidone-iodine solution 5% (4 applications, within 2 hours of the surgical incision) Chlorhexidine wipes 2% (6 applications, one time the evening before and the morning of the operation day)	.1
Rezapoor M [23], 2017	143	Randomized, placebo-controlled study	Intranasal povidone-iodine solution 5% (one time the morning of the operation day)	.003
Urias DS [24], 2018	962	Retrospective review	Intranasal povidone-iodine solution 5% (2 applications in each nostril, one time the morning of the operation day) Bathing with 2% CHG washcloths or Dynahex 4% CHG solution (one time the night before operation, if possible, and the morning of the operation day)	.020
Peng HM, [25], 2018	545	Prospective cross-sectional study	5% povidone-iodine nasal (both nostrils twice a day for 5 days prior to the surgery) Chlorhexidine gluconate (baths for five days before the operation)	<.001

CHG – chlorhexidine.

decolonization of *S. aureus* is considered to be dependent on both the antimicrobial or antiseptic applied and the dose of application. Therefore, this article aims to discuss the role of preoperative intranasal decolonization with a topical povidone-iodine antiseptic in the incidence of SSI, based on a review of the literature.

Observational Data

We identified 24 studies of intranasal povidone-iodine strategies for preoperative decontamination in patients undergoing surgery published since 2015, which combine the use of intranasal povidone-iodine and chlorhexidine gluconate-impregnated washcloths and include a total of >2500 patients [21–25]. In 2 studies with more than 500 patients each, regimens using intranasal povidone-iodine plus bathing with 2% chlorhexidine achieved infection cure rates of 94.2% to 100% (infections mainly caused by common pathogens *S. aureus* and MRSA) among patients of different ages, who had repairs of lower extremity fractures or elective orthopedic surgery (Tables 1, 2) [24,25].

One prospective clinical study analyzed the outcomes of patients whose treatment included a nasal 5% povidone-iodine solution, 2% chlorohexidine gluconate, and 0.12% chlorohexidine mouthwash regimen once the night before surgery and once the morning of the day of surgery (Table 1) [21]. Rezapoor et al. [23] assessed the experience of 95 patients with positive cultures for *S. aureus* at baseline, of whom 29 were decolonized with off-the-shelf povidone-iodine and 34 were treated with 5% povidone-iodine skin and nasal antiseptic solution. The application of the povidone-iodine-based skin and nasal antiseptic before surgery was effective in reducing nasal *S. aureus* in more than 95% of patients. The infecting pathogens included *S. aureus* (n=7) at 4 h after treatment and *S. aureus* (n=20) at 24 h after treatment. Their treatment regimens included cefazolin (n=90) and vancomycin (n=53). Antibiotics were administered randomly between the groups before surgery; however, the type of antibiotic did not affect *S. aureus* rates (P=0.90), and no significant differences between the groups were noticed (P=0.51).

In a large, randomized open-label trial, Phillips et al. [22] analyzed 1697 cases of patients with planned arthroplasty or spine fusion surgery, of whom 842 received intranasal 5% povidone-iodine solution (4 applications total, within 2 h of the operational incision), including 2% chlorhexidine wipes (6 applications total, once the night before and once the morning of surgery). A deep SSI occurred in 0.71% of their surgical

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Table 2. Summary of microorganism species and treatment in patients undergoing surgery from included studies.

Fisrt author	Type(s) of surgery	Microorganisms species ()	Treatment	Main result
Bebko SP [21], 2015	Elective orthopedic surgery with hardware implants	Coinfection of *S. epidermidis* and Enterococcus (2 cases) S. aureus (1 case)	NA	Preoperative Methicillin-resistant *Staphylococcus aureus* decontamination with CHG, mouth wash regimen, and intranasal povidone-iodine reduced about 50% the rate of surgical site infection in patients planned for surgery
Phillips M [22], 2016	Arthroplasty or spine fusion surgery	MRSA (1 case) Coagulase-negative staphylococci (1 case) *Streptococcus agalactiae* (1 case) *E. faecalis* (1 case) *E. coli* (1 case) *P. aeruginosa* (1 case)	Cefazolin (1 g) Clindamycin (600 mg) Vancomycin (1 g)	*Staphylococcus aureus* deep SSI occurred in 5 of 763 in the mupirocin group and 0 of 776 in the povidone-iodine group (P=0.03). Intranasal povidone-iodine may be admitted as an elective strategy to reduce surgical site infection
Rezapoor M [23], 2017	Primary or revision TJA, FAO, PO, or TSA	*S. aureus* (7 cases), at 4 hours post-treatment *S. aureus* (20 cases), at 24 hours post-treatment	Cefazolin Vancomycin	PI-SNA regimen was significantly more effective at decolonizing *Staphylococcus aureus* at 4 hours post-treatment (P=0.003), comparing to the other three groups. There is no significant difference at 24 hours post-treatment between the three groups
Urias DS [24], 2018	Repair of lower extremity fractures	*S. aureus* (2 cases)	NA	A 0.2% infection rate was noted among subjects in the intervention group (962) with P=0.020, however, in the pre-intervention group (930), a 1.1% infection rate was observed. PI-SNA regimen showed a significant decrease in the infection rate of subjects planned for surgery
Peng HM [25], 2018	Elective orthopedic surgery	MRSA (8) *S. aureus* (64)	Cefuroxime (1.5 mg) Clindamycin (600 mg) Vancomycin (1 g)	The decolonization of the MSSA was 94%, while the decolonization of the MRSA was 100% successful

MRSA – methicillin-resistant *Staphylococcus aureus*; NA – not available; CHG – chlorhexidine; PI-SNA – povidone-iodine skin and nasal antiseptic; *P. aeruginosa – Pseudomonas aeruginosa*; *S. epidermidis – Staphylococcus epidermidis*; *E. faecalis – Enterococcus faecalis; E. coli – Escherichia coli; S. aureus – Staphylococcus aureus*.

procedures in the povidone-iodine group (*P*=0.1); however, *S. aureus* deep SSI did not develop in the 776 remaining surgical procedures in the povidone-iodine group (*P*=0.03). The primary antibacterial therapy was 1 g of cefazolin. Patients with a confirmed b-lactam allergy were given 0.6 g of clindamycin, and those with MRSA were given 1 g of vancomycin. The antibiotic infusions began within 60 min of the incision. When the preoperative nasal culture developed *S. aureus*, a secondary nasal culture was requested to determine the rate of clearance. The percentage of nasopharyngeal cultures without bacterial growth after surgery was 54% in the intervention group (*P*=0.03).

Current approaches to the preoperative use of topical povidone-iodine and chlorhexidine gluconate in the prevention of SSI

The outcomes of topical povidone-iodine and chlorhexidine use on local bacteria have been well investigated. Studies have reported that the inhibitory effects of chlorhexidine gluconate on bacteria were significantly stronger than those of topical povidone-iodine [26,27]. In contrast, a different study found that the effect of topical povidone-iodine was more persistent than that of chlorhexidine gluconate [28].

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The instructions for the use of intranasal povidone-iodine and chlorhexidine gluconate are to apply chlorhexidine washcloths to the entire body of the patients, except the face, once the night before and once in the morning of the operation; and for the nasal povidone-iodine solution, a specialist nurse inserts a swab into both nostrils of patients, using a fresh swab each time and rotating for 15 s, once in the morning of the operation [4–7,9]. An amount of 15 mL of 0.12% chlorohexidine oral rinse is used as a mouthwash for 30 s and then spit out, once the night before and once in the morning of the operation. Following the mouthwash, patients are to wait at least 30 min before rinsing the mouth with water [4].

Studies supporting the use of intranasal povidone-iodine and chlorhexidine gluconate

Bebko et al. [21] reported that the procedure including nasal povidone-iodine could likely improve antibiotic resistance, noting that the length of hospitalization was longer in patients receiving a mupirocin and chlorhexidine decolonization protocol than in patients receiving chlorhexidine washcloths, chlorohexidine oral rinse, and nasal povidone-iodine (5 days *vs.* 2 days). Also, the cost of decontamination was higher in the mupirocin and chlorhexidine group than in the chlorhexidine washcloths, chlorohexidine oral rinse, and nasal povidone-iodine group ($54 per patient *vs.* $35 per patient, respectively). This is consistent with results of previous studies that showed the handmade nasal povidone-iodine swab is a simple, inexpensive, and effective decolonization protocol [20,25].

Patients who spent more than 2 h in the operating room were more likely to get an SSI 4 weeks after surgery than patients who spent less time in the operating room (odds ratio, 4.59 [95% confidence interval, 1.67–12.65]; *P*=.003) [21]. Rezapoor et al. [23] suggested conducting surgery within 12 h of applying the nasal povidone-iodine to reduce the amount of *S. aureus* in the nostrils at the time of surgery. Daniel et al. [24] reported that povidone-iodine was the better option for their patients who had surgery planned within 24 h. Phillips et al. [22] reported that the use of nasal povidone-iodine by the patient care team just before surgery may ensure greater treatment compliance. Bebko et al. reported that a hospital stay longer than 24 h is a significant risk factor for SSI and the authors noted a significant reduction in overall SSI rates among orthopedic patients after the use of a decontamination protocol [21]. However, the current WHO guidelines for the prevention of SSI mention that it is good clinical practice for patients to bathe or shower before surgery, and their panel has suggested that patients undergoing cardiothoracic and orthopedic surgery, who have been identified to have nasal carriage of *S. aureus*, should be given preoperative 2% intranasal mupirocin ointment with or without a chlorhexidine gluconate body wash [8,15].

The use of selective antibiotic therapy for SSI

We identified 3 studies using either first generation cephalosporin [22,23], second generation cephalosporin [25], and glycopeptide [22,23,25] classes of antibiotics for the postoperative management of SSI (Table 2).

To minimize the risk of SSI, the WHO guidelines recommend that surgical antibiotic prophylaxis should be given before the surgical incision, when indicated by the type of operation. The panel recommended the administration of surgical antibiotic prophylaxis within 2 h before the incision, while considering the half-life of the antibiotic [8,15].

Future directions of topical antiseptic agents and the prevention of SSI

Preventive protocols with topical povidone-iodine alone or in combination with chlorhexidine gluconate are now in use. The application of nasal povidone-iodine may be considered as an option to reduce SSI [21,22]. In addition to an intranasal decolonization protocol, it could be important to include other sites (throat, axilla, groin, and/or rectum) in a study with a much larger number of patients with long-term follow-up, which also includes surgical antibiotic prophylaxis [23,25]. In brief, an additional large-scale, robust study is needed to determine the effectiveness of these antiseptic agents in decreasing the rate of SSI in the clinical setting before evidence-based conventional infection treatment guidelines can be established.

Discussion

The present review included a search of the literature to identify studies on the effectiveness of preoperative intranasal decolonization with topical antiseptic agents in the prevention of SSI. Few controlled studies have been published, and most studies have involved the use of topical povidone-iodine [1,18,21–23,25,29–31]. One study, however, showed increased effectiveness when topical intranasal povidone-iodine was combined with the use of chlorhexidine gluconate-impregnated washcloths [21]. Data on the identified pathogens were available in all reported cases [21–25]. The most commonly reported microorganism species were MRSA and *S. aureus*. Gorwitz et al. [32] reported that *S. aureus* nasal colonization occurred in 28% of the general United States population from 2003 to 2004 and MRSA was colonized in the nasal cavity of 1.5% of the population. In 2014, the practical recommendations established by Anderson et al. reported that each SSI in a patient can lead to at least 1 additional week of hospitalization and increase the risk of mortality by 2- to 11-fold, compared with patients without an SSI [33]. A current study found a significant correlation between nasal MRSA found within 1

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month before surgery and MRSA SSI. The researchers demonstrated an increased risk of MRSA SSI among MRSA carriers, despite the application of multiple interventions aimed at decreasing MRSA SSI risk [34]. Anderson et al. suggested using vancomycin for patients with high endemic rates of MRSA SSI, targeted high-risk patients, and patients undergoing high-risk implant surgeries [33]. It is known that the colonization of multi-drug-resistant organisms is an increasing problem in healthcare facilities, which has a serious impact on society. Moreover, it is important to avoid such colonization at any cost to limit critical complications such as infection, particularly before surgical interventions.

Similar to how the mouth and throat cavities of healthy persons are known to be colonized by a multitude of diverse microorganisms which affect the health of the mouth and body [35], SSIs are caused by contamination of an incision with microorganisms from the patient's own body during surgery. Unfortunately, these microorganisms may develop biofilms, which are resistant to antibiotic therapy. And that is why the rate of resistant microorganisms has increased in clinical settings over the past years, leading to longer hospital stays. Urban et al. [36] reported that the costs per SSI caused by prolonged hospitalization, supplementary analyses, antibiotic therapy, and reoperation, range from $400 (USD) for superficial SSIs to more than $30 000 for serious infections. This indicates there is a need for antiseptic agents with broad-spectrum activity that ensure oral, oropharyngeal, and whole-body antiseptic coverage. Therefore, according to data from the literature, regimens using chlorohexidine and povidone-iodine can help patients and surgeons overcome the challenges of SSIs by minimizing *S. aureus* and other dangerous microorganisms on the skin and in the nose and mouth, thereby shortening hospital stays as well.

The intranasal povidone-iodine regimen was effective in the studies we reviewed. In the most comprehensive study, conducted by Daniel et al. [24], an intervention of nasal povidone-iodine and bathing with 2% chlorhexidine gluconate washcloths or Dynahex 4% chlorohexidine gluconate solution was compared with pre-intervention in trauma patients experiencing urgent repair of lower extremity fractures. Results showed better outcomes in the intervention group than in the pre-intervention group, including having no other risk factors correlated with the increase of SSI.

The timing of the intranasal povidone-iodine preoperative decontamination in the studies we reviewed varied, including once in the morning of the operation day, within 2 h of the surgical incision, and twice per day for 5 days before the operation [21–25]. The advantages of these antibacterial agent antisepsis regimens include a rapid bactericidal action against a broad spectrum of microorganisms, significant reduction in the number of microorganisms on intact skin, continued antimicrobial activity for up to 6 h after application, lack of contribution to antibiotic resistance, and lower cost than alternative treatments [4,5,7,12,14,21,23–25,31,36]. In other studies [29,30], the authors reported that povidone-iodine use resulted in hemostatic and anti-inflammatory outcomes during minor oral surgery.

The effectiveness of intranasal povidone-iodine solution does not indicate that this regimen is the correct choice for all patients undergoing surgery. Nevertheless, these data validate the use of intranasal povidone-iodine solution for suitable patients.

Based on available data and an evaluation of clinical suitability, intranasal povidone-iodine combined with chlorhexidine washcloths for patients with SSI should be considered if these patients are clinically stable with no immediate signs of postoperative infection, the application of intranasal povidone-iodine has completely cleared their bacteremia, and there are no concerns about the inhalation of nasal therapy into the upper respiratory system. More robust data on intranasal povidone-iodine combined with other antiseptics for the preoperative decontamination of MRSA are required to validate the effectiveness of this critical contamination.

Conclusions

Our review of the literature on the effectiveness of preoperative intranasal decolonization with topical antiseptic agents and the prevention of SSI has shown there is a lack of controlled studies. Although the use of topical intranasal povidone-iodine has been supported in the literature, and one study showed increased effectiveness when also using chlorhexidine gluconate washcloths, additional large-scale controlled clinical studies are needed before further guidelines or recommendations can be made for their routine use in the prevention of SSI.

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