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## Review

# Sequential use of povidone-iodine and chlorhexidine for cutaneous antisepsis: A systematic review

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**Abstract**

Cutaneous antisepsis with chlorhexidine or povidone-iodine, usually with alcohol, has been extensively studied. This review of published studies reveals that sequential use of povidone-iodine and chlorhexidine leads to a greater reduction in the bioburden of aerobic and anaerobic bacteria on the skin, lower risk of intravascular catheter colonization, and lower risk of surgical site infection compared to use of either agent alone. As such, sequential use of cutaneous antiseptic agents may further reduce risk of surgical site infections, as well as infections associated with insertion of transdermal devices such as nephrostomy tubes, left-ventricular assistance devices, and intravascular catheters.

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Chlorhexidine is a cationic bisbuguanidine that impairs microbial cell membrane integrity at low concentrations and congeals the cytoplasm at higher concentrations. Iodine is a halogen that rapidly penetrates the cell membrane and inactivates cytosolic proteins, nucleotides, and fatty acids.[1] The use of chlorhexidine or povidone-iodine, or more frequent use of one of these antiseptics combined with alcohol, is the standard of care for cutaneous antisepsis. However, studies in the peer-reviewed literature have examined the impact of sequential povidone-iodine and chlorhexidine use, with or without alcohol, on the microbial load at surgical sites, catheter insertion sites, and risk of surgical site infection. Ultimately, sequential povidone-iodine and chlorhexidine use is more efficacious than use of either agent alone.

## Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed.[2] PubMed was used to search for articles in any language published from January 1, 1970, through June 1, 2019, using the following search terms: chlorhexidine povidone-iodine (833 articles); and chlorhexidine combination povidone-iodine (54 articles); chlorhexidine combined povidone-iodine (27 articles). Bibliographies of articles with sequential use of antiseptic agents were also searched. The methods sections of all full-text articles were assessed for eligibility. For 1 study, the authors were contacted directly because sequential antiseptic use was not specified. Outcome measures included colonization of skin or deeper surgical sites, intravascular catheter tips, or surgical site infection. Studies were included if a concurrent control group was used to compare sequential povidone-iodine and chlorhexidine to use of either of the antiseptics alone and quantitative comparative results were provided. Studies were excluded if there was no comparison of sequential use to single antiseptic use or only qualitative comparative results were provided.

## Results

The 10 studies that met inclusion criteria revealed a reduction in the intended outcome with sequential use of povidone-iodine and chlorhexidine compared to use of either agent alone, regardless of the concentration of cutaneous antiseptics, regardless of whether or not the povidone-iodine or chlorhexidine was combined with alcohol, regardless of the sequence of cutaneous antiseptics (ie, povidone-iodine followed by chlorhexidine or vice-versa), and regardless of the outcome measure. Most, but not all, such differences in outcomes reached statistical significance (Table 1). With sequential use of povidone-iodine and chlorhexidine, studies demonstrated a reduction in the likelihood of cutaneous aerobic bacterial growth,[3,8,9] cutaneous anaerobic bacterial growth,[9] combined cutaneous aerobic and anaerobic bacterial growth,[4,6] as well as a reduction in the amount of cutaneous aerobic and anaerobic bacterial growth.[6] Sequential antiseptic use also reduced bacterial growth when cultures were obtained from within the surgical site, excluding the surrounding skin.[6]

Sequential antiseptic use was associated with reduced risk of a surgical site infection.[5,6,10] Sequential antiseptic use independently reduced the risk of craniotomy surgical site infections[10] and independently reduced the risk of cesarean surgical site infections in class III obese patients.[5] Lastly, sequential antiseptic use reduced the likelihood of central venous catheter colonization.[7]

## Discussion

Sequential use of povidone-iodine and chlorhexidine reduces aerobic and anaerobic bacterial growth on skin and within surgical sites, colonization of intravascular catheters, and surgical site

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**Table 1.** Published Studies Comparing the Use of Povidone-Iodine or Chlorhexidine with Sequential Use of These Cutaneous Antiseptic Agents

| Sequential order of cutaneous antiseptics: povidone-iodine (P-I) followed by chlorhexidine (CHG) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Sellers, et. al.** (3)*† | Proportion of umbilicus surgical site cultures without aerobic growth | **May, et. al.** (4)‡ | Proportion of skin allograft cultures without aerobic or anaerobic growth | **Ngai, et. al.** (5)‖ | Cesarean surgical site infection | **Patrick, et. al.** (6)‖ | Proportion of spine surgical site skin cultures + muscle biopsy cultures + wound wash out cultures without aerobic or anaerobic growth | Proportion of spine muscle biopsy cultures + wound wash out cultures without aerobic or anaerobic growth | Proportion of cultures without aerobic growth; proportion of cultures without anaerobic growth; proportion of cultures with high colony counts | Superficial surgical site infection |
| 0.5% CHG in 70% ethyl alcohol (N = 75)<br><br>P-I, then 0.5% CHG in 70% ethyl alcohol N = 30) | 36%<br><br>70% ($p < 0.01$) | 10% P-I surgical scrub, then 10% P-I solution, then 70% isopropanol (N = 2940)<br><br>10% P-I surgical scrub, then 4% aqueous CHG, then 70% isopropanol (N = 323) | 86%<br><br>94% ($p = 0.0002$) | P-I + alcohol (N = 463)<br><br>CHG + alcohol (N = 474)<br><br>P-I + alcohol, then CHG + alcohol (N = 467) | 4.6%<br><br>4.5%<br><br>3.9% (OR 0.85 [95% CI 0.44-1.61] compared to other groups; using multivariate regression analysis, OR 0.74 [95% CI 0.38-1.44] compared to other groups; OR 0.17 [95% CI 0.04-0.77] for 263 patients with Class III obesity compared to other groups) | 10% P-I + 95% ethanol with 5% methanol, then 10% P-I + 95% ethanol with 5% methanol (N = 204)<br><br>10% P-I + 95% ethanol with 5% methanol, then 2% CHG in 70% isopropyl alcohol (N = 203) | 58%<br><br>71% OR 0.57 [95% CI 0.38-0.87] | 70%<br><br>81% OR 0.55 [95% CI 0.34-0.86] | 78%; 61%; 67%<br><br>90% OR 0.39 [95% CI 0.22-0.68]; 71% OR 0.65 [95% CI 0.43-0.98]; 77% OR 0.62 [95% CI 0.40-0.96] | 3.4%<br><br>1.5% ($p = 0.3$) |
| Sequential order of cutaneous antiseptics: CHG followed by P-I | | | | | | | | | | |
| **Langgartner, et. al.** (7)‖ | Proportion of central venous catheter tip cultures without aerobic growth | **Guzel, et. al.** (8)+ | Cranial & spine surgical site cultures without aerobic growth | **Blonna et. al.** (9)+ | Proportion of shoulder surgical site cultures without growth of *S. epidermidis*; *P. acnes*; or *S. aureus* | Average number of colony forming units (CFU) of bacteria in shoulder surgical site cultures for *S. epidermidis*; *P. acnes*; or *S. aureus* | | | | |

(*Continued*)

**Table 1.** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| **Sequential order of cutaneous antiseptics: povidone-iodine (P-I) followed by chlorhexidine (CHG)** | | | | | | |
| 10% P-I (N = 97) | 69% | 15% aqueous CHG (N = 100) | 86% | 10% P-I + 50% isopropyl alcohol (N = 40) | 80%; 82%; 100% | 234 CFU; 961 CFU; 0 CFU |
| 0.5% CHG + 70% propanol, then P-I (N = 45) | 76% | 15% aqueous CHG, then 10% P-I (N = 100) | 100% (p < 0.001 compared to CHG alone) | 4% aqueous CHG, then 10% P-I + 50% isopropyl alcohol (N = 40) | 97% (p = 0.016); 82%; 100% | 7 CFU (p = 0.03); 161 CFU (p = 0.07); 0 CFU |
| 0.5% CHG + 70% propanol, then P-I (N = 43) | 95% (p = 0.001 compared to P-I; p = 0.009 compared to CHG + propanol) | 15% aqueous CHG, then 10% P-I, then 10% P-I (N = 100) | 100% (p < 0.001 compared to CHG alone) | | | |
| **Unspecified sequential order of cutaneous antiseptics** | | | | | | |
| **Davies et. al.** (10)° | Craniotomy surgical site infection | | | | | |
| 2% CHG +70% isopropyl alcohol, or 0.5% CHG + 70% ethanol (N = 276) | 2.5% | | | | | |
| 10% P-I + 95% ethanol with 5% methanol, or 10% aqueous P-I (N = 654) | 3.2% | | | | | |

Note: no concentration of cutaneous antiseptic is noted in the Table if it was not specified in the referenced publication.
*No mention of randomization; †CHG neutralization used; ‡Cohort study; ||Prospective, randomized study; ⁺Prospective, patients served as their own control; specimens not transported anaerobically but received in the microbiology lab within 1 hour of collection; °Retrospective, non-randomized study.

infections. A meta-analysis found that "complete bacterial decolonization" of surgical sites was more likely with sequential use of povidone-iodine and chlorhexidine than either antiseptic alone (odds ratio [OR], 0.18; 95% confidence interval [CI], 0.1–0.31]).[11] This finding may reflect different mechanisms of action of these antiseptic agents. In addition to the aforementioned studies, concurrent use of these antiseptics leads to a greater reduction of *Staphylococcus aureus* on mucosal tissue compared to either antiseptic alone.[12]

Multiple studies have found that heavy colonization of intravascular catheter insertion sites independently increases risk of catheter-related bloodstream infection.[13] Surprisingly, this correlation was not found in 2 studies that assessed the bioburden of the surgical site and surgical site infection.[14,15] However, these 2 latter studies involved 20 and 41 infections, respectively, and they may have been underpowered to unequivocally confirm or refute an association between heavy incisional colonization and surgical site infection.

This review has a number of limitations. The included studies differed by concentrations of povidone-iodine and chlorhexidine, whether or not povidone-iodine or chlorhexidine was combined with alcohol, duration of contact time with skin, mode of application (eg, paint or scrub), and study design (eg, prospective, randomized study). Only 3 studies[4,6,7] controlled for sequential use of the same cutaneous antiseptic agent twice (ie, povidone-iodine twice or alcoholic chlorhexidine twice) compared to applying these antiseptics sequentially (ie, alcoholic chlorhexidine followed by povidone-iodine). Sequential use led to significant improved outcome measures in each of these studies. One study used a neutralizer to minimize carryover of the antiseptic when culturing skin,[3] and others did not. These studies did not assess novel additional agents that penetrate deeper layers of the skin in an effort to reduce such potential pathogens as *Cutibacterium acnes*.[16,17] Lastly, some of the studies were underpowered to show a significant difference in outcomes.

In conclusion, a number of advances have led to a reduction in the risk surgical site infections and catheter-related infections. Despite the aforementioned limitations, the published data suggest that sequential use of povidone-iodine–containing and chlorhexidine-containing cutaneous antiseptics may be beneficial beyond use of either agent alone for surgical site preparation, particularly for high-risk cases, and for insertion and maintenance of transcutaneous devices that are left in situ (eg, tunneled intravascular catheters, left ventricular assist device, of nephrostomy tubes). Prospective, multicentered, randomized trials should be conducted to more rigorously address the utility of this relatively low cost, low-tech approach to prevention of healthcare-associated infections. We cannot sterilize living skin, but further reducing the bioburden prior to invasive procedures holds promise in mitigating risk.

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