Efficacy of surgical skin preparation with chlorhexidine in alcohol according to the concentration required to prevent surgical site infection: meta-analysis

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Abstract

Background: A combination of chlorhexidine gluconate and alcohol (CHG–alcohol) is recommended for surgical skin preparation to prevent surgical site infection (SSI). Although more than 1 per cent CHG–alcohol is recommended to prevent catheter-related bloodstream infections, there is no consensus regarding the concentration of the CHG compound for the prevention of SSI.

Methods: A systematic review and meta-analysis was performed. Four electronic databases were searched on 5 November 2020. SSI rates were compared between CHG–alcohol and povidone-iodine (PVP-I) according to the concentration of CHG (0.5 per cent, 2.0 per cent, 2.5 per cent, and 4.0 per cent).

Results: In total, 106 of 2716 screened articles were retrieved for full-text review. The risk ratios (RRs) of SSI for 0.5 per cent (6 studies) and 2.0 per cent (4 studies) CHG–alcohol were significantly lower than those for PVP-I (RR = 0.71, 95 per cent confidence interval (c.i.) 0.52 to 0.97; RR = 0.52, 95 per cent c.i. 0.31 to 0.86 respectively); however, no significant difference was observed in the compounds with a CHG concentration of more than 0.2 per cent.

Conclusions: This meta-analysis is the first study that clarifies the usefulness of an alcohol-based CHG solution with a 0.5 per cent or higher CHG concentration for surgical skin preparation to prevent SSI.

Introduction

Surgical site infection (SSI) is the third most common category of healthcare-associated infections, with a prevalence of 15.7 to 31.0 per cent among all healthcare-associated infections1,2. In one systematic review, most studies revealed an economic benefit associated with prevention of SSI3. Several guidelines for the prevention of SSI have been published4–6. Approximately half of SSIs are estimated to be preventable by application of evidence-based strategies7. A bundle approach is suggested to decrease SSIs, and surgical site skin preparation is one of the essential elements used in bundle approaches8–10. In particular, Leaper and Ousey11 recommended the use of a 2 per cent chlorhexidine gluconate in alcohol (CHG–alcohol) skin preparation, postoperative negative-pressure wound therapy, and antiseptic surgical dressings because of the high quality of evidence. Two meta-analyses suggested a significant benefit of using CHG–alcohol compared with aqueous povidone-iodine (PVP-I) with moderate-quality evidence6,12; however, a low quality of evidence was shown when the risk of SSI was compared between CHG–alcohol and PVP-I in alcohol-based solutions.

The concentration of the CHG solution ranges from 0.5 per cent to 4.0 per cent, but there are no data that specify the ideal concentration for surgical preparation to prevent SSI. In contrast, the Centers for Disease Control and Prevention guidelines for the prevention of intravascular catheter-related bloodstream infection recommend preparing clean skin with a higher than 0.5 per cent chlorhexidine (not 0.5 per cent preparation) in alcohol solution. This recommendation is based on the fact that when 0.5 per cent chlorhexidine preparation was compared with 10 per cent PVP-I, no differences were seen in either central venous catheter colonization or catheter-related bloodstream infection13,14. Pages et al15 reported that compared with PVP-I in alcohol, the incidence of catheter-related infection was lower with 2 per cent chlorhexidine-alcohol and similar with higher than 1 per cent CHG–alcohol after controlling for potential confounders.

A 2 per cent CHG–70 per cent isopropyl alcohol solution has become widely used for both preparation during central venous catheter insertion and preparation of the surgical site16,17; however, such compounds are not available in some countries, including Japan, and they often have irritating effects on the skin when a 2 per cent or higher concentration is used18–20. The efficacy of a 0.5 per cent or 1.0 per cent chlorhexidine skin preparation with alcohol for the prevention of SSI remains unclear. The present study was performed to identify the concentration of CHG in alcohol-based solution for skin...
preparation to prevent SSI compared with PVP-I. The secondary aim was to compare the SSI rate between skin preparations of CHG–alcohol and PVP-I in alcohol.

**Methods**

**Search strategy**

This work is reported according to the PRISMA guidelines. The PRISMA checklist is provided in Table S1. Four electronic databases (PubMed, Cochrane Library, Web of Science, and Clinicaltrials.gov) were searched on 5 November 2020. Three reviewers (T.H., S.T., and T.M.) independently searched these literature databases using the following search terms: ‘Chlorhexidine’, ‘Chlorhexidine gluconate’, ‘CHG’, ‘Povidone-iodine’, ‘Povidone-iodines’, ‘Povidone iodines’, ‘Povidone iodine ethanol’, ‘Povidone Iodine’, ‘Povidone-Iodine’, ‘PVP-I’, ‘PVP-Iodine’, ‘PVPI’, and 60 other words with one or more search results in the databases (Table S2). After the search, the pooled articles were screened and duplicated articles were excluded.

**Selection of studies**

Randomized clinical trials (RCTs) that met the following criteria were included in the meta-analysis: comparison of the SSI rate after skin preparations for surgery using CHG–alcohol and PVP-I; use of antiseptics for preparation of the surgical site in the operating room, not for washing (bathing and showering) separately outside of the operating room; and availability of detailed information in English. At least two authors (T.H., T.M., J.K., I.S., Y.T., and T.M.) independently screened the literature. During the screening, disagreements were resolved through discussions with a third reviewer (S.T.).

**Data extraction**

Two authors (T.H. and S.T.) independently extracted data from the included studies. Disagreements were resolved by discussions. The following information was extracted: study design, country, study interval, detailed information of each antiseptic (concentration and solution), reported outcome, skin preparations before use of the two antiseptics, observation interval, definition of SSI, patients included, exclusion criteria, number of participants based on intention-to-treat (ITT) (or per-protocol set if ITT was unavailable), number of participants with SSI, and number of participants with adverse events.

**Outcomes analysed**

The primary purpose of this study was the efficacy of decreasing the SSI risk by CHG–alcohol versus PVP-I (alcohol-based/aqueous solution) according to the CHG concentration. The following terms in each study were defined as SSI: wound infection, postoperative infection, wound complication, and postoperative
Table 1 Characteristics of studies included in the present meta-analysis

| Study               | Study design    | Country, time interval | CHG (concentration, solution) (%) | PVP-I (concentration, solution) (%) | Reported outcome                                                                 | Skin washing before use of the two antiseptics | Observation interval | Definition of SSI |
|---------------------|-----------------|------------------------|-----------------------------------|-------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------|---------------------|-------------------|
| Berry 1982          | Prospective, randomized study | England, 1978-1980     | 0.5, 70 isopropyl alcohol         | A: 10, alcohol B: 7.5, N/A          | Wound infection                                                                  | Two applications with sterile sponges         | 3 to 4 days          | N/A               |
| Brown 1984          | Prospectively randomized study | India, 1979-1980       | 0.5, 70 isopropyl alcohol         | 7.5, N/A                            | Wound infection                                                                  | Removal of obvious foreign material present with a clean sponge followed by a spray application of 0.5% CHG in 70% isopropyl alcohol | 6 min scrub with PVP-I soap, then painted with aqueous PVP-I solution that absorbed with a sterile towel | N/A               | A minor wound infection: an infected wound with superficial, separation (less than 1 cm) involving less than one-third of the incision or induration of the wound edge believed by the surgeon to be secondary to infection. A major wound infection: an infected wound with separation of the wound edges greater than one-third of the length of the incision or frank wound infection with evidence of purulent exudate or abscess. |
| Veiga 2008          | RCT             | Brazil, N/A            | 0.5, alcohol                       | 10, alcohol                         | Postoperative infection                                                          | A vigorous scrub with antiseptic soap, followed by absorption with a sterile towel and painting | 30 days              | N/A               |
| Cheng 2009          | Prospective randomized study | England, 2007-2008     | 0.5, 70 isopropyl alcohol         | 10, 23 isopropyl alcohol            | Postoperative infections or wound complications                                  | Scrubbed with a sterile surgical bristled brush for 3 min and then painted | N/A                 | N/A               |
| Paocharoen 2009     | Prospective randomized trial | Thailand, 2006-2008    | 4, 70 isopropyl alcohol           | N/A, N/A                            | Postoperative surgical wound infection                                           | 5 min scrubbing, then paint                  | 1 month              | If a surgical wound drained purulent material or if the surgeon judges it to be infected and opens it |
| Sistla 2010         | Prospective randomized trial | India, N/A             | 2.5, 70 ethanol                    | 10, N/A                             | SSI                                                                             | Applied in concentric circles beginning from the site of incision to the periphery and allowed to dry before the surgical site was draped | 30 days              | The CDC criteria  |
| Rodrigues 2013      | Randomized, longitudinal study | Brazil, 2011           | 0.5, alcohol                       | 10, hydro alcohol                   | SSI                                                                             | The skin was prepared in the same manner as it was for the PVP-I group; however, the cleaning was carried out with water and 20 ml 2% CHG soap, and complementation with 0.5% alcoholic CHG | N/A                 | The presence of at least one of the following signs: fever, without other apparent cause, pain, heat, swelling, or confluent erythema around the incision and extrapolating the boundaries of the wound, pus in the incision site or in the deep soft tissue, or in organ/cavity handled during operation; presence of abscesses or, in the case of deep tissues, histological or radiological evidence suggestive of infection, isolated |
Table 1 (continued)

| Study | Study design | Country, time interval | CHG (concentration, solution) (%) | PVP-I (concentration, solution) (%) | Reported outcome | Skin washing before use of the two antiseptics | Observation interval | Definition of SSI |
|-------|--------------|------------------------|-----------------------------------|-------------------------------------|------------------|-----------------------------------------------|---------------------|------------------|
| HK2020 | RCT          | Turkey, 2017–2019      | 4, alcohol                        | N/A, N/A                            | SSI              | Habitanol 1000 ml solution (Kimpa Drugs, Istanbul, Turkey) | 30 days | CDC guidelines |
| Kesani 2019 | Randomized prospective study | N/A, 2017 | 2, 70 isopropyl alcohol | 1, 50 2-propanol | SSI | Before operation, scrubbed at the surgical site by either the CHG–alcohol (2% CHG and 70% isopropyl alcohol) or PVP-I and 50% 2-propanol (B Braun Medical AG; Melsungen, Germany) | 30 days | CDC definitions |
| Ritter 2019 | Prospective randomized trial | N/A, 2014–2015 | 2, 70 isopropyl alcohol | 1, 50 2-propanol | SSI | Scrubbed that contained 10% PVP-I, followed by drying with a sterile towel after 1 min and 3 applications of 10% PVP-I in 70% alcohol | 30 days | CDC criteria |
| Springel 2017 | RCT          | USA, 2014–2016         | 2, 70 isopropyl alcohol | 10, aqueous    | SSI | Paint that contained 0.75% PVP-I aqueous scrub followed by 1.0% PVP-I aqueous paint | N/A | US National Healthcare Safety Network, CDC definitions |
| Nabeel 2014 | RCT          | USA, 2013–2014         | N/A, alcohol                      | N/A, 50 propyl alcohol | SSI | Had a shower and a bath with CHG soap on the day before surgery, then disinfected twice | 30 days | CDC guidelines |
| Kesani 2019 | Randomized prospective study | N/A, 2017 | 2, 70 isopropyl alcohol | 10, surgical spirit | SSI | Before operation, scrubbed at the surgical site by either the CHG–alcohol (2% CHG and 70% isopropyl alcohol) or PVP-I and 50% 2-propanol (B Braun Medical AG; Melsungen, Germany) | 30 days | CDC definitions |
| Kesani 2019 | Randomized prospective study | N/A, 2017 | 2, 70 isopropyl alcohol | 10, surgical spirit | SSI | Before operation, scrubbed at the surgical site by either the CHG–alcohol (2% CHG and 70% isopropyl alcohol) or PVP-I and 50% 2-propanol (B Braun Medical AG; Melsungen, Germany) | 30 days | CDC definitions |
| Perek 2019 | Randomized clinical study | Poland, 2011 | N/A, 70 ethanol | 10, 70 alcohol | SSI | Painted with 5% PVI-I solution three times | 30 days | CDC criteria |

N/A, not available; CHG, chlorhexidine gluconate; PVP-I, povidone-iodine; RCT, randomized clinical trial; SSI, surgical site infection; CDC, Centers for Disease Control and Prevention.

surgical wound infections. As the secondary purpose of this study, the following analyses for SSI risk were performed: overall comparison between CHG–alcohol and PVP-I; comparison between CHG–alcohol and PVP-I-alcohol; comparison between CHG–alcohol and PVP-I according to the PVP-I concentration; comparison of the two antiseptic groups stratified by wound classification (clean, clean-contaminated, and contaminated wound)22; and comparison of the two antiseptic groups stratified by SSI type (superficial incisional, deep incisional, and organ/space SSI)22. The comparative risk of adverse events between CHG–alcohol and PVP-I was also evaluated.

Assessment of risk of bias and publication bias

The two authors (T.H. and S.T.) independently assessed the risk of bias using the Cochrane Handbook for Systematic Reviews of Interventions23. The bias assessments performed in the present study were random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. The risk of other bias was judged to be low when the trials received no financial support from pharmaceutical companies.
### Table 2 Characteristics of participants

| Study               | Patients included                                                                 | Exclusion criteria                                                                                                                                                                                                 | Number of participants | Number of SSIs |
|---------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------------|
| Berry 1982<sup>24</sup> | Elective surgical cases Patients from both private and clinic services            | Patients sensitive to one or other preparation. Patients underwent operations not included in the study protocol. Patients with death within 48 h of the operation. Patients required a second operation within 48 h. | 453                    | 413            |
| Berry 1984<sup>25</sup> |                                                                                   |                                                                                                                                                                                                                     | 378<sup>*</sup>         | 359            |
| Veiga 2008<sup>26</sup> | Age 18 years or older Scheduled for elective and clean plastic surgery procedures | N/A                                                                                                                                                                                                                 | 0                      | 125            |
| Cheng 2009<sup>27</sup> | Undergoing foot surgery                                                          | Patients with current open wounds skin ulcers and/or sores. Patients with a history of onychomycosis, paronychia, or nail deformity. Patients with poorly controlled diabetes mellitus or recent antibiotic use (within 1 week of surgery). | 0                      | 25             |
| Pacharoen 2009<sup>28</sup> | Age 18–60 years                                                                   | Patients with a history of allergy to study agent. Patients with recurrent or complicated inguinal hernia. Patients with a history of allergy to the antiseptics.                                                                 | 250                    | 250            |
| Sistla 2010<sup>29</sup> | Elective inguinal hernia repair                                                  | Patients with breaches in the rules of antisepsis and asepsis, changing the classification of the surgical site. Patients with an abandoned follow-up.                                                                 | 271                    | 285            |
| Rodrigues 2013<sup>30</sup> | Age 18 years or older Open-access elective procedures, with subcostal abdominal, vertical abdominal and thoracic incisions | Patients with pre-existing infections (for example infective endocarditis) treated with antibiotics. Patients operated on emergently due to complications resulting from percutaneous interventions. Patients treated surgically for aortic aneurysms or acute dissections (due to more aggressive perioperative antibiotic prophylaxis). Patients requiring prolonged (exceeding 72 h) intubation and mechanical ventilation. | 103<sup>*</sup>         | 102            |
| Perek 2013<sup>31</sup>  | Elective cardiac procedures carried out via median sternotomy                    | Patients with pre-existing infections (for example infective endocarditis) treated with antibiotics. Patients operated on emergently due to complications resulting from percutaneous interventions. Patients treated surgically for aortic aneurysms or acute dissections (due to more aggressive perioperative antibiotic prophylaxis). Patients requiring prolonged (exceeding 72 h) intubation and mechanical ventilation. | 47                     | 47             |
| Ngai 2015<sup>32</sup>   | Gestation period 37 or more weeks on best obstetric estimate scheduled or non-emergent Caesarean delivery | Patients had a urogenital tract infection within 2 weeks of delivery. Patients with a 2-week or more history of steroid delivery during their pregnancy. Patients younger than 18 years old.                                                                 | 474                    | 463            |
| Srinivas 2015<sup>33</sup> | Age 18–70 years Uniformly received the preoperative antibiotic during the induction of anaesthesia | Patients with no consent for the trial. Patients with a history of allergy to CHG, alcohol, or iodophors. Clinical/microbiological evidence of infection at/adjacent to the surgical site. Patients with ongoing systemic sepsis. Patients died intraoperatively or before the completion of the 30-day follow-up interval. Patients left the hospital against medical advice or lost to follow-up. Patients required a second operation within two weeks of the first operation. | 163                    | 188            |
| Salama 2016<sup>34</sup> | Age 18–42 years BMI 20–35 Elective and non-elective Caesarean sections           | Patients with a history of allergy to CHG, alcohol, or iodophors. Patients with a history of rupture of membranes more than 24 h. Patients with documented concomitant infections such as chorioamnionitis, pyelonephritis, mastitis. Patients with diabetics or obese. Patients with BMI greater than 35. | 204                    | 201            |
| Springel 2017<sup>35</sup> | Age 18 years or older Delivery, or intrapartum once a plan for Caesarean         | Patients with no key study personnel to complete study-related procedures. Patients allergic to PVP-I or CHG.                                                                                                                                  | 461                    | 471            |

(continued)
If sufficient information for assessment was not described, the risk of bias was judged to be unclear. In addition, publication bias was assessed by visual examination of a funnel plot and statistical analyses using Egger’s test.

Results analyses and statistical analyses
The extracted data were analysed using Review Manager for Windows (RevMan version 5.4.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and forest plots were prepared. The Mantel–Haenszel random-effects model was used to calculate the risk ratios (RRs) and 95 per cent confidence intervals (95 per cent c.i.). Between-study heterogeneity was quantified using the $I^2$ statistic, which was assessed according to the following criteria: $I^2$ less than 25 per cent, no heterogeneity; $I^2$ of 25–50 per cent, moderate heterogeneity; and $I^2$ greater than 50 per cent, high heterogeneity. A $P$ value of less than 0.050 was considered to indicate a significant difference.

Results

**Literature search results**

Figure 1 shows the screening and selection of studies. From the four electronic databases, 2716 articles were obtained to be screened and 382 duplicate articles were excluded. After screening the titles and abstracts, 2228 articles were excluded, and 106 articles were retrieved for full-text review. Of these 106 articles, 91 did not meet the inclusion criteria. Finally, 15 studies were included in the meta-analysis.

**Characteristics of included studies and participants and assessment of risk of bias**

Table 1 summarizes the characteristics of the studies included in the present meta-analysis. The CHG concentration ranged from 0.5 per cent to 4.0 per cent, and the PVP-I concentration ranged from 1.0 per cent to 10.0 per cent. Data on the CHG and PVP-I concentrations were unavailable in two studies and four studies respectively. Of 15 included studies, 14 studies described the follow-up interval, and nine studies had a follow-up of 30 days. Table 2 summarizes the characteristics of the participants. In each article, the number of participants was extracted based on ITT. The number of ITT participants was unavailable in three studies; therefore, the number of per-protocol set patients was extracted instead of ITT participants in these three studies. In total, 6974 participants were involved in the studies: 3472 participants were disinfected with CHG–alcohol and 3502 participants were disinfected with PVP-I.

**Overall comparison of SSI rate between CHG–alcohol and PVP-I**

SSIs were detected in 516 participants (208 in the CHG–alcohol group and 308 in the PVP-I group). CHG–alcohol was significantly more effective than PVP-I (RR = 0.69, 95 per cent c.i. 0.56 to 0.84, $P = 0.0002$, $I^2 = 18$ per cent) (Fig. 3).
Comparison of SSI rate between CHG–alcohol and PVP-I (alcohol-based/aqueous solution) according to CHG concentration

The CHG concentrations in CHG–alcohol were stratified into 0.5 per cent, 2.0 per cent, 2.5 per cent, and 4.0 per cent. No RCTs compared 1.0 per cent CHG–alcohol and PVP-I. Six studies compared 0.5 per cent CHG–alcohol and PVP-I. The SSI rate in the 0.5 per cent CHG–alcohol group was significantly lower than that in the PVP-I group (RR = 0.71, 95 per cent c.i. 0.52 to 0.97, P = 0.03, I² = 21 per cent) (Fig. 4a). Four RCTs compared 2.0 per cent CHG–alcohol and PVP-I. A significantly lower SSI rate was observed in the 2.0 per cent CHG–alcohol group than in the PVP-I group (RR = 0.52, 95 per cent c.i. 0.31 to 0.86, P = 0.01, I² = 55 per cent) (Fig. 4b). No significant difference in the SSI rate was found between the greater than 2.0 per cent CHG group and the PVP-I group (2.5 per cent CHG, RR = 0.77, 95 per cent c.i. 0.40 to 1.51, P = 0.46, 4.0 per cent CHG, RR = 0.86, 95 per cent c.i. 0.46 to 1.61, P = 0.64, I² = 0 per cent) (Fig. 4c, d), possibly because of the lack of power caused by an insufficient number of included studies. Other PVP-I concentrations, commonly using concentrations such as 5 per cent and 7.5 per cent, could not be analysed because only one study was available at each concentration.

Other comparisons of SSI rate between CHG–alcohol and PVP-I

In the comparison among the alcohol-based solutions (Fig. 5), CHG–alcohol was associated with a significantly lower SSI rate than alcohol-based PVP-I (RR = 0.58, 95 per cent c.i. 0.35 to 0.97, P = 0.04, I² = 52 per cent) (26, 27, 30–33, 35–38). In the comparison of the SSI risk associated with these antiseptic solutions according to the PVP-I concentration (lower than 10 per cent and 10 per cent), significantly higher risks were found with PVP-I irrespective of the PVP-I concentration (RR = 0.67, 95 per cent c.i. 0.46 to 0.98, P = 0.04, I² = 0 per cent and RR = 0.62, 95 per cent c.i. 0.40 to 0.96, P = 0.03, I² = 53 per cent respectively) (Fig. S1a, b).

Subgroup analyses of the effectiveness of preventing SSI between CHG–alcohol and PVP-I were conducted according to the wound classification (Fig. S2a–c) and SSI type (Fig. S3a–c). Four studies showed data for clean wounds, four for clean-contaminated wounds, and one for contaminated wounds. The effectiveness of CHG–alcohol over PVP-I was demonstrated only for clean-contaminated wounds (RR = 0.56, 95 per cent c.i. 0.37 to 0.85, P = 0.006, I² = 50 per cent) (Fig. S2b); no significant difference was observed in the other wound classes (Fig. S2a, c). In the analyses of SSI type, significant benefits in reducing the SSI risk with CHG–alcohol compared with PVP-I were observed for superficial incisional SSI (26, 30–33) and deep incisional SSI (26, 30–33) (RR = 0.71, 95 per cent c.i. 0.54 to 0.93, P = 0.01, I² = 9 per cent and RR = 0.47, 95 per cent c.i. 0.24 to 0.91, P = 0.03, I² = 0 per cent respectively) (Fig. S3a, b). No significant difference between the two antiseptic groups was observed for organ/space SSI (RR = 1.23, 95 per cent c.i. 0.54 to 2.82, P = 0.62, I² = 0 per cent) (Fig. S3c).

Comparison of adverse events between CHG–alcohol and PVP-I

Allergic reactions were the only reported adverse events in the included studies, and no significant difference was observed between the CHG–alcohol group and PVP-I group (RR = 0.75, 95 per cent c.i. 0.17 to 3.29, P = 0.70) (Fig. S4) (26, 30–33).

Assessment of publication bias

Publication bias was assessed using funnel plotting and Egger’s test (Fig. 6). No statistically significant publication bias was found (P = 0.5703).

Discussion

This is the first meta-analysis to compare the risk of SSI between CHG–alcohol and PVP-I according to the CHG concentration. The results showed that both 2.0 per cent compound and 0.5 per cent alcohol.
### Fig. 3 Forest plot comparing SSI rate between CHG–alcohol and PVP-I

Risk ratios are represented by diamond shapes, and 95 per cent confidence intervals (c.i.) are represented by horizontal lines. CHG, chlorhexidine gluconate; PVP-I, povidone-iodine.

### Fig. 4 Forest plot of subgroup analyses comparing SSI rate among different concentrations ranging from 0.5 per cent to 4.0 per cent CHG–alcohol and PVP-I. 

(a) CHG–alcohol = 0.5%, (b) CHG–alcohol = 2.0%, (c) CHG–alcohol = 2.5%, (d) CHG–alcohol = 4.0%

Risk ratios are represented by diamond shapes, and 95 per cent confidence intervals (c.i.) are represented by horizontal lines. CHG, chlorhexidine gluconate; PVP-I, povidone-iodine.
Hasegawa et al. treated a 9 percent compound more effectively prevented SSI than PVP-I. This is an important step in clinical practice for countries in which 2 percent CHG–alcohol is not available. Because of the risk of anaphylaxis, Japanese pharmaceutical regulations prohibit the application of CHG to mucosal surfaces, including in dental care, and limit the CHG concentration in skin antiseptics to a maximum of 1 percent.

To determine the recommended CHG concentration in CHG–alcohol, direct comparison with different CHG concentrations is required. In one study, the antimicrobial activity of a 2.0 percent CHG–alcohol solution was superior to that of a 0.5 percent CHG–alcohol solution when challenged with a Staphylococcus epidermidis biofilm; however, significantly increased preventative effects against SSI have not been demonstrated by head-to-head RCTs between different CHG concentrations. Three studies compared the efficacy of CHG–alcohol with different CHG concentrations by skin cultures. In a study that evaluated the mean bacterial count reductions for the use of surgical skin preparation, the antimicrobial effectiveness of 1.0 percent CHG–alcohol was superior to that of 0.5 percent CHG–alcohol, particularly at the abdominal site.

CHG–alcohol has immediate and persistent activity, with the alcohol having a rapid mode of action and the CHG offering residual activity. CHG binds to anionic cutaneous protein, resulting in a prolonged antiseptic effect. Hence, a higher concentration might be required for surgical skin preparation.

Similarly, Casey et al. compared 0.5 percent CHG–alcohol with 2.0 percent CHG–alcohol for skin antisepsis in patients undergoing vein graft harvesting for coronary artery bypass graft surgery. There was a significant difference in the culture-positive rate between 0.5 percent CHG–alcohol and 2.0 percent CHG–alcohol after incision closure, which occurred at approximately 90 min after application of the skin antiseptics in each group (33.3% versus 12.5% respectively). In addition, significantly fewer microorganisms within the adhesive dressings removed 24 h after application were observed in the 2.0 percent CHG–alcohol group than in the 0.5 percent CHG–alcohol group, which might indicate that 2.0 percent CHG–alcohol more effectively kills microorganisms located in the lower layers of the skin. In contrast, Nishihara et al. reported that there was no significant difference in the log reduction of the bacterial count among CHG preparations of 0.5 percent, 1.0 percent, and 2.0 percent.

Although the precise prevalence of CHG allergy is unclear, the numbers of case reports describing such allergy have recently increased, especially in the perioperative setting. A study compared the efficacy of CHG–alcohol with different CHG concentrations by skin cultures. In a study that evaluated the mean bacterial count reductions for the use of surgical skin preparation, the antimicrobial effectiveness of 1.0 percent CHG–alcohol was superior to that of 0.5 percent CHG–alcohol, particularly at the abdominal site. CHG–alcohol has immediate and persistent activity, with the alcohol having a rapid mode of action and the CHG offering residual activity. CHG binds to anionic cutaneous protein, resulting in a prolonged antiseptic effect. Hence, a higher concentration might be required for surgical skin preparation.

Fig. 5 Forest plot comparing SSI rate between CHG–alcohol and PVP-I-alcohol

Risk ratios are represented by diamond shapes, and 95 per cent confidence intervals (c.i.) are represented by horizontal lines. CHG, chlorhexidine gluconate; PVP-I, povidone-iodine.

Fig. 6 Funnel plot of primary outcome

SSI rate based on 15 studies comparing chlorhexidine gluconate-alcohol and povidone-iodine. The dashed line indicates the pooled risk ratio (RR) of 0.69.
concentrations of CHG (2–4 per cent) possibly have irritant effects on the skin, leading to an impaired skin barrier and increasing the risk of allergy. Nishihara et al. reported the mean visual scores of skin irritation and the total cumulative irritation scores after repeated exposure to test products, and lower scores were found in the 1 per cent than 2 per cent CHG–alcohol group. The potential risks versus benefits should be considered before proposing an adequate CHG concentration.

Previous meta-analyses have shown that alcohol-based antiseptic solutions are more effective than aqueous solutions in reducing the risk of SSI. The present meta-analysis demonstrated that CHG was more protective than PVP-I in the evaluation limited to alcohol-based solution. Skin preparation is performed to prevent wound infection, and this meta-analysis confirmed that CHG–alcohol was significantly more protective than PVP-I against both superficial and deep incisional SSI but not against organ-space SSI. Surgical skin preparation with CHG–alcohol was superior to skin preparation with PVP-I for preventing SSI only after clean-contaminated surgery. An additional RCT is required to evaluate the effectiveness of CHG–alcohol in clean surgery.

This study had some limitations. First, washing the patient’s skin with antiseptics, which was performed separately outside the operating room, might have impacted the results. Some studies adopted the same antiseptic compound for both preoperative body washing (CHG soap or PVP-I soap) and skin preparation at the surgical site. Second, bias caused by the heterogeneity of SSI prevention protocols, including antimicrobial prophylaxis, and normothermia, should be considered. Of the 15 studies, 12 described the use of prophylactic antimicrobials; however, it was not possible to compile detailed information on criteria for use. Third, comparison with PVP-I in alcohol should be performed to confirm the effectiveness of 0.5 per cent CHG–alcohol. Fourth, considering the time course between the first and the last studies included in this meta-analysis, the improvement of medical care and medical technology during this interval should be considered as an important confounder. Last, only three studies described the time of exposure. Although application time of 3–5 min is recommended in PVP-I solution, a shorter drying time is permitted in CHG–alcohol.

An alcohol-based CHG solution with a CHG concentration of 0.5 per cent or higher can be used for surgical skin preparation to prevent SSI. CHG–alcohol was more effective than PVP-I irrespective of the type of solution (alcohol versus aqueous). Additional studies are required to propose an adequate CHG concentration by head-to-head comparison of the SSI rate and skin complications according to the CHG concentration.

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**Supplementary material**

Supplementary material is available at BJS Open online.

**Data availability**

All data generated or analysed during this study are included in this published article.

**References**

1. Magill SS, Hellinger W, Cohen J, Kay R, Bailey C, Boland B et al. Prevalence of healthcare-associated infections in acute care hospitals in Jacksonville, Florida. Infect Control Hosp Epidemiol 2012; 33:283–291
2. Health Protection Agency. Surveillance of Surgical Site Infections in NHS Hospitals in England, 2010/2011. London: Health Protection Agency, 2011
3. McFarland A, Reilly J, Manoukian S, Mason H. The economic benefits of surgical site infection prevention in adults: a systematic review. J Hosp Infect 2020; 106:76–101
4. Ban KA, Minei JP, Laronga C, Hartbrecht BG, Jensen EH, Fry DE et al. American College of Surgeons and Surgical Infection Society: surgical site infection guidelines, 2016 update. J Am Coll Surg 2017; 224:59–74
5. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg 2017; 152:784–791
6. World Health Organization. Global Guidelines for the Prevention of Surgical Site Infection. Geneva: World Health Organization 2018.
7. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. Infect Control Hosp Epidemiol 2011; 32:101–114
8. Mcgee MF, Kreutzer L, Quinn CM, Yang A, Shan Y, Halverson AL et al. Leveraging a comprehensive program to implement a colorectal surgical site infection reduction bundle in a statewide quality improvement collaborative. Ann Surg 2019; 270:701–711
9. Keenan JE, Speicher PJ, Thacker JKM, Walter M, Kuchibhatla M, Mantyh CR. The preventive surgical site infection bundle in colorectal surgery an effective approach to surgical site infection reduction and health care cost savings. JAMA Surg 2014; 149:1045–1052
10. Zywot A, Lau CSM, Stephen Fletcher H, Paul S. Bundles prevent surgical site infections after colorectal surgery: meta-analysis and systematic review. J Gastrointest Surg 2017; 21:1915–1930
11. Leaper D, Ousey K. Evidence update on prevention of surgical site infection. *Curr Opin Infect Dis* 2015;28:158–163
12. Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016; 16:e276–e287
13. O’Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011;39:S1–S34
14. Humar A, Ostromnecki A, Direnfeld J, Marshall JC, Lazar N, Houston PC et al. Prospective randomized trial of 10 per cent povidone-iodine versus 0.5 per cent tincture of chlorhexidine as cutaneous antiseptic for prevention of central venous catheter infection. *Clin Infect Dis* 2000;31:1001–1007
15. Pages J, Hazera P, Mégarbane B, du Cheyron D, Thuong M, Dutheil JJ et al. Chlorhexidine-alcohol versus povidone-iodine cutaneous antiseptics for the prevention of central venous catheter-related infection: a cohort and quasi-experimental multicenter study. *Intensive Care Med* 2016;42:1418–1426
16. Darouiche RO, Wall MJ Jr, Itani KMF, Otterson MF, Webb AL, Carrick MM et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med* 2010;362:18–26
17. Mimoz O, Lucte JC, Kerforne T, Pascal J, Souweine B, Goudet V et al. Skin antisepsis using chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet* 2015;386:2069–2077
18. Chiewchalemsri C, Somponrottanaphan M, Wongsa C, Thongngart T. Chlorhexidine allergy: current challenges and future prospects. *J Asthma Allergy* 2020;13:127–133
19. Nagendran V, Wicking J, Ekbote A, Ornyekwe T, Garvey LH. IgE-mediated chlorhexidine allergy: a new occupational hazard? *Occup Med (Chic Ill)* 2009;59:270–272
20. Bahal S, Sharma S, Garvey LH, Nagendran V. Anaphylaxis after disinfection with 2 per cent chlorhexidine wand applicator. *BMJ Case Rep* 2017:bcr2017219794
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71
22. Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN) Patient Safety Component Manual. https://www.cdc.gov/nhsn/pdfs/pscmanual/pscmanual_current.pdf (accessed January 2022)
23. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0, London, UK. (Cochrane Collaboration, 2011)
24. Berry AR, Watt B, Goldacre MJ, Thomson JW, McNair TJ. A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of postoperative wound infection. *J Hosp Infect* 1982;3:55–63
25. Brown TR, Ehrlich CE, Stehman FB, Golichowski AM, Madura JA, Eitzen HE. A clinical evaluation of chlorhexidine gluconate spray as compared with iodophor scrub for preoperative skin preparation. *Surg Gynecol Obstet* 1984;158:363–366
26. Veiga DF, Damasceno CAV, Veiga-Filho J, Figueiras RG, Vieira RB, Florenzano FH et al. Povidone iodine versus chlorhexidine in skin antisepsis before elective plastic surgery procedures: a randomized controlled trial. *Plast Reconsr Surg* 2008;122:170e–171e
27. Cheng KCK, Robertson H, St. Mart JP, Leanord A, McLeod I. Quantitative analysis of bacteria in footture surgery: a comparison of skin preparation techniques. *Foot Ankle Int* 2009;30:992–997
28. Paoccharoen V, Mingmalairak C, Apisarnthanarak A. Comparison of surgical wound infection after preoperative skin preparation with 4 per cent chlorhexidine and povidone iodine: a prospective randomized trial. *Artic J Med Assoc Thail* 2009;92:898–902
29. Sistla SC, Prabhu G, Sistla S, Sadasivan J. Minimizing wound contamination in a ‘clean’ surgery: comparison of chlorhexidine-ethanol and povidone-iodine. *Chemotherapy* 2010;56:261–267
30. Rodrigues AL, Simões MLFB. Incidência de infeccão do sítio cirúrgico com o preparo pré-operatório utilizando iodopovidonida 10 per cent hidroxicloína e clorexidina alcoólica 0,5 per cent. *Rev Col Bras Cir* 2013;40:443–448
31. Perek B, Lipski A, Stefaniak S, Jemielity M. Comparative analysis of the antiseptic effectiveness of two commercially available skin disinfectants in cardiac surgery—a preliminary report. *Kardiiochirurgia i Torakochirurgia Pol* 2013;10:177–181
32. Srinivas A, Kaman L, Raj P, Gautam V, Dahiya D, Singh G et al. Comparison of the efficacy of chlorhexidine gluconate versus povidone iodine as preoperative skin preparation for the prevention of surgical site infections in clean-contaminated upper abdominal surgeries. *Surg Today* 2015;45:1378–1384
33. Ngai IM, Van Arsdale A, Govindappagari S, Judge NE, Neto NK, Bernstein J et al. Skin preparation for prevention of surgical site infection after Cesarean delivery. *Obstet Gynecol* 2015;126:1251–1257
34. Salama FA, Yehia AH, Wahba KA, Abdelmoniem RM. Efficacy and safety of chlorhexidine versus povidone-iodine skin antisepsis in reducing surgical site infection in Cesarean sections. *Evid Based Women’s Heal* 2016;6:32–36
35. Springel EH, Wang XY, Sarfoh VM, Stetzer BP, Weight SA, Mercer BM. A randomized open-label controlled trial of chlorhexidine-alcohol versus povidone-iodine for Cesarean antisepsis: the CAPICA trial. *Am J Obstet Gynecol* 2017;217:e463.e1–e463.e8
36. Kesani VP, Talasila S SRS. Chlorhexidine-alcohol versus povidone-iodine-alcohol for surgical site antisepsis in caesarean section. *Int J Reprod Contraception Obstet Gynecol* 2019;8:1359–1362
37. Ritter B, Herlyn PKE, Mittlmeier T, Herlyn A. Preoperative skin antisepsis using chlorhexidine may reduce surgical wound infections in lower limb trauma surgery when compared to povidone-iodine—a prospective randomized trial. *Am J Infect Control* 2019;48:167–172
38. Gezer S, Yalvac HM, Gungör K, Yucesoy I. Povidone-iodine versus chlorhexidine alcohol for skin preparation in malignant and premalignant gynaecologic diseases: a randomized controlled study. *Eu J Obstet Gynecol Reprod Biol* 2020;244:45–50
39. Horan T, Gaynes R, Martone W, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol* 1992;13:606–608
40. Adams D, Quayum M, Worthington T, Lambert P, Elliott T. Evaluation of a 2 per cent chlorhexidine gluconate in 70 per cent isopropyl alcohol skin disinfectant. *J Hosp Infect* 2005;61:287–290
41. Nishihara Y, Kajiura T, Yokota K, Kobayashi H, Okubo T. Efficacy and safety of chlorhexidine gluconate in the prevention of intravascular catheter-related infection: a cohort study. *Control Clin Infect Dis* 2009;49:1251–1257
with either 0.5 per cent w/v or 2 per cent w/v chlorhexidine gluconate for skin preparation before harvest of the long saphenous vein used in coronary artery bypass grafting. *Am J Infect Control* 2015;43:816–820

43. Nishihara Y, Kajiura T, Katsuhiko Y, Kobayashi H, Okubo T. A comparative clinical study focusing on the antimicrobial efficacies of chlorhexidine gluconate alcohol for patient skin preparations. *J Infus Nurs* 2012;35:44–50

44. Rose MA, Garcez T, Savic S, Garvey LH. Chlorhexidine allergy in the perioperative setting: a narrative review. *Br J Anaesth* 2019;123:e95–e103

45. Beaudouin E, Kanny G, Morisset M et al. Immediate hypersensitivity to chlorhexidine: literature review. *Eur Ann Allergy Clin Immunol* 2004;36:123–126

46. Egner W, Helbert M, Sargur R, Swallow K, Harper N, Garcez T et al. Chlorhexidine allergy in four specialist allergy centres in the UK, 2009–13: clinical features and diagnostic tests. *Clin Exp Immunol* 2017;188:380–386

47. Fernandes M, Lourenço T, Lopes A, Spinola Santos A, Pereira Santos MC, Pereira Barbosa M. Chlorhexidine: a hidden life-threatening allergen. *Asia Pac Allergy* 2019;9:e29

48. Odedra KM, Farooque S. Chlorhexidine: an unrecognised cause of anaphylaxis. *Postgrad Med J* 2014;90:709–714

49. Antunes J, Van VR, Kochuyt A, Ceuppens J. Causes of perioperative anaphylaxis: A Flemish referral center experience. *J Allergy Clin Immunol* 2012;96:213

50. Durani P, Leaper D. Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation. *Int Wound J* 2008;5:376–387

51. Stinner DJ, Krueger CA, Masini BD, Wenke JC. Time-dependent effect of chlorhexidine surgical prep. *J Hosp Infect* 2011;79:313–316