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Title

The comparative efficacy of chlorhexidine gluconate and povidone-iodine antiseptics for the prevention of infection in clean surgery: A systematic review and network meta-analysis

Running head

NMA of antiseptics in clean surgery

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Competing Interests

None declared

Key words

Antiseptics; antisepsis; povidone-iodine; chlorhexidine gluconate; skin prep; infection; surgery; meta-analysis; network.

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Conflicts of Interest

There are no conflicts of interest.

Ethical review

Ethical review was not required as this is a review of published literature.

Mini abstract

Annually, there are >10 million clean operations worldwide, and infection is the most common and costly complication. Our network meta-analysis synthesizes 17 studies comparing five antiseptics in 14,593 individuals showing that alcoholic chlorhexidine gluconate 4-5% halves the risk of surgical site infection when compared to aqueous or alcoholic povidone-iodine preparations.

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Abstract

Objective: There is uncertainty around preoperative skin antisepsis in clean surgery. Network meta-analysis provides more precise estimates than standard pairwise meta-analysis and can rank interventions by efficacy, to better inform clinical decisions.

Background: Infection is the most common and costly complication of surgery. The relative efficacy of chlorhexidine gluconate (CHG) and povidone-iodine (PVI) based skin antiseptics in clean surgery remains unclear.

Methods: We searched for randomized or non-randomized studies comparing the effect of different preparations of CHG and PVI on the dichotomous outcome of surgical site infection. We included studies of adults undergoing clean surgery. We excluded studies concerning indwelling vascular catheters, blood sampling, combination antiseptics or sequential applications of different antiseptics. We performed a network meta-analysis to estimate the relative efficacy of interventions using relative risks.

Results: We included 17 studies comparing five antiseptics in 14,593 individuals. The overall rate of surgical site infection was 3%. Alcoholic CHG 4-5% was ranked as the most effective antiseptic as it halved the risk of surgical site infection when compared to Aqueous PVI (RR 0·49 [95% CI 0·24, 1·02]) and also to Alcoholic PVI, although uncertainty was larger (RR 0·51 [95% CI 0·21, 1·27]). Adverse events related to antiseptic application were only observed with patients exposed to PVI.

Conclusions: Alcoholic formulations of 4-5% chlorhexidine gluconate appear to be safe and twice as effective as povidone-iodine (alcoholic or aqueous solutions) in preventing infection following clean surgery in adults. Our findings concur with the literature on contaminated and clean-contaminated surgery, and endorse guidelines worldwide which advocate the use of alcoholic chlorhexidine gluconate for preoperative skin antisepsis.

Registration: PROSPERO ID CRD42018113001

Introduction

In 2010, there were approximately 10 million clean operations worldwide[1]. Clean operations are defined as surgery in the absence of infection and inflammation which avoids entering the respiratory, alimentary, genital, or uninfected urinary tracts[2,3]. Surgical site infection (SSI) is the most common and costly postoperative complication.[4,5] The risk of SSI depends on many factors, including the type of surgical wound. The United States (US) Centre for Disease Control (CDC) and National Healthcare Safety Network[3] categorises surgical wounds and procedures into clean, clean-contaminated, contaminated and dirty.

To reduce the risk of SSI the World Health Organisation[6], US CDC[7] and United Kingdom National Institute for Health and Care Excellence[8] recommend alcoholic chlorhexidine gluconate (CHG) for skin preparation prior to surgery. These recommendations are based upon an abundance of evidence concerning skin antiseptic preparations in contaminated and clean-contaminated surgery. However, there is a gap in the literature concerning skin preparations in clean surgery and the current evidence may not be generalisable[9–11]. Despite to international guidance, surgeons continue to use Povidone-Iodine (PVI, alcoholic or aqueous)[12–14] skin preparation prior to clean surgery for many reasons. Firstly, two systematic reviews concerning skin preparation prior to clean surgery did not find evidence of a difference between aqueous or alcoholic CHG and PVI antiseptics in pairwise analyses[10,11]. Secondly, some surgeons avoid alcoholic preparations in tourniquet-controlled surgery due to the perceived risk of fire and burns beneath the tourniquet[15].

A network meta-analysis (NMA) has the potential to resolve uncertainties over the efficacy and safety of CHG versus PVI preparations in clean surgery. NMA synthesizes evidence from multiple studies enabling clinicians to make comparisons of (in this case) the efficacy of several different preparation agents. NMA gives more precise estimates of relative treatment effects than standard pairwise meta-analyses[16,17] and can be used to rank all competing treatments, to inform clinical decisions[18].

Methods

This review is registered on the PROSPERO database (CRD42018113001); it was designed and conducted in accordance with the Cochrane Handbook of Systematic Reviews[19] and has been authored in accordance with the PRISMA checklist[20] and the PRISMA Network Meta-Analysis extension statement[21] (Appendix 1).

Study selection

We included randomized and observational studies that directly compared the outcomes of any formulation of CHG or PVI in adults (>16 years) undergoing clean surgery. Clean surgery was defined as surgery in the absence of infection and inflammation, which avoids entering the respiratory, alimentary, genital, or uninfected urinary tracts[2,3]. We excluded studies concerning: indwelling vascular catheters, arterial or venous puncture for blood sampling, combination (mixtures of) antiseptics or sequential applications of different antiseptics and case reports.

Outcomes

The primary outcome was the binary event of SSI. There are several tools for diagnosing SSI[22], which have poor agreement[23], so we used the definition of SSI from the index study (Supplementary Table 1). In the discussion section, we consider the strengths and limitations of this approach. The secondary outcome was adverse events directly attributable to the preparatory agent (e.g. contact dermatitis, burns, etc). Where studies reported outcomes at multiple time points, we used data from the final time point.

Search strategy

PubMed and Embase were interrogated according to the search strategy in Appendix 2. No language restrictions were applied. Our searches yielded 283 hits in Medline and 435 in Embase on the 19th October 2018. After de-duplication, there were 522 citations, which were independently screened by two review authors (RGW and GM). The full texts of all potentially relevant articles were obtained. The reference lists for included articles and previous systematic reviews[24,25] of this

topic were also scrutinised. Final lists of included articles were compared and disagreements resolved by discussion.

Data extraction

We extracted details of the study design and the statistics relating to the outcomes of interest. Where data was missing or unclear, we contacted the corresponding author by email and/or phone and, if no reply was received, 4 weeks later, all authors were contacted. The authors of two articles[26,27] provided information upon request. We extracted data concerning elective breast surgery only from one study[28] as we were unable to disaggregate clean from clean-contaminated vascular surgeries.

Risk of bias assessment

The risk of methodological bias was assessed by two review authors independently, using the Cochrane Risk of Bias[29] (for randomized trials) or ROBINS-I tool[30] (for observational studies). These assessments were displayed graphically using RevMan v5.0 (Cochrane Collaboration,) and the Confidence in Network Meta-Analysis (CINEMA) tool[31]. Disagreements were resolved by discussion.

Assessing the transitivity assumptions of network meta-analysis

We assessed the validity of the transitivity assumption underlying NMA, by considering whether participants in the identified studies could in principle receive any of the treatments in the network. This also relates to the requirement of treatments being 'jointly randomizable' for an NMA to be valid. Another requirement for NMA is that the distribution of effect modifiers is similar across treatment comparisons[17]. However, after reviewing the best available evidence to-date we could not identify effect modifiers for SSI in clean surgery[32]. None-the-less the transitivity assumption was evaluated by grouping studies by treatment comparison and comparing the distribution of clinical and methodological variables that might potentially moderate the relative effects of the treatments; these included age, study design, surgeries performed and the definition of SSI.

Statistical analysis

We produced a network plot to summarize the treatments and the available studies. We then performed a series of frequentist, random-effects network meta-analysis, using the netmeta package in R[33], as described below. In all NMAs we assumed a single heterogeneity parameter in the network.

To assess the agreement between randomized and non-randomized evidence, we first performed separate NMAs and compared results[34]. If no important discrepancies were observed, we performed a joint analysis including both study types ("naïve" NMA). We ranked preparations according to their efficacy in reducing SSI using the corresponding P-scores. P-scores are a ranking metric for NMA. After fitting a NMA, a P-score is calculated for each treatment. It assumes values between 0 and 1, with a higher score indicating a better treatment[35]. A P-score near 1 suggests that the corresponding treatment is the best, with perfect certainty. We summarized the NMA results in league tables which show the estimated relative effects for all treatment comparisons in the network. Heterogeneity in the network was quantified through the standard deviation of random effects (τ, assumed common for all comparisons in the network). In order to assess the extent of heterogeneity we compared the estimated value of τ with its empirical distribution[36]. Network inconsistency was assessed using a global and a local method[37,38]. This was further explored and quantified via heat plots[37,39]. We produced forest plots showing the relative risk (RR) and 95% confidence intervals (CI) for the outcomes of interest. In order to assess possible small-study effects in the network, we produced a comparison adjusted funnel plot in Stata v15 (Stata Corp, Texas, USA)[40]. The funnel plot is a scatterplot of effect size versus precision, measured using the inverse of the standard error; symmetry around the effect estimate line indicates the absence of small-study effects. In order to construct the funnel plot in a meaningful way, it is required to determine the expected direction of small-study effects in each pairwise comparison in the network[40]. For this, we used the risk of site infection (highest to lowest) based on the literature concerning dirty, contaminated and clean-contaminated surgery, as follows: Aqueous PVI > Alcoholic PVI > increasing strengths of CHG. This means that in order to produce

the funnel plot, we assumed that, for example, small-study effects act in favour of Alcoholic PVI over Aqueous PVI.

Next, we performed a series of "designed-adjusted analyses"[34], whereby data from randomized studies were combined with data from non-randomized studies (NRS) after down-weighting the impact of the latter in NMA. These analyses involve a "variance-inflation factor"[34], i.e. an extra parameter used to increase the variance of NRS, so as to reduce their impact on the pooled NMA estimate. We used the following values for the variance inflation factor: w=1 (corresponding to the naïve NMA, i.e. including all studies at face value), 0.8, 0.6, 0.4, 0.2 and 0 (i.e. excluding non-randomized studies from the analysis). Note that randomized studies were not down-weighted in this analysis. We produced forest-plots with the results of all treatments vs. the reference (Aqueous PVI) from all analyses, aiming to show the influence of gradually allowing non-randomized evidence to inform the estimates of relative treatment effects.

Given that the outcomes of interest are rare, we performed a sensitivity fixed-effects Mantel-Haenszel NMA[41]. This model synthesizes odds ratios but for rare events, odds and risks are almost identical. For this model we used the SIDDE approach to assess inconsistency[41]. Finally, the Stata package Metaprop[42] was used to estimate the prevalence of adverse events using the exact method with random-effects.

Following recent publications on problems regarding null hypothesis testing[43,44] in general, and particularly NMA[45], we did not use the concept of "statistical significance" when presenting or discussing results but instead focused on the clinical interpretation of all findings, in relation to the corresponding point estimates and their respective CIs.

Results

Study selection

After reviewing 30 full texts, 13 were excluded and 17 articles were included[26–28,46–59] (Supplementary Figure 1). One study was excluded from the NMA due to unresolved concerns over the methodology and unit of analysis[27]. The 16 included studies formed a network of 5 different antiseptics (Figure 1).

Study characteristics

This review comprised information on 14,593 adults undergoing clean surgery and the characteristics of the included studies are summarized in Supplementary Table 2. Overall, there were 382 events of SSI in 14,361 adults, giving an overall infection rate of 3%.

Data were derived from 7 RCTs[48,49,51,53,54,56,57], one quasi-RCT[46], six prospective cohort studies[47,50,52,55,58,59] and three retrospective cohort studies[26–28] conducted over 12 years (2004-2016). Studies were derived from North America[27,46,50,51,53], Europe[28,47,55,56,59], Asia[54484952], South America[57] and Australasia[26]. The outcomes of orthopaedic surgery[26,46,51,53,58], spinal procedures[50,52], cardiac surgery[47,56,59], general plastic[57] and burn reconstruction surgery[27], cranial neurosurgery[55], breast surgery[28], open inguinal hernia repair[49] and other undefined clean general surgical procedures[48,54] were reported.

There were nine formulations of antiseptic used within the included studies. These were assimilated into five clinically applicable nodes. Studies using 7·5% and 10% PVI in water were combined into “Aqueous PVI”. The node “Alcoholic PVI” represents studies using 1% PVI in 70% alcohol and 0·7% PVI in 74% alcohol. Studies using CHG 0·5% in 70% or 79% alcohol were condensed into “CHG 0·5%”, which is typically available in a spray form-factor. Studies reporting the use of alcoholic CHG 2% or 2·5% were pooled into the node “CHG 2-3%” and studies using 4% or 5% CHG were grouped as “CHG 4-5%”.

Risk of bias within studies

The average risk of bias for each comparison within the network is summarised in Figure 2.

Concerning the eight randomized studies (Supplementary Figure 2): seven were at high[46,53,54,57] or unclear[48,51,56] risk of bias in the randomization domain, typically because the methods were not adequately described. All studies were at unclear risk of bias in the assignment to intervention domains due to lack of information. The judgements of the risk of bias arising from failure to adhere to the allocated intervention was high in seven studies[26–28,46–55,57–59] owing to a lack of information. The risk of missing data bias was high in three studies[46,49,54] (given the high attrition or acknowledged missing data, which was accounted for) and unclear in two studies[56,57] as patients died before their outcome assessment and it's unclear if they died from infection. The risk of reporting bias was unclear in all studies given the absence of a protocol to cross-reference.

Concerning the nine NRS (Supplementary Figure 3), all of them were at high risk of bias overall. The risk of bias due to confounding was serious in four studies[28,47,50,52] given the lack of adjustment, moderate in three studies[26,55,59] given that adjustments were made and unclear in two owing to a lack of information[27,58]. The risk of selection bias was moderate in six studies[26–28,52,58,59] because the eligibility criteria might be related to the risk of SSI. One study[59] was at moderate risk of misclassification bias because one the CHG group was accompanied by an antiseptic education program; three studies[28,52,58] were at unclear risk given a lack information. One study[55] was at critical risk of bias given that 1121 of 2603 cases had missing data; the remaining studies lacked information on which to make a judgement. The risk of bias in the measurement of SSI was critical in two studies[28,59] because the outcome was judged over different timeframes for different operations; the risk was serious in three studies[26,27,50] owing to the subjectivity of the assessor. The risk of reporting bias was serious in two studies[28,59] because SSI was defined differently for different operations.

Assessment of transitivity

After considering the inclusion criteria of the identified studies we deemed that the treatments were jointly randomizable. After grouping the studies by treatment comparison and inspecting their characteristics, we judged them to be sufficiently similar to be jointly synthesized in a NMA (Supplementary Table 1).

Agreement between randomized and non-randomized studies

Figure 3 and Supplementary Figure 4 show how the estimates derived from a NMA of only RCTs compare to those from a NMA of NRSs only, for all treatment comparisons versus Aqueous PVI. A visual inspection of the graphs showed no evidence of important discrepancies between randomized and non-randomized evidence. This was further corroborated after testing for differences between the two estimates for each treatment comparison. The corresponding p-values of the Chi-square tests were 0.60, 0.12, 0.99 and 0.55 for the comparisons of Alcoholic PVI, 0.5% CHG, 2-3% CHG and 4-5% CHG versus Aqueous PVI, respectively. Thus, we concluded that there was no evidence of incompatibility between the two types of evidence (randomized and non-randomized) and proceeded with a joint analysis of the data.

Effects of the intervention

According to results from the naïve NMA, CHG 4-5% was ranked as the most effective antiseptic, (P-score = 0.91) and it halved the risk of infection when compared to aqueous PVI in the primary analysis (RR 0·49 [95% CI 0·24, 1·02]). Furthermore, CHG 4-5% led to a 33% decrease in the risk of surgical site infection compared to the second ranking treatment (CHG 2-3%); however, uncertainty was large due to the limited number of studies (RR 0·67 [95% CI 0·29, 1·55]). Detailed results for all treatment comparisons are shown in Figure 3 and Table 1. The estimated heterogeneity of the network was deemed small (τ^2=0.1), when compared to the empirical distribution. A local method ("back-calculation") did not provide any evidence for inconsistency, although there were no direct comparisons between alcoholic and aqueous PVI, or any preparation of CHG (Supplementary Figure 5 and Supplementary Table 3). The global test for inconsistency ("design-by-treatment" test) gave a p-value of 0.15 (Q=14.5, 10 degrees of freedom). Thus, inconsistency was not a source of concern.

Next, we performed a series of design-adjusted analyses (Supplementary Figure 6). Overall, inclusion of non-randomized evidence in the network did not alter the findings. Especially for the comparisons of 2-3% CHG versus Aqueous PVI and 4-5% versus Aqueous PVI, randomized and non-randomized evidence were in remarkable agreement. The inclusion of the latter in the NMA corroborated findings from the former and increased precision.

All findings presented above were consistent with the sensitivity analysis using the Mantel-Haenszel method for NMA (Figure 3 and Supplementary Table 4). The SIDDE also did not provide evidence for inconsistency (Supplementary Table 5).

Regarding the secondary outcome of adverse events, three studies[48,54,58] described 9 allergic skin reactions (contact dermatitis) in 859 individuals, all of which occurred with PVI whilst there were no preparation related adverse reactions documented in patients when any formulation of CHG was used. Thus, we performed a pairwise meta-analysis of the prevalence of adverse outcomes. The pooled prevalence of PVI related contact dermatitis was 1% [95% CI 0%, 2%]. There were no reports of alcoholic or chemical burns beneath the limb tourniquets, or fires in any of the included studies.

Small-study effects

The comparison adjusted funnel plot is asymmetrical and thus, suggests the presence of small-study effects (Supplementary Figure 7), favouring the more efficacious treatments. This might be due to publication bias, selective reporting in smaller studies, or due to other methodological differences between smaller and larger studies.

Assessing confidence in results from the analyses

Overall, there was moderate confidence in the results (except for the comparison of Aqueous PVI and CHG 4-5% which had low confidence) given major concerns over the risk of bias both with and across-studies, and imprecision of the estimates (Supplementary Table 6).

Discussion

This review demonstrates that chlorhexidine gluconate 4-5% in alcohol is the most effective antiseptic for reducing the risk of surgical site infection following clean surgery. Our findings are in keeping with the literature on clean-contaminated and contaminated surgery, and proves (where several historical pairwise meta-analyses could not) that chlorhexidine gluconate 4-5% in alcohol is also superior in the context of clean surgery. Network meta-analysis enables the comparison of antiseptics which have not been clinically tested head-to-head and therefore can utilise more sources data to inform the estimates; therefore, NMAs typically provides more precise estimates than standard pairwise meta-analyses which can be ranked to inform decisions. Further, we provide evidence to show that the documented risk of adverse skin reactions is higher with povidone-iodine based preparations, contrary to popular belief. We identified no instances of burns beneath tourniquets with alcoholic preparation solutions in the included studies. Our findings are important because they provide an evidence-base for international guidelines on perioperative antiseptics and identify deficits in the literature concerning specific fields of surgery.

The WHO[6], the UK NICE[8] and the US CDC[7] advocate the use of alcoholic CHG for skin antisepsis immediately prior to surgery. These guidelines are based on a large body of evidence derived from contaminated and clean-contaminated surgery. However, the ideal skin antiseptic for patients undergoing clean surgery has been unresolved in four reviews to-date due to the limitations of conventional pairwise meta-analyses and sparsity of data. It is important to resolve this uncertainty with respect to clean surgery because annually approximately 10 million people undergo clean operations worldwide[1], and SSI is the most common and costly complication[4,5]. Further, with the rising problem of antimicrobial resistance (whereby in 2050 there will be 10 million preventable deaths owing to antimicrobial resistance[60]) there is a need to reduce SSI following clean surgery. The Cochrane review by Dumville and colleagues[9] included 13 studies of 2623 participants, resulting in 11 separate pairwise analyses; they concluded that there was a 78% probability that alcoholic CHG was the best treatment for preventing SSI, although there were several limitations; the quality of the evidence was poor, only 4 of the planned 12 meta-analyses had sufficient studies

(>1) but still, most reported few or zero events weakening the output and lastly, the risk of side effects was not considered. The review by Yuanzhen[61] was in agreement and showed that in 6 studies of primary hip and knee arthroplasty, CHG reduced the risk of SSI and was associated with a similar reduction in the risk of revision surgery. The meta-analysis by Ayoub et al[10] included 6 studies of 2484 participants undergoing clean or clean-contaminated surgery and showed that alcoholic CHG was superior to PVI solutions (RR 0·62 [95% CI 0·48, 0·81]); however, they did not discriminate between alcoholic and aqueous preparations of PVI in the prevention of SSI which hindered its translation to practice. Similarly, a systemic review was conducted by The World Health Organisation[62] to inform their Surgical Site Infection Prevention Guidelines; it included 17 moderate-quality studies of patients undergoing clean and clean-contaminated surgery and found evidence that alcoholic CHG reduced the risk of surgical site infection compared to aqueous PVI. Our NMA synthesized the clean surgery data from all the individual studies included the aforementioned systematic reviews[9-10,61-62] and we verify their guarded conclusions (that alcoholic CHG is superior) through the synthesis of robust real-world data on commonly used antiseptics. Our NMA unifies the disparate comparisons of several historical systematic reviews and represents a single (and more reliable) point-of-reference for clinicians performing clean surgery. Moreover, we also address a gap in the literature concerning antiseptic-related adverse events, which is a vital part of the decision-making process. Notwithstanding, further studies may be needed to address a) surgical specialties which are not represented in the current body of evidence (e.g. hand surgery), and b) concerns over the use of alcoholic antiseptics in specific situations, such as tourniquet-controlled limb surgery.

Adverse events

Overall, the incidence of adverse events appears to be small (~1%). One systematic review on the topic[63] found no evidence of difference in the rate of skin reactions (e.g. pruritis, erythema, blistering or eczema) between PVI and CHG antiseptics, although in this review these events only occurred in patients exposed to PVI. Further, there were no reports of alcoholic or chemical burns beneath tourniquets, but this might reflect the scarcity of studies on antiseptic skin prep in

tourniquet-controlled surgery. A recent review on chemical burns beneath tourniquets showed that these are rare events and can also occur with aqueous PVI[64]. There were no alcohol ignition fires which also agrees with the literature[65]. Overall, this review adds to the evidence to suggest that alcoholic CHG is safe in tourniquet-controlled clean surgery provided tourniquets are isolated and pooling is avoided.

Limitations

There are three major limitations of this NMA: a) the low quality of the included studies (Figure 2, and Supplementary Figures 2 and 3) and b) the evidence of SSE, both of which are likely to contribute to an overestimation of the true effects. Finally, c) there were no studies directly comparing the various concentrations of CHG. Future studies should be preceded by a peer-reviewed and published protocol and recruit prospectively to minimise methodological biases. Although all operations were classed as clean, we have pooled studies of individuals undergoing a wide array of different operations which might affect the estimates. Inferences about adverse events are limited because the included studies might have been underpowered to identify these rare events and the reporting was sparse; improving the evidence base for this topic is difficult given the scarcity of events, so future researchers should seek to include antiseptic-related adverse events as a secondary outcome in large-scale cohort studies or trials. Whilst there are several tools for diagnosing SSI[22], there is no consensus on the definition and the tools have poor agreement[23] which limits the transferability of our findings to practice (Supplementary Table 2); future researchers might consider using the Bluebelle Wound Healing Questionnaire[66,67] which has been purposely and robustly developed for evaluating surgical sites. Nevertheless, results of this network meta-analysis are likely to be important for patients and policy makers to help inform the choice of skin antisepsis prior to surgery.

We recognise that there is some uncertainty around the point estimate for CHG 4-5% compared to Aqueous PVI, as captured by the 95% CI, and that this finding is not “statistically significant”. However, readers should note that the use of hypothesis testing (i.e. the dichotomization of findings according to an arbitrary threshold for the p-value, such as 0.05) have been the aim of

much criticism in the wider scientific community lately[43,44]. The problems associated with hypothesis testing have been also highlighted for the case of NMA[45]. In this paper we have avoided using the concept of "statistical significance" and instead tried to interpret the estimated values of relative efficacy and their corresponding CIs. Our findings imply that, most probably, CHG 4-5% is superior, and the risk of SSI may be halved by using this antiseptic. Although the CI implies that the benefit of using CHG 4-5% might be as high as a 76% reduction in risk or, as low as zero, it is important to highlight that a) avoiding SSI is of critical importance to both patients and the health services, and b) there is no additional cost or risk from using CHG 4-5% instead of Aqueous PVI (or indeed other preps). Therefore, our findings suggest that alcoholic CHG should be the first-choice antiseptic for skin preparation prior to clean surgery, because it is potentially safer than the alternatives, without being associated with additional side effects or extra costs

Conclusions

Alcoholic CHG 4-5% skin antisepsis was estimated to be twice as effective as PVI (alcoholic or aqueous) in preventing infection following clean surgery, although the evidence is at high risk of bias. These findings are in keeping with the literature and endorse global guidelines which advocate the use of alcoholic chlorhexidine gluconate for skin antisepsis prior to clean surgery.

References

1 Rose J, Weiser TG, Hider P, *et al.* Estimated need for Surgery Worldwide Based on Prevalence of Diseases: Implications for public health planning of surgical services. *Lancet Glob Heal* 2017; **3**: s13–20.

2 World Health Organization (WHO). Protocol for surgical site infection surveillance with a focus on settings with limited resources. 2018 http://www.who.int/infection-prevention/tools/surgical/SSI-surveillance-protocol.pdf.

3 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36**: 309–32.

4 Gibson A, Tevis S, Kennedy G. Readmission after delayed diagnosis of surgical site infection: a focus on prevention using the American College of Surgeons National Surgical Quality Improvement Program. *Am J Surg* 2014; **207**: 832–9.

5 Zimlichman E, Henderson D, Tamir O, *et al.* Health care-associated infections: AMeta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013; **173**: 2039–46.

6 World Health Organisation (WHO). WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. *World Health* 2009; **30**: 270.

7 Berríos-Torres SI, Umscheid CA, Bratzler DW, *et al.* Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg* 2017; **152**: 784.

8 Excellence TNI for H and C. Surgical site infections: prevention and treatment. 2019; : [NG125].

9 Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. In: Dumville JC, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd, 2013. DOI:10.1002/14651858.CD003949.pub3.

10 Ayoub F, Quirke M, Conroy R, Hill A. Chlorhexidine-alcohol versus povidone-iodine for pre-operative skin preparation: A systematic review and meta-analysis. *Int J Surg Open* 2015; **1**:

41–6.

11 Dumville JC, Norman G, Westby MJ, *et al.* Intra-operative interventions for preventing surgical site infection: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017; **2017**. DOI:10.1002/14651858.CD012653.

12 Best BA, Best TJ. Skin preparation in the hand surgery clinic : A survey of Canadian plastic surgeons and a pilot study of a new technique. *Can J Infect Control* 2018; **33**: 2016–9.

13 Thakkar M, Wearn C, Al-Himdani S, Sack A, Sen S, Estela C. Burns surgery antiseptic preparation: A UK national survey. *Burns* 2019; : 10–1.

14 Jurado-Ruiz M, Slobogean GP, Bzovsky S, *et al.* Large variations in the practice patterns of surgical antiseptic preparation solutions in patients with open and closed extremity fractures: a cross-sectional survey. *Antimicrob Resist Infect Control* 2018; **7**: 148.

15 Madhok R. Chemical burns beneath tourniquets. *BMJ* 1989; **298**: 254–254.

16 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012; **3**: 80–97.

17 Efthimiou O, Debray TPA, van Valkenhoef G, *et al.* GetReal in network meta-analysis: a review of the methodology. *Res Synth Methods* 2016; **7**: 236–63.

18 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64**: 163–71.

19 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *Cochrane Collab* 2011.

20 Moher D, Liberati A, Tetzlaff J, Altman DG. Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Annu Intern Med* 2009; **151**: 264–9.

21 Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med* 2015; **162**: 777.

22 Petherick ES, Dalton JE, Moore PJ, Cullum N. Methods for identifying surgical wound infection after discharge from hospital: a systematic review. *BMC Infect Dis* 2006; **6**: 170.

23 Wilson APR, Gibbons C, Reeves BC, *et al.* Surgical wound infection as a performance indicator: agreement of common definitions of wound infection in 4773 patients. *BMJ* 2004; **329**: 720.

24 Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2015; : CD003949.

25 Ayoub F, Quirke M, Conroy R, Hill A. Chlorhexidine-alcohol versus povidone-iodine for pre-operative skin preparation: A systematic review and meta-analysis. *Int J Surg Open* 2015; **1**: 41–6.

26 Carroll K, Dowsey M, Choong P, Peel T. Risk factors for superficial wound complications in hip and knee arthroplasty. *Clin Microbiol Infect* 2014; **20**: 130–5.

27 Potenza BM, Noordenhos RN, Lee J, Tenehaus M, Bhavsar D. Surgical Prep of Donor Sites With Chlorhexidine Results in Reduced Donor Site Infectons. *J Burn Care Res* 2011; **32**: S173.

28 Charehbili A, Swijnenburg R-J, van de Velde C, van den Bremer J, van Gijn W. A Retrospective Analysis of Surgical Site Infections after Chlorhexidine–Alcohol versus Iodine–Alcohol for Pre-Operative Antisepsis. *Surg Infect (Larchmt)* 2014; **15**: 310–3.

29 Higgins JP, Savović J, Page MJ, Sterne JA. Revised Cochrane risk-of-bias tool for randomized trials (RoB2). 2016 DOI:10.1002/14651858.CD201601.

30 Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.

31 Nikolakopoulou A, Higgins JP, Papakonstantinou T, *et al.* ASSESSING CONFIDENCE IN THE RESULTS OF NETWORK META-ANALYSIS (CINEMA). .

32 Gibbons C, Bruce J, Carpenter J, *et al.* Identification of risk factors by systematic review and development of risk-adjusted models for surgical site infection. *Health Technol Assess (Rockv)* 2011; **15**. DOI:10.3310/hta15300.

33 Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: Network Meta-Analysis using Frequentist Methods. 2019. https://github.com/guido-s/netmeta http://meta-analysis-with-r.org.

34 Efthimiou O, Mavridis D, Debray TPA, *et al.* Combining randomized and non-randomized evidence in network meta-analysis. *Stat Med* 2017; **36**: 1210–26.

35 Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015; **15**: 58.

36 Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015; **34**: 984–98.

37 Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012; **3**: 98–110.

38 König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Stat Med* 2013; **32**: 5414–29.

39 Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013; **13**: 35.

40 Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical Tools for Network Meta-Analysis in STATA. *PLoS One* 2013; **8**: e76654.

41 Efthimiou O, Rücker G, Schwarzer G, Higgins JPT, Egger M, Salanti G. Network meta-analysis of rare events using the Mantel-Haenszel method. *Stat Med* 2019; **38**: 2992–3012.

42 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Heal* 2014; **72**: 39.

43 Wasserstein RL, Lazar NA. The ASA Statement on p -Values: Context, Process, and Purpose. *Am Stat* 2016; **70**: 129–33.

44 Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019; **567**: 305–7.

45 Efthimiou O, White IR. The dark side of the force: Multiplicity issues in network meta-analysis and how to address them. *Res Synth Methods* 2019; **101**-**B**: jrsm.1377.

46 Ostrander R V, Botte MJ, Brage ME. Efficacy of Surgical Preparation Solutions in Foot and Ankle Surgery. *J Bone Jt Surg* 2005; **87**: 980–5.

47 Raja SG, Rochon M, Mullins C, *et al.* Impact of choice of skin preparation solution in cardiac surgery on rate of surgical site infection: a propensity score matched analysis. *J Infect Prev* 2018; **19**: 16–21.

48 Paocharoen V, Mingmalairak C, Apisarnthanarak A. Comparison of surgical wound infection after preoperative skin preparation with 4% chlorhexidine and povidone iodine: a prospective randomized trial. *J Med Assoc Thail* 2009; **92**: 898–902.

49 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**: 261–7.

50 Ghobrial GM, Wang MY, Green BA, *et al.* Preoperative skin antisepsis with chlorhexidine gluconate versus povidone-iodine: a prospective analysis of 6959 consecutive spinal surgery patients. *J Neurosurg Spine* 2018; **28**: 209–14.

51 Saltzman MD, Nuber GW, Gryzlo SM, Marecek GS, Koh JL. Efficacy of Surgical Preparation Solutions in Shoulder Surgery. *J Bone Joint Surg Am* 2009; **91**: 1949–53.

52 Yoshii T, Hirai T, Yamada T, *et al.* A Prospective Comparative Study in Skin Antiseptic Solutions for Posterior Spine Surgeries. *Clin Spine Surg* 2018; **31**: E353–6.

53 Bibbo C, Patel D V, Gehrmann RM, Lin SS. Chlorhexidine Provides Superior Skin Decontamination in Foot and Ankle Surgery. *Clin Orthop Relat Res* 2005; : 204–8.

54 Bibi S, Shah SA, Qureshi S, *et al.* Is chlorhexidine-gluconate superior than Povidone-Iodine in preventing surgical site infections? A multicenter study. *J Pak Med Assoc* 2015; **65**: 1197–201.

55 Davies BM, Patel HC, B.M. D, H.C. P. Does chlorhexidine and povidone-iodine preoperative antisepsis reduce surgical site infection in cranial neurosurgery? *Ann R Coll Surg Engl* 2016; **98**: 405–8.

56 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. *Polish J Cardio-Thoracic Surg* 2013; **2**: 178–82.

57 Veiga DF, Damasceno CA V, Veiga-Filho J, *et al.* Povidone Iodine versus Chlorhexidine in Skin Antisepsis before Elective Plastic Surgery Procedures: A Randomized Controlled Trial.

Plast Reconstr Surg 2008; **122**: 170e-171e.

58 Das DA, Samant DS, Dash DP. A comparison study of preoperative skin preparation using chlorhexidine vs povidone iodine in cases of elective orthopaedic surgery. *Int J Orthop Sci* 2017; **3**: 12–5.

59 Hannan MM, O'Sullivan KE, Higgins AM, *et al.* The Combined Impact of Surgical Team Education and Chlorhexidine 2% Alcohol on the Reduction of Surgical Site Infection following Cardiac Surgery. *Surg Infect (Larchmt)* 2015; **16**: 799–805.

60 O 'neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations the Review on Antimicrobial Resistance. 2016. DOI:10.1016/j.jpha.2015.11.005.

61 Cai Y, Xu K, Hou W, Yang Z, Xu P. Preoperative chlorhexidine reduces the incidence of surgical site infections in total knee and hip arthroplasty: A systematic review and meta-analysis. *Int J Surg* 2017; **39**: 221–8.

62 World Health Organisation. WHO Surgical Site Infection Prevention Guidelines. *Summ a Syst Lit Rev Surg site Prep* 2016. http://www.who.int/gpsc/appendix8.pdf.

63 Privitera GP, Costa AL, Brusaferro S, *et al.* Skin antisepsis with chlorhexidine versus iodine for the prevention of surgical site infection: A systematic review and meta-analysis. *Am J Infect Control* 2017; **45**: 180–9.

64 Supradeeptha C, Shandilya SM, Naresh A, Satyaprasad J. Aqueous based Povidone-iodine related chemical burn under the tourniquet (a case report) and literature review. *J Orthop* 2013; **10**: 152–4.

65 Vo A, Bengezi O. Third-degree burns caused by ignition of chlorhexidine: A case report and systematic review of the literature. *Plast Surg (Oakville, Ont)* 2014; **22**: 264–6.

66 Macefield RC, Reeves BC, Milne TK, *et al.* Development of a single, practical measure of surgical site infection (SSI) for patient report or observer completion. *J Infect Prev* 2017; **18**: 170–9.

67 Macefield R, Blazeby J, Reeves B, *et al.* Validation of the Bluebelle Wound Healing Questionnaire for assessment of surgical-site infection in closed primary wounds after hospital discharge. *BJS* 2019; **106**: 226–35.

Tables

Table 1. League table of pairwise comparisons in network meta-analysis for the relative risk of surgical site infection with 95% confidence intervals. A relative risk smaller than 1 favors the row-defining treatment. Antiseptics are ordered according to their ranking, based on the P-score; the P-score is a value between 0 and 1, with a higher score indicating a better treatment. The best treatment is shown in the top left cell, whilst the worst is in the bottom right. Estimates in the upper triangle are direct comparisons (i.e. from studies comparing treatments head-to-head); estimates on the bottom triangle are from the network meta-analysis. CHG = alcoholic chlohexidine gluconate, PVI = povidone-iodine

CHG 4-5% (P-score 0·91)	.	0·49 (0·08, 2·85)	0·50 (0·23, 1·09)	.
0·67 (0·29, 1·55)	**CHG 2-3%** (P-score 0·68)	0·72 (0·42, 1·23)	0·78 (0·46, 1·32)	.
0·51 (0·21, 1·27)	0·77 (0·46, 1·27)	**Alcoholic PVI** (P-score 0·35)	.	0·73 (0·32, 1·69)
0·49 (0·24, 1·02)	0·74 (0·45, 1·21)	0·96 (0·49, 1·89)	**Aqueous PVI** (P-score 0·30)	3·20 (0·31, 32·9)
0·44 (0·14, 1·42)	0·66 (0·26, 1·64)	0·86 (0·39, 1·90)	0·89 (0·33, 2·40)	**CHG 0·5%** (P-Score 0·26)

Figure Legends

Figure 1. Network plot of studies included in the analysis. The size of the nodes correspond to the number of patients, the thickness of the connecting lines corresponds to the number of studies and the colour of the lines corresponds to the average risk of bias assessment (yellow = unclear or moderate risk, red = high risk). NRS = non-ransomised studies, RCT = randomised controlled trias.

Figure 2. The average risk of bias contributions for each comparison within the network estimates. Each horizontal bar represents the evidence for relative treatment comparisons. The vertical lines separate risk of bias contributions for individual studies, whereby yellow is moderate risk and red is high risk of bias. CHG = alcoholic chlohexidine gluconate, PVI = povidone-iodine

Figure 3. Forest plots of the network estimates for the relative risk (RR) of surgical site infection of all treatments compared to Aqueous PVI. NMA estimates derived from randomised, non-randomised and all studies are shown, alongside a sensitivity analysis using the Mantel-Haenszel (fixed-effects) method. Both forest plots of 'all studies' show that CHG 4-5% is more effective in reducing the risk of infection, compared to aqueous PVI.