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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

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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 CHG and PVI based skin antiseptics in clean surgery remains unclear.

Methods: We searched for randomized or nonrandomized 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 (RR).

Results: We included 17 studies comparing 5 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% confidence interval 0.24, 1.02)] and also to alcoholic PVI, although uncertainty was larger [RR 0.51 (95% confidence interval 0.21, 1.27)]. Adverse events related to antiseptic application were only observed with patients exposed to PVI.

Conclusions: Alcoholic formulations of 4%–5% CHG seem to be safe and twice as effective as PVI (alcoholic or aqueous solutions) in preventing infection after 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 CHG for preoperative skin antisepsis.

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Keywords: antisepsis, antiseptics, chlorhexidine gluconate, infection, meta-analysis, network, povidone-iodine, skin prep, surgery

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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 the National Healthcare Safety Network[3] categorizes surgical wounds and procedures into clean, clean-contaminated, contaminated, and dirty.

To reduce the risk of SSI the World Health Organization (WHO),[6] US CDC,[7] and United Kingdom (UK) National Institute for Health and Care Excellence (NICE)[8] recommend alcoholic chlorhexidine gluconate (CHG) for skin preparation before 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 generalizable.[9–11] Despite international guidance, surgeons continue to use povidone-iodine (PVI, alcoholic or aqueous)[12–14] for skin preparation before clean surgery for many reasons. First, 2 systematic reviews concerning skin preparation before clean surgery did not find evidence of a difference between aqueous or alcoholic CHG and PVI antiseptics in pairwise analyses.[10,11] Second, 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 antiseptic 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

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

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in accordance with the PRISMA checklist[20] and the PRISMA NMA extension statement[21] (Appendix 1, http://links. lww.com/SLA/C257).

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, http://links.lww.com/SLA/C252). 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 (eg, contact dermatitis, burns, etc). Where studies reporteded 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, http://links.lww.com/SLA/C258. No language restrictions were applied. Our searches yielded 283 hits in Medline and 435 in Embase on the October 19th, 2018. After de-duplication, there were 522 citations, which were independently screened by 2 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[10,24] of this topic were also scrutinized. 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. If no reply was received, 4 weeks later, all authors were contacted. The authors of 2 articles[25,26] provided information upon request. We extracted data concerning elective breast surgery only from 1 study[27] as we were unable to disaggregate clean from clean-contaminated vascular surgeries.

Risk of Bias Assessment

The risk of methodological bias was assessed by 2 review authors independently, using the Cochrane Risk of Bias[28] (for randomized trials) or ROBINS-I[29] (for observational studies) tool. These assessments were displayed graphically using RevMan v5.0 (Cochrane Collaboration,) and the Confidence in Network Meta-analysis tool.[30] Disagreements were resolved by discussion.

Assessing the Transitivity Assumptions of NMA

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.[31] Nonethe-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 NMA, using the netmeta package in R,[32] as described below. In all NMAs we assumed a single heterogeneity parameter in the network.

To assess the agreement between randomized and nonrandomized evidence, we first performed separate NMAs and compared results.[33] 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.[34] 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). To assess the extent of heterogeneity we compared the estimated value of τ with its empirical distribution.[35] Network inconsistency was assessed using a global and a local method.[36,37] This was further explored and quantified via heat plots.[36,38] We produced forest plots showing the relative risk (RR) and 95% confidence intervals (CI) for the outcomes of interest. To assess possible small-study effects in the network, we produced a comparison adjusted funnel plot in Stata v15 (Stata Corp, College Station, TX).[39] 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. 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.[39] 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 to produce the funnel plot, we assumed that, for example, small-study effects act in favor of alcoholic PVI over aqueous PVI.

Next, we performed a series of ''designed-adjusted analyses,''[33] whereby data from randomized studies were combined with data from nonrandomized studies (NRS) after down-weighting the impact of the latter in NMA. These analyses involve a ''variance-inflation factor,''[33] that is, 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, ie, including all studies at face value), 0.8, 0.6, 0.4, 0.2, and 0 (ie, excluding NRS from the analysis). Note that randomized studies were not down-weighted in this analysis. We produced forest-plots with the results of all treatments versus the reference (aqueous PVI) from all analyses, aiming to show the influence of gradually allowing nonrandomized 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.[40] 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.[40] Finally, the Stata package Metaprop[41] 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[42,43] in general, and particularly NMA,[44] 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[25–27,45–58] (Supplementary Fig. 1, http://links.lww.com/SLA/C252). One study was excluded from the NMA due to unresolved concerns over the methodology and unit of analysis.[26] The 16 included studies formed a network of 5 different antiseptics (Fig. 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, http://links.lww.com/SLA/C252. Overall, there were 382 events of SSI in 14,361 adults, giving an overall infection rate of 3%.

Data were derived from 7 RCTs,[47,48,50,52,53,55,56] 1 quasi-RCT,[45] 6 prospective cohort studies,[46,49,51,54,57,58] and 3 retrospective cohort studies[25–27] conducted over 12 years (2004–2016). Studies were derived from North America,[26,45,49,50,52] Europe,[27,46,54,56,58] Asia,[53,47,48,51] South America,[56] and Australasia.[25] The outcomes of

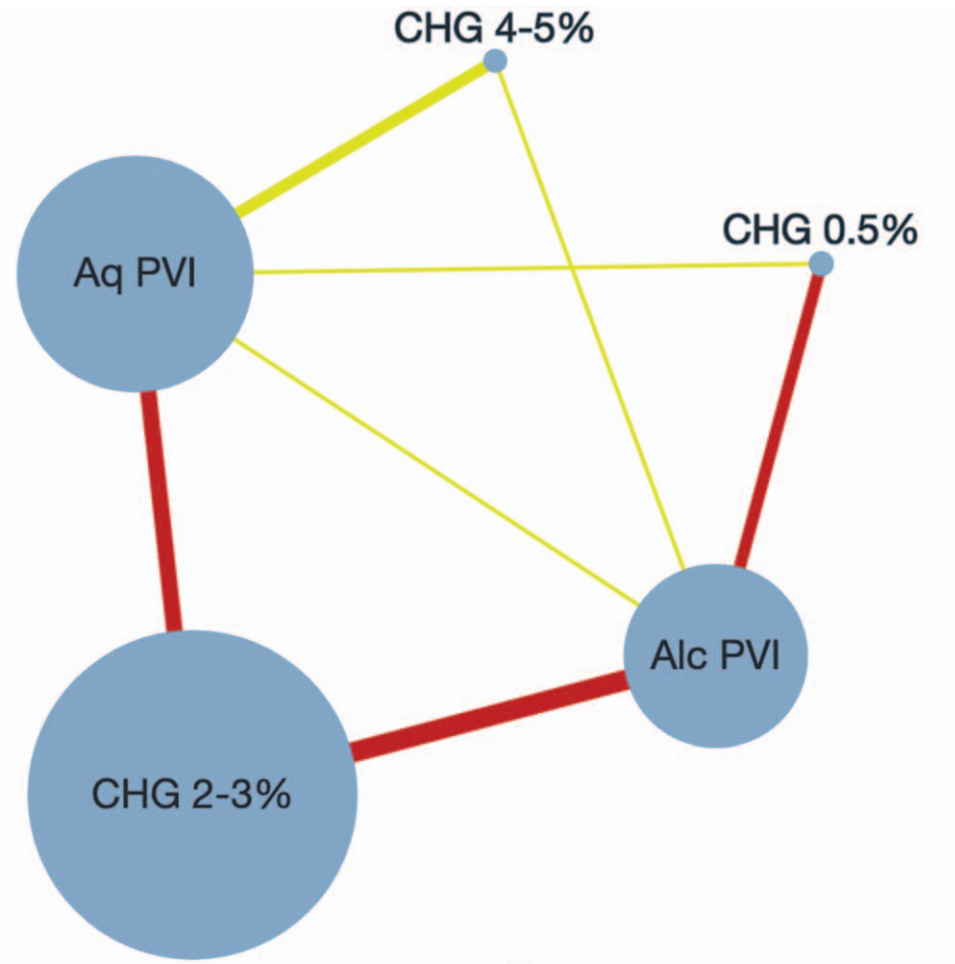

FIGURE 1. Network plot of studies included in the analysis. The size of the nodes correspond to the number of patients, the thickness of the connecting lines corresponds to the number of studies and the color of the lines corresponds to the average risk of bias assessment (yellow = unclear or moderate risk, red = high risk). NRS indicates nonransomized studies; RCT, randomized controlled trias.

Antiseptic	Label	Number of studies		Number of patients	Number of events
		RCT	NRS		
Alcoholic Chlorhexidine 4-5%	CHG 4-5%	3	3	412	18
Alcoholic Chlorhexidine 2-3%	CHG 2-3%	4	2	5628	98
Alcoholic Chlorhexidine 0·5%	CHG 0·5%	1	3	433	4
Alcoholic Povidone-Iodine	Alc PVI	4	6	3147	158
Aqueous Povidone-Iodine	Aq PVI	5	2	4041	100

orthopaedic surgery,[25,45,50,52,57] spinal procedures,[49,51] cardiac surgery,[46,55,58] general plastic[56] and burn reconstruction surgery,[26] cranial neurosurgery,[54] breast surgery,[27] open inguinal hernia repair,[48] and other undefined clean general surgical procedures[47,53] were reported.

There were 9 formulations of antiseptic used within the included studies. These were assimilated into 5 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 summarized in Fig. 2.

Concerning the 8 randomized studies (Supplementary Fig. 2, http://links.lww.com/SLA/C252): 7 were at high[45,52,53,56] or unclear[47,50,55] 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 7 studies[25–27,45–54,56–58] owing to a lack of information. The risk of missing data bias was high in 3 studies[45,48,53] (given the high attrition or acknowledged missing data, which was accounted for) and unclear in 2 studies[55,56] as patients died before their outcome assessment and it is 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 9 NRS (Supplementary Fig. 3, http://links.lww.com/SLA/C252), all of them were at high risk of bias overall. The risk of bias due to confounding was serious in 4 studies[27,46,49,51] given the lack of adjustment, moderate in 3 studies[25,54,58] given that adjustments were made and unclear in 2 owing to a lack of information.[26,57] The risk of selection bias was moderate in 6 studies[25–27,51,57,58] because the eligibility criteria might be related to the risk of SSI. One study[58] was at moderate risk of misclassification bias because one of the CHG group was accompanied by an antiseptic education program; 3 studies[27,51,57] were at unclear risk given a lack information. One study[54] 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 2 studies[27,58] because the outcome was judged over different timeframes for different operations; the risk was serious in 3 studies[25,26,49] owing to the subjectivity of the assessor. The risk of reporting bias was serious in 2 studies[27,58] 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, http://links.lww.com/SLA/C252).

Agreement Between Randomized and NRS

Fig. 3 and Supplementary Fig. 4, http://links.lww.com/SLA/C252 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 nonrandomized evidence. This was further corroborated after testing for differences between the 2 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 2 types of evidence (randomized and nonrandomized) and proceeded with a joint analysis of the data.

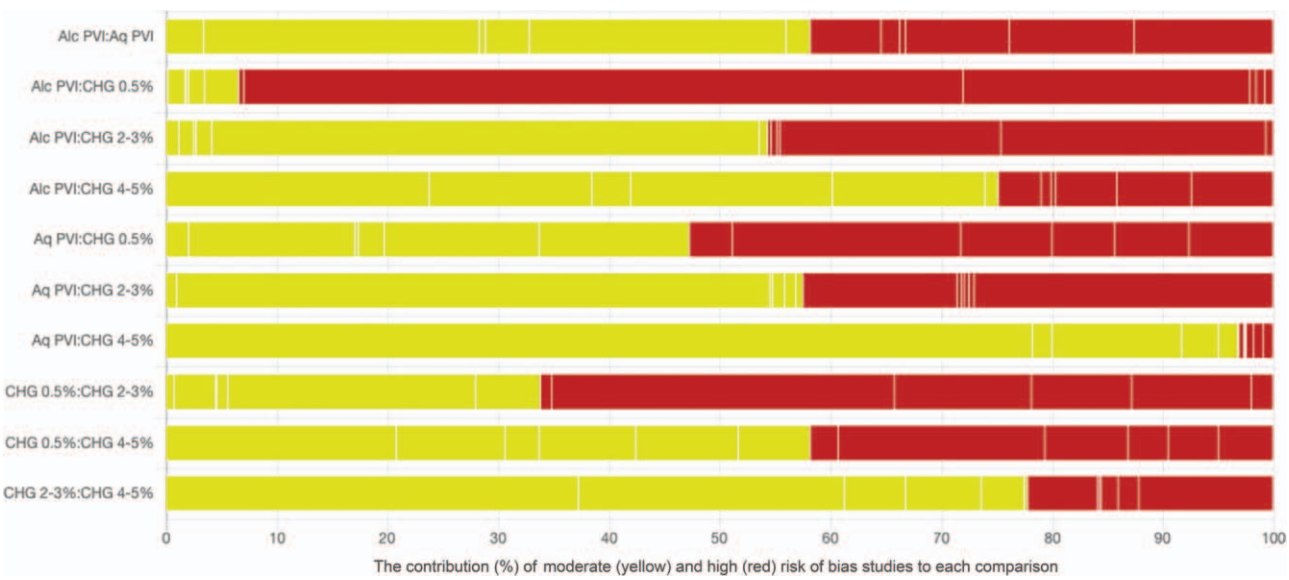

FIGURE 2. The average risk of bias contributions for each comparison within the network estimates. Each horizontal bar represents the evidence for relative treatment comparisons. The vertical lines separate risk of bias contributions for individual studies, whereby yellow is moderate risk and red is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

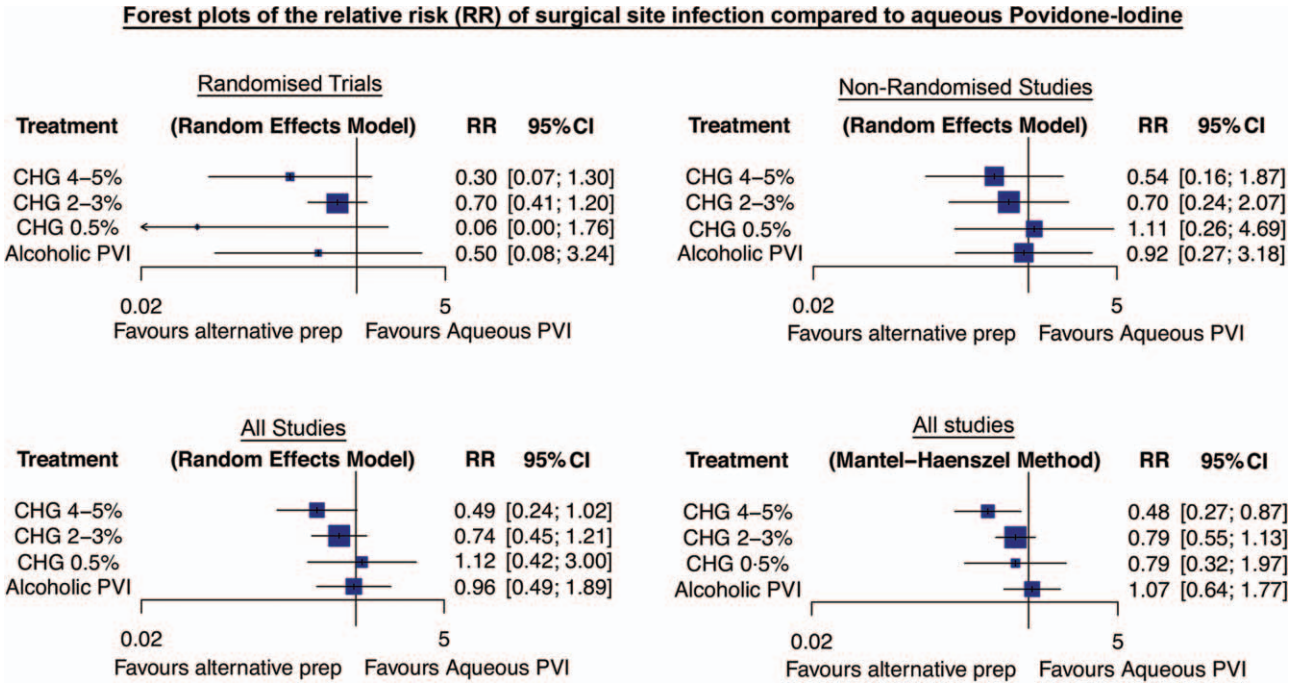

FIGURE 3. Forest plots of the network estimates for the relative risk (RR) of surgical site infection of all treatments compared to aqueous PVI. NMA estimates derived from randomized, nonrandomized and all studies are shown, alongside a sensitivity analysis using the Mantel-Haenszel (fixed-effects) method. Both forest plots of ''all studies'' show that CHG 4%–5% is more effective in reducing the risk of infection, compared to aqueous PVI. CHG indicates alcoholic chlohexidine gluconate; NMA, network meta-analysis; PVI, povidone-iodine.

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 SSI 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 Fig. 3 and Table 1. The estimated heterogeneity of the network was deemed small ($\tau^2 = 0.1$), 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 Fig. 5 and Supplementary Table 3, http://links.lww.com/SLA/C252). 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 Fig. 6, http://links.lww.com/SLA/C252). Overall, inclusion of nonrandomized 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 nonrandomized 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 (Fig. 3 and Supplementary Table 4, http://links.lww.com/SLA/C252). The SIDDE also did not provide evidence for inconsistency (Supplementary Table 5, http://links.lww.com/SLA/C252).

Regarding the secondary outcome of adverse events, 3 studies[47,53,57] 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

TABLE 1. League Table of Pairwise Comparisons in Network Meta-analysis for the Relative Risk of Surgical Site Infection With 95% Confidence Intervals

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)

The best treatment is shown in the top left cell, whilst the worst is in the bottom right. 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. Estimates in the upper triangle are direct comparisons (ie, from studies comparing treatments head-to-head); estimates on the bottom triangle are from the network meta-analysis. CHG indicates alcoholic chlohexidine gluconate; PVI, povidone-iodine.

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 Fig. 7, http://links.lww.com/SLA/C252), favoring 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, http://links.lww.com/SLA/C252).

DISCUSSION

This review demonstrates that CHG 4%–5% in alcohol is the most effective antiseptic for reducing the risk of SSI after 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 CHG 4%–5% in alcohol is also superior in the context of clean surgery. NMA enables the comparison of antiseptics which have not been clinically tested head-to-head and therefore can utilize 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 PVI 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 before 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 4 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[59]) there is a need to reduce SSI after 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[60] 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 WHO[61] 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 SSI compared to aqueous PVI. Our NMA synthesized the clean surgery data from all the individual studies included the aforementioned systematic reviews[9,10,60,61] 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 (eg, 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 seems to be small (~1%). One systematic review on the topic[62] found no evidence of difference in the rate of skin reactions (eg, 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.[63] There were no alcohol ignition fires which also agrees with the literature.[64] 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 3 major limitations of this NMA: (a) the low quality of the included studies (Fig. 2, and Supplementary Figs. 2 and 3, http://links.lww.com/SLA/C252) 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 minimize 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, http://links.lww.com/SLA/C252); future researchers might consider using the Bluebelle Wound Healing Questionnaire[65,66] which has been purposely and robustly developed for evaluating surgical sites. Nevertheless, results of this NMA are likely to be important for

patients and policy makers to help inform the choice of skin antisepsis before surgery.

We recognize 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 (ie, 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.[42,43] The problems associated with hypothesis testing have been also highlighted for the case of NMA.[44] 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 0, 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 before 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 after 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 CHG for skin antisepsis before clean surgery.

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