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State of the Science Review

Chlorhexidine disinfectant can reduce the risk of central venous catheter infection compared with povidone: a meta-analysis

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Key Words:
Central venous catheters
Chlorhexidine
Povidone
Catheter infection

Objective: Assess the efficacy of chlorhexidine with povidone solutions as a skin disinfectant for central venous catheter (CVC) care.

Background: Central venous catheters are widely used for critically ill patients. Catheter maintenance can easily lead to a catheter-related bloodstream infection (CRBSI), which is the manifestation of a bloodstream infection (BSI) in a patient who carries a catheter or removes the catheter within 48 hours. There is no clear source of BSIs except for indwelling catheters in the blood vessels, and BSIs significantly increase the morbidity and mortality of patients. We assess the efficacy of chlorhexidine with povidone as a skin disinfectant for CVC care.

Methods: In July 2018, we searched the Cochrane Library, PubMed, EMBASE, Web of Science, OVID, CNKI, SinoMed, WanFangData, CqVip, and DuXiu for publications in English and Chinese. By searching articles published before July 2018, we were able to extract data on study design, participants, antiseptics compared, sample size, and main outcomes. We conducted meta-analyses of the efficacy of chlorhexidine vs povidone solutions as a skin disinfectant for CVC care.

Results: We included 10 randomized controlled trial studies. After conducting subgroup analysis, the results indicated that chlorhexidine was significantly better than povidone in preventing CRBSIs ($P = .12$; $I^2 = 36\%$; risk ratio [RR] = 0.49; 95% confidence interval [CI], 0.29-0.85). Compared with povidone, the chlorhexidine catheterization rate of CRBSIs was reduced ($P = .16$; $I^2 = 32\%$; RR = 0.54; 95% CI, 0.42-0.69). There was no clear difference in the rates of skin reaction between chlorhexidine and povidone ($P = .006$; $I^2 = 87\%$; RR = 1.92; 95% CI, 0.55-6.72). The comparison was underpowered for BSIs without a clear source.

Conclusions: Chlorhexidine solution for CVC care may significantly reduce rates of CRBSIs and catheter colonization compared with povidone solutions. The disinfection effect of chlorhexidine-alcohol is better than that of other solutions. Because the quality of the studies evaluated is relatively low, the true effects may be different, so more evidence is needed.

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INTRODUCTION

Central venous catheters (CVCs) provide secure vascular access for critically and chronically ill patients. They are widely used for intravenous medication administration, fluid replacement, parenteral nutrition, and hemodynamics monitoring.[1] However, catheter maintenance can easily lead to a catheter-related bloodstream infection (CRBSI), which is the manifestation of a bloodstream infection (BSI) in a patient who carries a catheter or removes the catheter within 48 hours. There is no clear source of BSIs except for indwelling catheters in the blood vessels. From January 2007 to December 2012, the International Nosocomial Infection Control Consortium conducted a multicenter, prospective surveillance cohort study of 503 intensive care units (ICUs) in 43 countries and reported a rate for CRBSIs in ICUs of 4.78 cases per 1000 catheter-days.[2] When a patient develops a CRBSI, the infection will significantly increase the morbidity and mortality of the patient, prolong the patient's hospital stay, and increase the burden of disease;[3] therefore, it is crucial to take positive preventive measures to reduce the incidence of infection.

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Conflicts of interest: None to report.

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In order to reduce catheter-related infections, health care staff must be able to choose the best skin disinfectant, during both insertion of the catheter and maintenance, to kill more microorganisms at the catheter insertion point and prevent bacteria from spreading into the body. Many types of disinfectants are currently in use, but, because their application is not strictly regulated, it is difficult to say which disinfectant is better. Some meta-analyses[4-8] have assessed chlorhexidine vs povidone for CVC care; however, these analyses also evaluated other disinfection methods, as well as CVCs for hemodialysis and plasma exchange and peripherally inserted central catheters. We found no recent comparison of only chlorhexidine and povidone, so we performed a meta-analysis of all available published studies comparing the efficacy of chlorhexidine to povidone as a skin disinfectant for CVC care.

METHODS

Literature search strategy

In July 2018, we searched online using a combination of subject words: central venous catheter, chlorhexidine, chlorhexidine gluconate, iodophor, povidone-iodine, povidone, central line-associated blood stream infection, catheter-related bloodstream infection (CRBSI), catheter-related infections, central venous catheter-related infections, disinfectant, care, infection. We manually searched the Cochrane Library, PubMed, EMBASE, Web of Science, OVID, CNKI, SinoMed, WanFangData, CqVip, DuXiu for publications in English and Chinese. We searched articles published before July 2018.

Selection criteria

The types of studies we included were randomized controlled trials (RCTs) in which any type of chlorhexidine solution was compared to a povidone solution for CVC care. Locations of the central venous catheters included subclavian, internal jugular, and femoral venous sites. Also, each study had to report the incidence of CRBSIs or catheter colonization, skin reactions, or BSIs without a clear source. The diagnosis of each observation was based on international diagnostic criteria. The following studies were excluded: (1) pediatric studies, (2) duplicate studies, (3) studies with incomplete data, (4) low-quality studies, and (5) studies involving CVCs for hemodialysis and plasma exchange.

Data extraction and quality assessment

Two authors independently extracted data on study design, participants, antiseptics compared, sample size, and main outcome. Two authors also independently evaluated the quality of each article

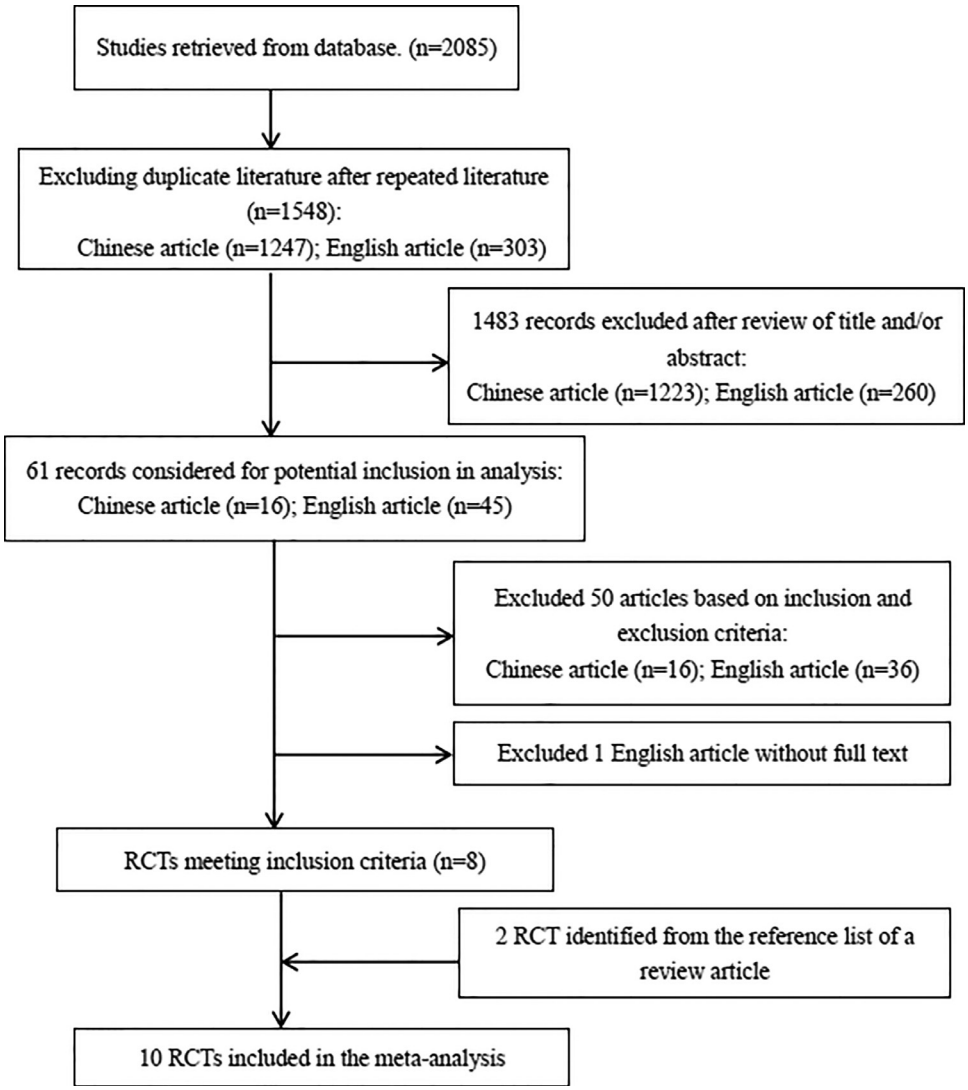

Figure 1. Flow diagram of the literature search and study selection. *RCT*, randomized controlled trial.

Table 1
Characteristics of studies comparing chlorhexidine solutions with povidone solutions for central venous catheters

Reference	Study design	Type of population (sample size)	Antiseptics compared	Outcomes, n/n
Yasuda et al[9]	RCT	Adult patients from ICUs (n = 997)	I: (1) 0.5% chlorhexidine-aqueous; (2) 1% chlorhexidine-aqueous C: 10% povidone iodine	Catheter colonization I: (1) 5/329; (2) 6/339 C: 13/329
Mimoz et al[10]	RCT	Adult patients from ICUs (n = 2349)	I: 2% chlorhexidine-alcohol C: 10% povidone iodine	CRBSI I: 6/1181 C: 39/1168 Skin reaction I: 27/1181 C: 7/1168
Yamamoto et al[11]	RCT	Adult patients from hematology departments (n = 107)	I: 1% chlorhexidine-alcohol C: 10% povidone iodine	CRBSI I: 2/59 C: 7/48 Catheter colonization I: 7/59 C: 14/48
Vallés et al[12]	RCT	Adult patients from ICUs (n = 631)	I: (1) 0.5% chlorhexidine-alcohol; (2) 2% chlorhexidine-aqueous C: 10% povidone iodine	CRBSI I: (1) 9/226; (2) 9/211 C: 9/194 Catheter colonization I: (1) 34/226; (2) 38/211 C: 48/194 Skin reaction I: (1) 38/226; (2) 35/211 C: 30/194
Mimoz et al[13]	RCT	Adult patients from ICUs (n = 481)	I: 0.25% chlorhexidine, 0.025% benzalkonium chloride, and 4% benzylic alcohol C: 5% povidone-iodine in 70% ethanol	CRBSI I: 4/242 C: 10/239 Catheter colonization I: 28/242 C: 53/239
Humar et al[14]	RCT	Adult patients from ICUs (n = 242)	I: 0.5% chlorhexidine-aqueous C: 10% povidone iodine	CRBSI I: 4/125 C: 4/117 Catheter colonization I: 34/125 C: 40/117 Bloodstream infections without a clear source I: 22/125 C: 13/117
Mimoz et al[15]	RCT	Adult patients from ICUs (n = 315)	I: 0.25% chlorhexidine, 0.025% benzalkonium chloride, and 4% benzyl alcohol C: 10% povidone iodine	CRBSI I: 3/170 C: 3/145 Catheter colonization I: 12/170 C: 24/145
Meffre et al[16]	RCT	Adult patients from any unit in the hospital (n = 1117)	I: 0.5% chlorhexidine in alcohol C: 10% povidone iodine	CRBSI I: 3/568 C: 3/549 Catheter colonization I: 9/568 C: 22/549
Sheehan et al[17]	RCT	Adult patients from ICUs (n = 346)	I: 2% chlorhexidine-aqueous C: 10% povidone iodine	CRBSI I: 1/169 C: 1/177 Catheter colonization I: 3/169 C: 14/177
Maki et al[18]	RCT	Adult patients from ICUs (n = 441)	I: 2% chlorhexidine-aqueous C: 10% povidone iodine	CRBSI I: 1/214 C: 6/227 Catheter colonization I: 5/214 C: 6/227

C, control; *CRBSI*, catheter-related bloodstream infection; *I*, intervention; *RCT*, randomized controlled trial; *ICUs*, intensive care units.

by using the Cochrane risk-of-bias tool. If there was a disagreement, they would consult a third person. The quality of each article was rated as good if all biases were low. The quality was rated as low if all biases were high and medium if some biases are high.

Data analysis

We used the Cochrane RevMan 5.2 software to analyze the data by calculating risk ratios (RRs) and 95% confidence intervals (CIs). The

heterogeneity of the study was evaluated by χ^2 and I^2 tests. If the study had statistical heterogeneity ($I^2 \geq 50\%$; $P \leq .10$), we used a random-effects model. In contrast, if $I^2 < 50\%$ and $P > .10$, then a fixed-effects model was used. Because of differences in the disinfectant ingredients, we conducted some subgroup analyses. We also conducted sensitivity analyses for some comparisons.

RESULTS

Study selection and characteristics

We first retrieved 2085 articles from various databases. Excluding duplicate articles reduced that number to 1548 articles, and, after screening based on inclusion and exclusion criteria, we finally narrowed our focus to 10 RCT articles (Fig 1).[9-18] Table 1 shows the characteristics of the included studies; the 10 trials involved a total of 7026 catheters.

Assessment of risk of bias in included studies

In general, there was wide variation in the risk of bias for the included studies. With the exception of the 2015 study by Mimoz et al,[10] the studies were assessed to be at high risk for performance bias. Only the 1991 study by Maki et al[18] had a high risk of bias in random sequence generation; the others were judged to be at low risk. The risks of bias for the studies are shown in Figure 2.

Outcomes

First, we comprehensively analyzed the effects of chlorhexidine and povidone solutions in CVCs. Second, we divided the included studies into 3 subgroups for comparison according to the composition of the disinfectant: (1) chlorhexidine in aqueous solution vs povidone in aqueous solution; (2) chlorhexidine in alcohol solution vs povidone in aqueous solution; and (3) chlorhexidine in alcohol solution vs povidone in alcohol solution. We performed a subgroup analysis of each observation (CRBSI, catheter colonization, skin reaction, and BSIs without a clear source).

Catheter-related bloodstream infections

We conducted a comprehensive analysis of 9 articles that involved 6029 catheters. Before subgroup analysis, the analysis showed no clear difference in the rates of CRBSI ($P = .08$; $I^2 = 43\%$; RR = 0.47; 95% CI, 0.26-0.85). When we conducted some subgroup analyses according to the various disinfectant ingredients, the results indicated that chlorhexidine was significantly better than povidone ($P = .12$; $I^2 = 36\%$; RR = 0.49; 95% CI, 0.29-0.85) (Fig 3). There were no significant differences in the comparisons of chlorhexidine in aqueous solution vs povidone in aqueous solution (RR = 0.64; 95% CI, 0.26-1.58) or chlorhexidine in alcohol solution vs povidone in aqueous solution (RR = 0.74; 95% CI, 0.39-1.39). However, the risk for CRBSIs was significantly lower for chlorhexidine-alcohol than povidone-alcohol (RR = 0.23; 95% CI, 0.09-0.57). We analyzed the published bias according to the funnel plot and found that the bias had a greater impact (Fig 4).

Catheter colonization

We conducted a comprehensive analysis of 8 articles involving 4352 catheters. Chlorhexidine showed a significant advantage for reducing catheter colonization compared to povidone ($P = .22$; $I^2 = 25\%$; RR = 0.54; 95% CI, 0.45-0.65). The heterogeneity of the research was acceptable. After conducting subgroup analysis, we found that chlorhexidine performed significantly better than povidone ($P = .16$; $I^2 = 32\%$; RR = 0.54; 95% CI, 0.42-0.69) (Fig 5). Analyses

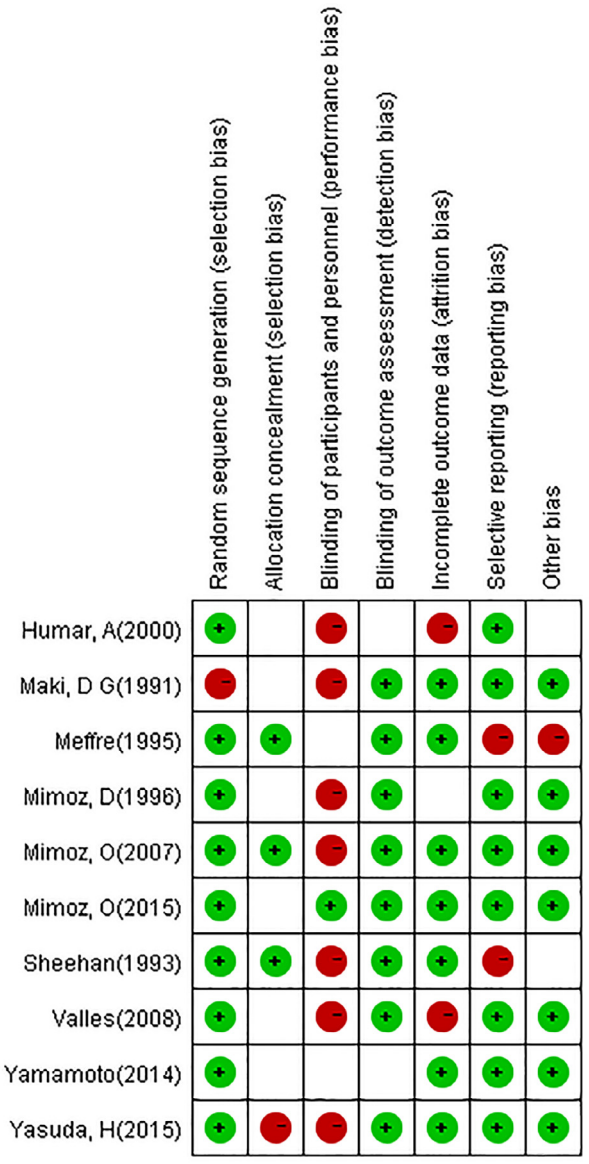

Figure 2. Risk of bias graph showing review authors' judgments about each risk of bias item presented as percentages across all included studies.

of subgroups showed that any solution of chlorhexidine was associated with a lower rate of catheter colonization than any solution of povidone: (1) chlorhexidine in aqueous solution vs povidone in aqueous solution (RR = 0.42; 95% CI, 0.23-0.76); (2) chlorhexidine in alcohol solution vs povidone in aqueous solution (RR = 0.60; 95% CI, 0.44-0.83); or (3) chlorhexidine in alcohol solution vs povidone in alcohol solution (RR = 0.52; 95% CI, 0.34-0.80). The results of the subgroup analysis indicated a reduction in the rate of catheter colonization in chlorhexidine compared with povidone. We analyzed the published bias based on the funnel plot and found that the bias had a greater impact (Fig 6).

Skin reactions

Two studies reported the occurrence of skin reactions. Before subgroup analysis, meta-analyses showed no clear difference in the rates of skin reaction for chlorhexidine compared to povidone ($P = .006$; $I^2 = 87\%$; RR = 1.92; 95% CI, 0.55-6.72). The clinical heterogeneity was large. After grouping according to the composition of the disinfectant,

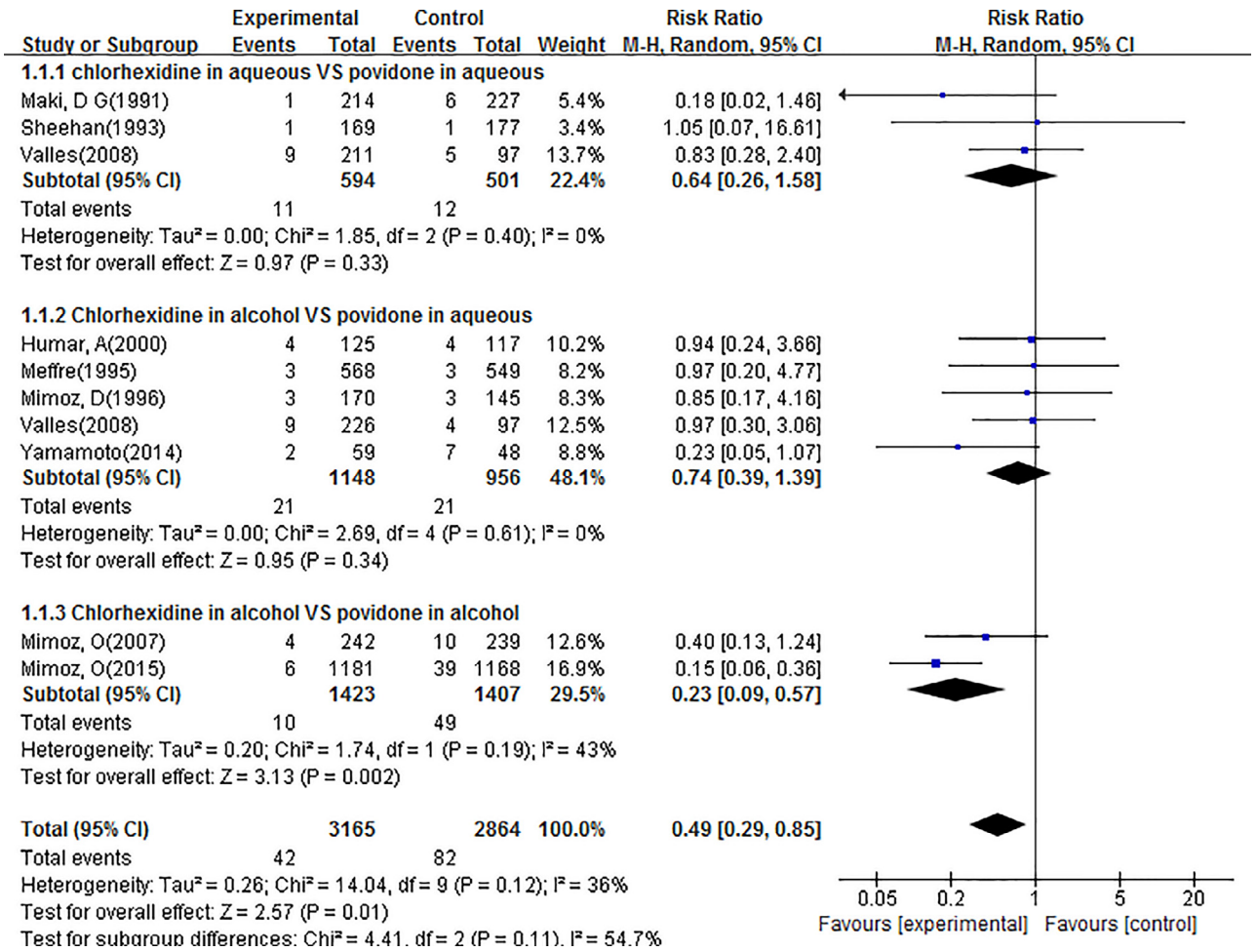

Figure 3. Forest plot of catheter-related bloodstream infections for chlorhexidine vs povidone. *M-H*, Mantel-Haenszel; *CI*, confidence interval.

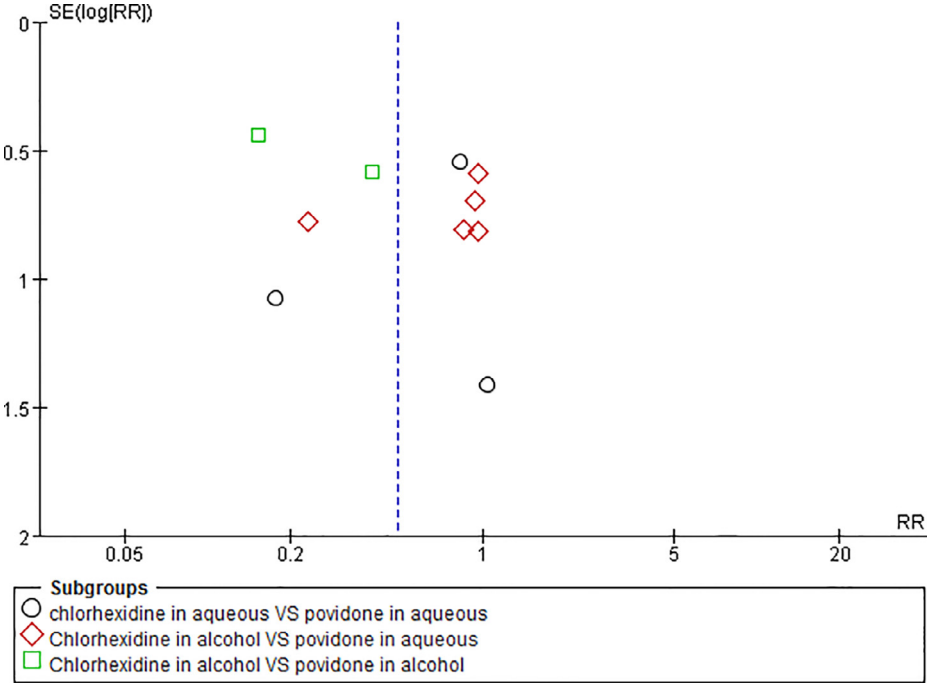

Figure 4. Funnel plot of catheter-related bloodstream infections for chlorhexidine vs povidone. *SE*, standard error; *RR*, risk ratio.

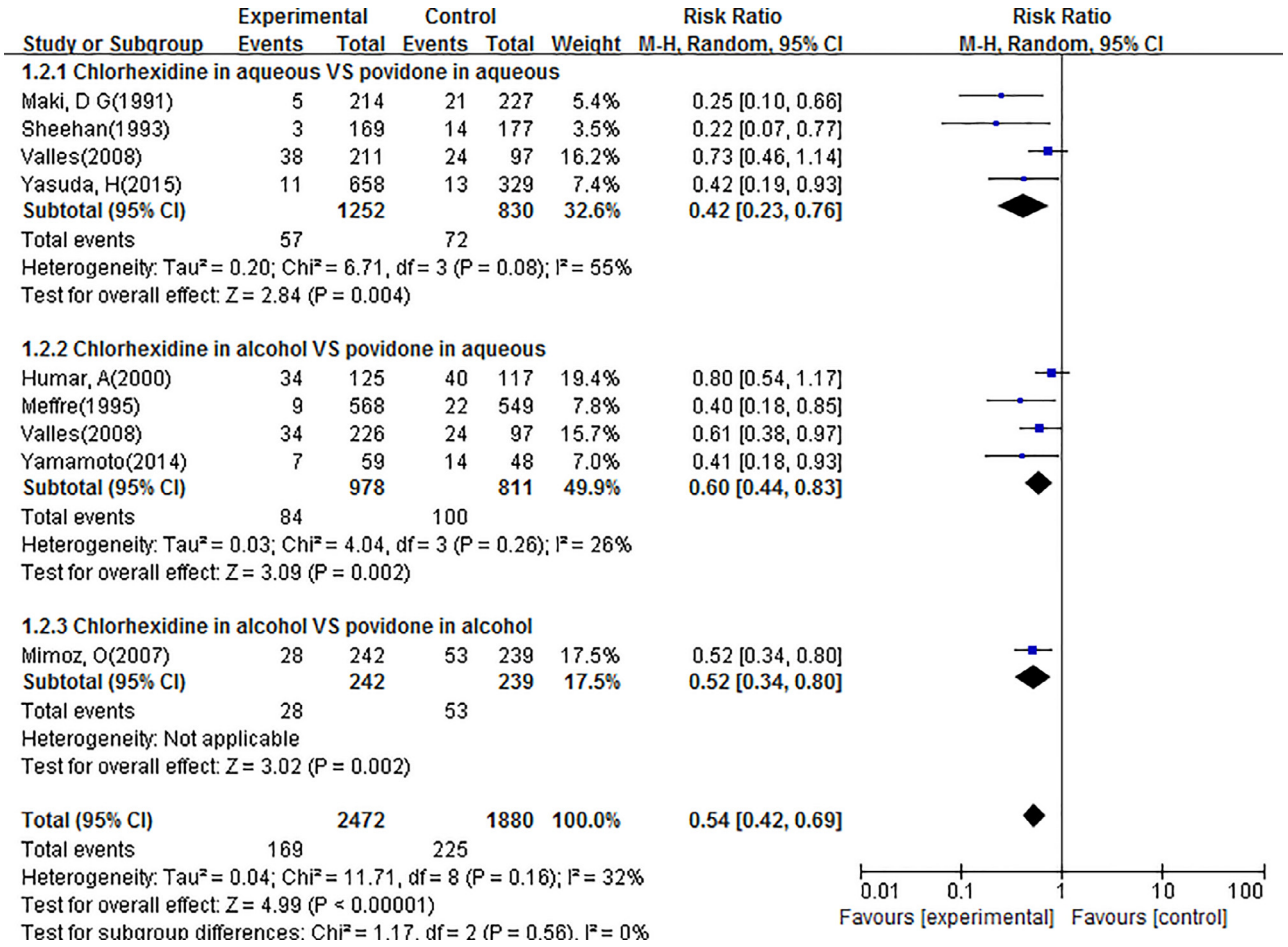

Figure 5. Forest plot of catheter colonization for chlorhexidine vs povidone. *M-H*, Mantel-Haenszel; *CI*, confidence interval.

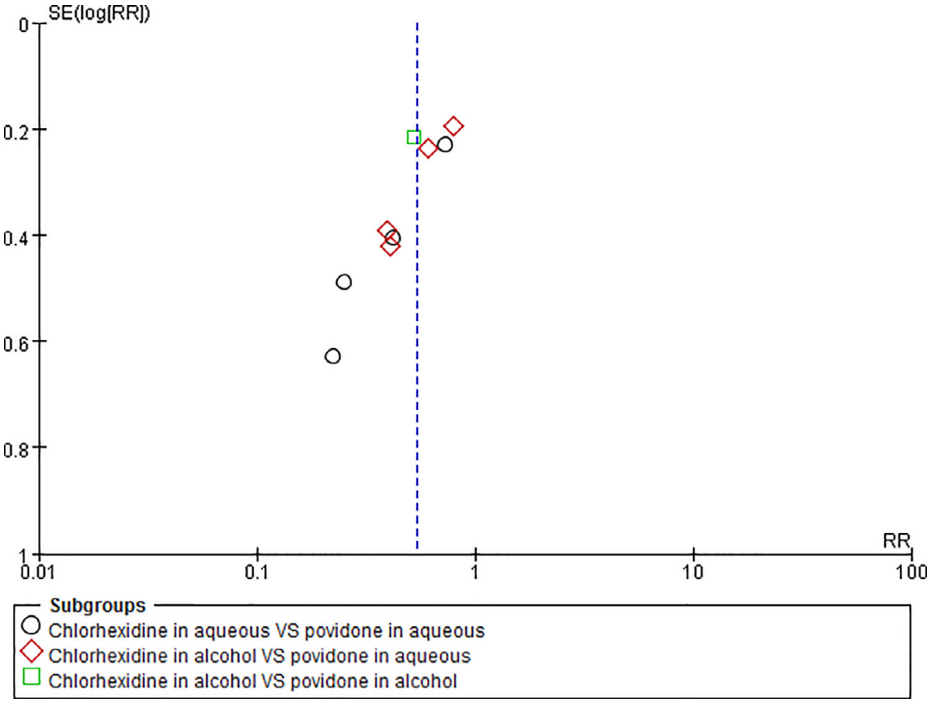

Figure 6. Funnel plot of catheter colonization for chlorhexidine vs povidone. *SE*, standard error; *RR*, risk ratio.

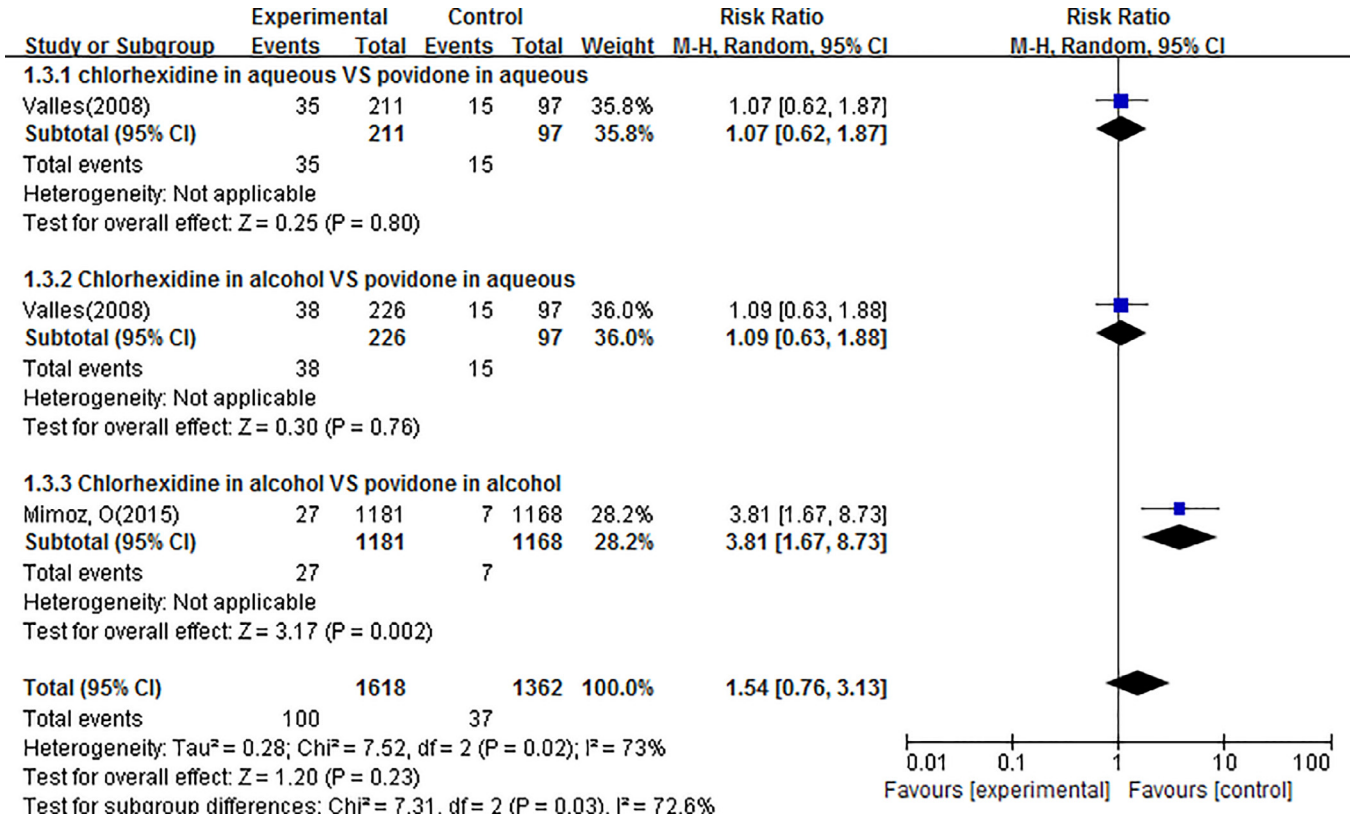

Figure 7. Forest plot of skin reaction for chlorhexidine versus povidone. *M-H*, Mantel-Haenszel; *CI*, confidence interval.

the result also showed no clear difference ($P = .02$; $I^2 = 73\%$; RR = 1.54; 95% CI, 0.76-3.13) (Fig 7). Analyses according to the 3 subgroups showed no clear differences in the rates of skin reaction for chlorhexidine in aqueous solution vs povidone in aqueous solution (RR = 1.07; 95% CI, 0.62-1.87) or chlorhexidine in alcohol solution vs povidone in aqueous solution (RR = 1.09; 95% CI, 0.63-1.88). Analysis showed that chlorhexidine in alcohol solution was associated with a higher rate of skin reaction than povidone in alcohol (RR = 3.81; 95% CI, 1.67-8.73).

Bloodstream infections without a clear source

The single article[14] included in our analysis involved 35 catheters. Analyses showed no clear difference in the rates of this outcome between chlorhexidine in aqueous solution and povidone in aqueous solution (RR = 1.58; 95% CI, 0.84-3.00) (Fig 8). Because the sample size of this study was very small, the comparison was underpowered and evidence insufficient.

Limitations of the review studies

First, the number of studies included was small, and some studies did not specify the occurrence of outcomes in each site; therefore, we were unable to perform further subgroup analyses of each site. Second, due to insufficient data, we did not conduct further analysis on the concentration of these disinfectants. Third, several studies had an unclear risk of bias due to insufficient allocation information, so there may be some selection bias. Fourth, we included only Chinese and

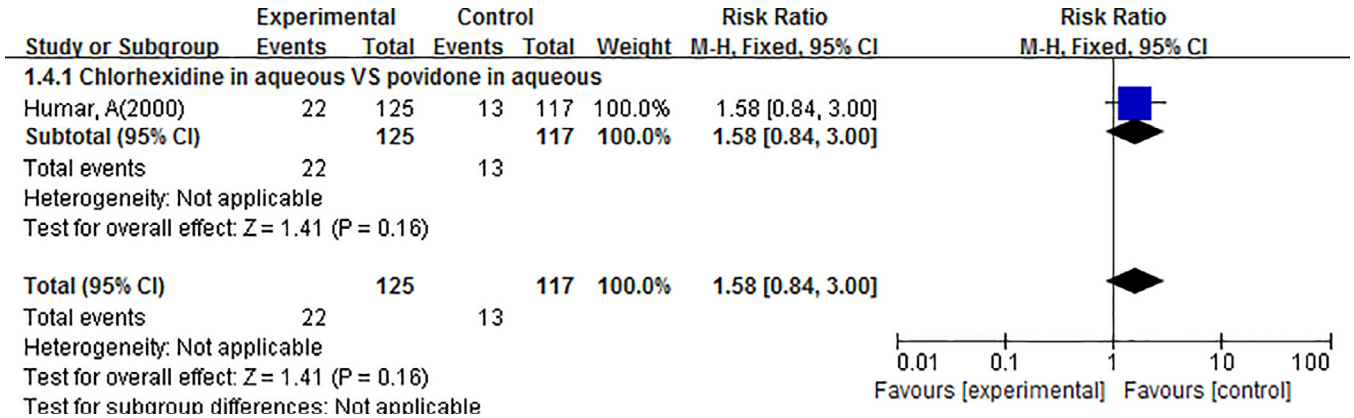

Figure 8. Forest plot of bloodstream infections without a clear source for chlorhexidine versus povidone. *M-H*, Mantel-Haenszel; *CI*, confidence interval.

English articles, so there may be a language bias. More RCT studies are necessary to confirm and update our conclusions.

CONCLUSIONS

This review compared the application of chlorhexidine or povidone in the maintenance of CVCs. In our analyses, we not only comprehensively compared the 2 types of disinfectants but also divided the included studies into 3 subgroups for comparison according to the composition of the disinfectant. In general, the findings of this review are broadly in line with other reviews,[4-7] all of which reported that a chlorhexidine solution was better than a povidone solution for CVC care. However, we cannot be certain whether each disinfectant was combined with alcohol or an aqueous solution, the latter of which was found to be better. We need more evidence.

The heterogeneity of the research on CRBSIs was acceptable. There was a significantly lower risk of CRBSIs in chlorhexidine in alcohol solution than for povidone in alcohol solution. Although the relevant articles included only the subgroups of chlorhexidine-alcohol vs povidone-alcohol, the number of catheters included in each group was acceptable. With regard to catheter colonization, chlorhexidine in any solution performed better than povidone in any solution. Chlorhexidine is a potent broad-spectrum germicide that is popular because its antimicrobial activity can persist longer than that of other agents. In recent years, reports on skin reactions caused by chlorhexidine have gradually increased,[19,20] but our analyses found no clear difference in the rates of skin reactions for chlorhexidine compared to povidone. Although only 2 articles collected data on skin reactions, the studies involved 2980 catheters. Certainly, we need more evidence regarding skin reactions. Finally, the evidence was underpowered for any definitive conclusion about BSIs without a clear source.

In general, the chlorhexidine disinfectant was more widely used in clinical practice. Some studies showed that some bacteria have developed a resistance to chlorhexidine.[21,22] We need more data from evidence-based nursing studies to illustrate such effects of chlorhexidine and povidone; therefore, chlorhexidine disinfectants should be applied carefully and only as required.

Acknowledgments

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