Systematic Review and Meta-Analysis

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Preoperative bathing with chlorhexidine reduces the incidence of surgical site infections after total knee arthroplasty

A meta-analysis

Zhen Wang, MD[a], Jia Zheng, MD[a], Yongqiang Zhao, MD[a], Yungai Xiang, MD[b], Xiao Chen, MD[a], Fei Zhao, MD[a], Yi Jin, MD[a,*]

Abstract

Background: Surgical site infection is a devastating postoperative complication, and the occurrence ranges from 1% to 2% after total knee arthroplasty (TKA). The efficacy of the preoperative use of chlorhexidine for reducing infection has been debated. This meta-analysis aimed to examine the efficacy of the use of chlorhexidine to prevent surgical site infections after TKA.

Methods: In February 2017, a systematic literature review was conducted using the following electronic databases: PubMed, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, and the Google database. Data from randomized controlled trials (RCTs) and retrospective comparative study (RCS) that compared the use of chlorhexidine versus control washes to prep patients for TKA were retrieved. The primary endpoint was to compare the total incidence of infection with and without the use of chlorhexidine. The secondary outcomes were the incidence of infection in low-risk category patients, moderate-risk category patients, and high-risk category patients. After testing for publication bias and heterogeneity between studies, data were aggregated for random-effects modeling when necessary.

Results: Four clinical trials that included 8787 patients (chlorhexidine group: n = 2615, control group: n = 6172) were ultimately included in the meta-analysis. Chlorhexidine was associated with a reduced total incidence of infection, corresponding to a reduction of 1.69% [risk ratio (RR) = 0.22; 95% confidence interval (95% CI) = 0.12–0.40; *P* = .000]. Similarly, chlorhexidine was associated with a reduction in the incidence of infection among patients in the moderate-risk category (RR, 0.18; 95% CI, 0.05–0.63; *P* = .007) and the high-risk category (RR, 0.13; 95% CI, 0.03–0.67; *P* = .014). There was no significant difference between the incidence of infection in low-risk category patients with chlorhexidine use compared with the use of control washes (RR, 0.60; 95% CI, 0.22–1.60; *P* = .330).

Conclusion: The preoperative use of chlorhexidine could reduce the total incidence of infection and the incidence of infection in moderate-risk and high-risk category patients. The overall evidence and the number of included studies was limited; thus, a greater number of high-quality RCTs is still needed to further identify the effects of chlorhexidine on reducing the incidence of infection after TKA.

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence interval, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, NNT = number need to treat, NOS = Newcastle–Ottawa Scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCS = retrospective comparative study, RCT = randomized controlled trials, RR = risk ratio, THA = total hip arthroplasty, THAs = total hip arthroplasties, TKA = total knee arthroplasty.

Keywords: chlorhexidine, meta-analysis, total knee arthroplasty

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[a] Department of Orthopaedics, Henan Provincial People's Hospital, [b] Department of Reproductive Center, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China.

[*] Correspondence: Yi Jin, Department of Orthopaedics, Henan Provincial People's Hospital, 7. No, Weiwu Road, Zhengzhou, Henan Province 450003, China (e-mail: scisubmit123@163.com).

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1. Introduction

Total knee arthroplasty (TKA) is one of the most successful procedures for decreasing pain and improving function in patients with end-stage knee osteoarthritis.[1] Nevertheless, site infection complications will prolong a treatment period that may last for several months. Infection is one of the most devastating postsurgical complications, and the rate of occurrence after TKA ranges from 1% to 2%.[2,3] Furthermore, the incidence reaches 10% in TKA revisions.[4] Sources of wound infection following TKA include airborne bacteria in the operating room and native skin flora.[5] Numerous methods have been developed for reducing the incidence of surgical site infections following TKA. Bathing with antiseptic agents on the evening before surgery is recommended by the Centers for Disease Control and Prevention and is the standard-of-care.[6] Chlorhexidine exerts its bactericidal effects through direct disruption of the organisms' membrane permeability and is thus an effective broad-spectrum biocide agent.[7] Several studies have shown that chlorhexidine

Table 1

The general characteristic of the included studies.

	No. of patients		Male, %		Mean age, y						
Reference	Intervention	C	Intervention	C	Intervention	C	No. of bathings (h before surgery)	Outcomes	Study design	Follow-up	Surgery
Johnson et al[14]	488	1735	34	31	63	63	2% chlorhexidine gluconate and night before and morning of surgery	1,2,3,4	RCS	1 y	Primary and revision TKA
Kapadia et al[15]	991	2726	42	51	NS	NS	NS	1	RCS	NS	Primary TKA
Kapadia et al[16]	1000	1000	62	61	62	62	2	1,2,3,4	RCS	1 y	Primary and revision TKA
Zywiel et al[4]	136	711	51	50	63	63	2% chlorhexidine-impregnated cloths at night before surgery	1,2,3,4	RCS	NS	Primary TKA

1, total incidence of infection, 2, incidence of infection with low-risk category; 2, Incidence of infection with moderate-risk category; 3, Incidence of infection with high-risk category.
C = control; NS = not stated; RCS = retrospective comparative study; y = years.

was efficacious to decrease postoperative infection risk.[8] However, another clinical trial did not support the routine administration of chlorhexidine for the prevention of surgical site infections.[7] A previous meta-analysis investigated the efficacy of the preoperative use of chlorhexidine to prevent surgical site infection in patients undergoing TKAs and total hip arthroplasties (THAs)[9]; however, because that study included both patients undergoing TKA and patients undergoing THA, we cannot determine whether chlorhexidine is certain to have exerted a significant influence on infection after TKA. Thus, we selected relevant studies from the electronic databases and used the summarized data to perform a meta-analysis to examine the effects of preoperative bathing with chlorhexidine on the incidence of surgical site infection after TKA.

2. Materials and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[10] and was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist.[11]

2.1. Search strategy and study selection

The following electronic databases were systematically searched from their inception through February 2017: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and the Google database. The detailed PubMed search strategy was as follows: ((((chloraprep) OR chlorhexidine-isopropyl) OR chlorhexidine-alcohol)) AND (((((“Arthroplasty, Replacement, Knee”[Mesh]) OR TKR) OR TKA) OR total knee replacement) OR total knee arthroplasty). Meta-analysis was collected data from published papers and thus no ethical approval was need for this meta-analysis.

2.2. Eligibility criteria

1. Participants: Patients who underwent TKA (including primary TKA and TKA revisions).
2. Interventions: Chlorhexidine was used preoperatively for the intervention group.
3. Comparisons: No chlorhexidine was used preoperatively for the comparison group.
4. Outcomes: Total infection rate and incidence of surgical site infection stratified by risk category.
5. Study design: RCTs and retrospective comparative study (RCS) were included.

2.3. Data extraction and outcome measures

For each published study included in the meta-analysis, 2 authors independently extracted the following data: author, publication year, number of patients in the intervention and control groups, proportion of male patients, mean age of the patients, outcomes, duration of the follow-up period, and surgery type. Any disagreement was resolved by discussion. In the present meta-analysis, patient infection risk categories were classified according to the National Healthcare Safety Network surgical risk rating system.[12,13] The detailed information can be seen in Table 1.[4,14–16] The outcome measures were total infection rate, and the infection rate among low-risk, moderate-risk, and high-risk category patients. If the data were not reported numerically, we extracted the mean and standard deviation values using *GetData Graph Digitizer* software (Xinzhong Co, Beijing, China) as needed.[10]

2.4. Risk of bias assessment

Two reviewers independently evaluated the risk of bias in non-RCTs according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[10]; the assessment criteria were assessed by the Newcastle–Ottawa Scale (NOS) as previously described.[17]

2.5. Quality of evidence assessment

Two reviewers independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.[18] Assessment items included the following: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[18,19] The quality of evidence of each result was classified as high, moderate, low, or very low. GRADE Pro software (Grade

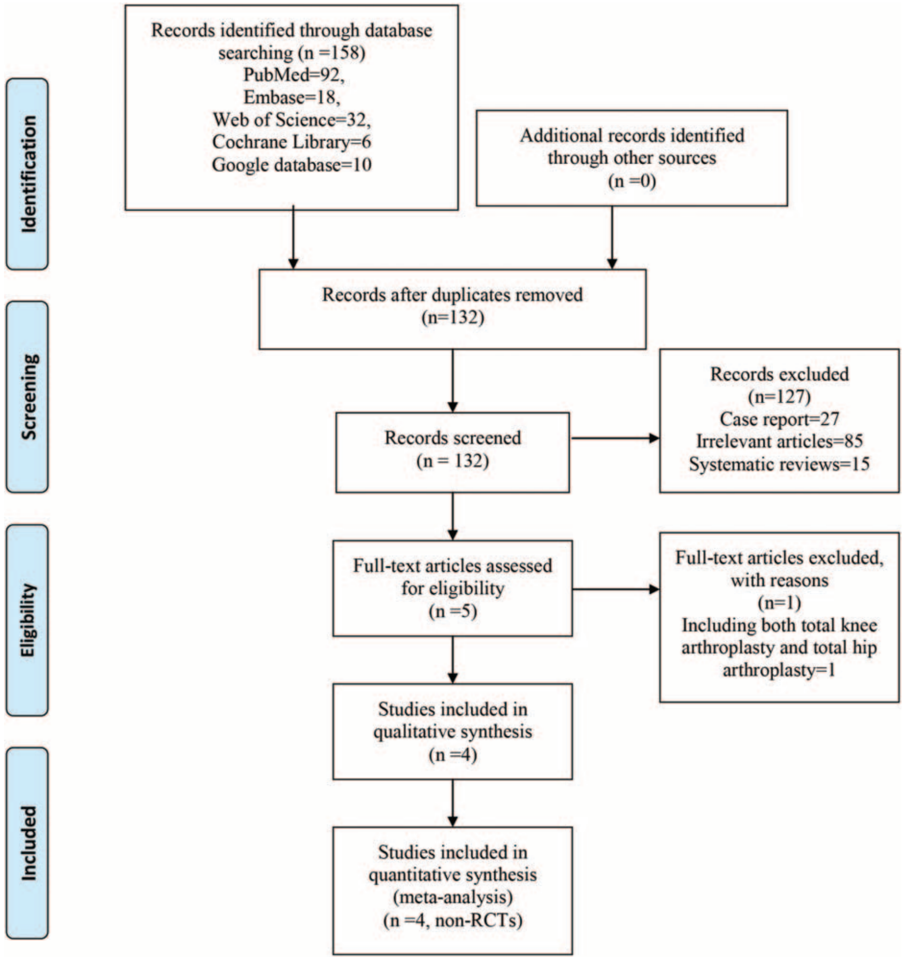

Figure 1. PRISMA flow chart of retrieved studies.

co. California) was used to construct summary tables for the included studies.

2.6. Statistical analysis

For dichotomous outcomes (total incidence of infection and the incidence of infection in low-risk, moderate-risk, and high-risk category patients), we calculated the risk ratio (RR) and the 95% confidence interval (CI). Heterogeneity was considered to be statistically significant if the I^2 value was greater than 50%. A fixed-effects model was applied if the I^2 value was less than 50%. All statistical analyses were conducted using Stata 12.0 (Stata Corp., College Station, TX). A *P* value less than .05 was considered statistically significant. Kappa values were used to measure the degree of agreement between the 2 reviewers and were rated as follows: fair, 0.40 to 0.59; good, 0.60 to 0.74; and excellent, 0.75 or higher.[20]

3. Results

3.1. Search results

The literature search and selection process are illustrated in Fig. 1. The initial search yielded 158 articles (PubMed = 92, Embase = 18, Web of Science = 32, Cochrane Library = 6, Google database = 10). After excluding duplications, 132 studies were examined. Next, 127 of the 132 studies were excluded on the basis of the inclusion criteria. One additional study was excluded, as it included both TKA and THA.[8] Finally, the remaining 4 clinical studies with 8787 patients (chlorhexidine group n = 2615, control group n = 6172) were included in this meta-analysis.[4,14–16]

3.2. Study characteristics

Detailed baseline characteristics of the included studies are presented in Table 2. Four studies were included in the meta-analysis. All articles were published in English between 2011 and 2016. The sample sizes ranged from 136 to 2726 (total = 8787), and the mean ages ranged from 62 to 63 years. The follow-up period was 1 year in 2 studies and the rest 2 studies did not state the follow-up period.

3.3. Risk of bias among the included studies

Supplement S1, http://links.lww.com/MD/B976 presents the details of the risk of bias assessment for each included study. The total scores of Johnson et al,[14] Kapadia et al,[15] Kapadia et al,[16] and Zywiel et al[4] were 18, 24, 17, and 23, respectively. The overall kappa value regarding the evaluation of risk of bias in the included RCS was 0.872, indicating an excellent degree of agreement between the 2 reviewers.

Table 2

Patient infection risk categories according to the National Healthcare Safety Network surgical risk rating system.

	Score	
Wound class		
Clean or clean-contaminated	0	
Contaminated, dirty	1	
American Society of Anesthesiologists score		
<3	0	
3+	1	
Surgical cut time		
<2h	0	
≥2h	1	
Total score	0	Low risk
	1	Moderate risk
	2,3	High risk

3.4. Quality of evidence assessment

A summary of the quality of the evidence as assessed according to the GRADE methodology is shown in Supplement S2, http://links.lww.com/MD/B976. The level of evidence was classified as "low" according to the GRADE methodology for all outcomes including the total incidence of infection, and the incidence of infection in the low, moderate, and high-risk categories.

3.5. Total incidence of infection

Data regarding the total incidence of infection were available for 4 studies,[4,14–16] which included a total of 8787 patients. The pooled RR for all patients showed no significant heterogeneity ($I^2=0.0\%$, $P=.824$). Analysis revealed that the preoperative use of chlorhexidine could reduce the incidence of surgical site infections by 1.69% (RR, 0.22; 95% CI, 0.12–0.40; $P=.000$, Fig. 2).

3.6. Incidence of infection in low-risk category patients

The incidence of infection among low-risk category patients was examined in 3 trials,[4,14,16] which included a total of 2606 patients. The pooled RR for all patients revealed no significant heterogeneity ($I^2=0.0\%$, $P=.858$). The results showed that the preoperative use of chlorhexidine could reduce the incidence of infection in low-risk category patients by 0.52%. However, the difference was not statistically significant (RR, 0.60; 95% CI, 0.22–1.60; $P=.330$, Fig. 3).

3.7. Incidence of infection in moderate-risk category patients

The incidence of infection among moderate-risk category patients was examined in 3 trials,[4,14,16] which included a total of 2985 patients. The pooled RR for all patients revealed no significant heterogeneity ($I^2=0.0\%$, $P=.835$). The results showed that the preoperative use of chlorhexidine could reduce the incidence of infection among moderate-risk category patients by 1.95% (RR, 0.18; 95% CI, 0.05–0.63; $P=.007$, Fig. 4).

3.8. Incidence of infection among high-risk category patients

The incidence of infection among high-risk category patients was examined in 3 trials,[4,14,16] which included a total of 1186

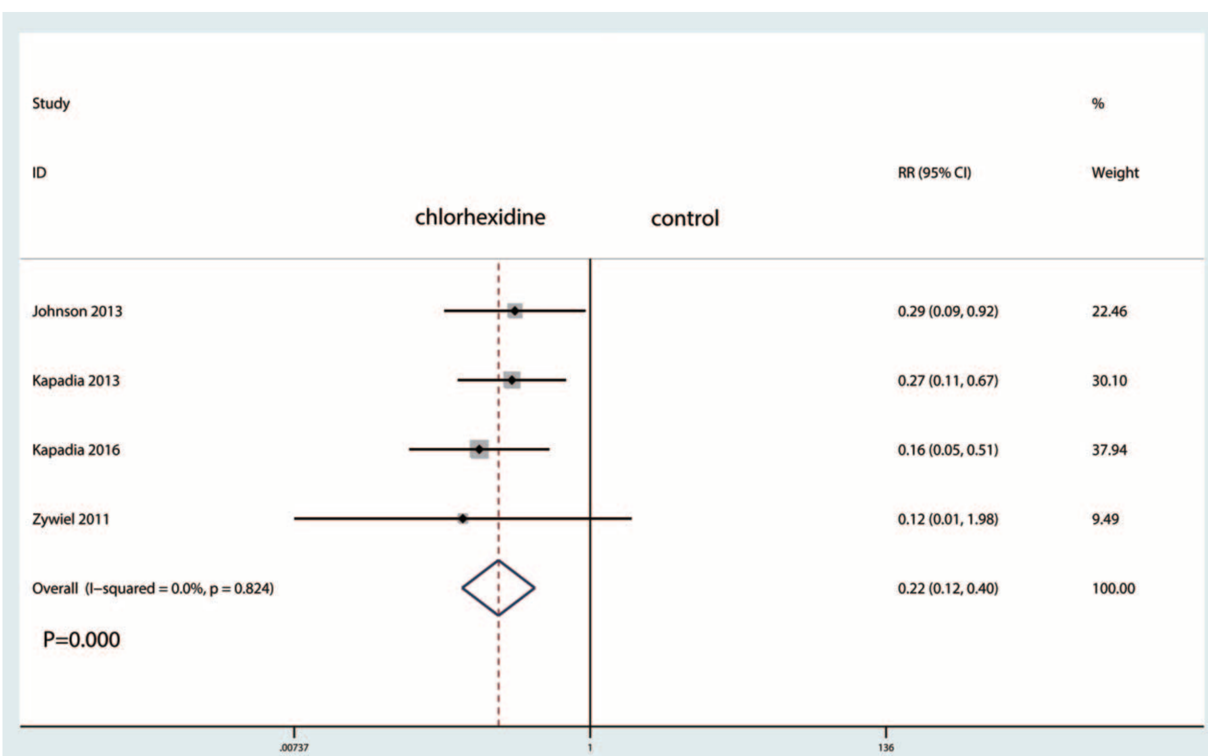

Figure 2. Forest plot comparing the total incidence of infection between the 2 groups.

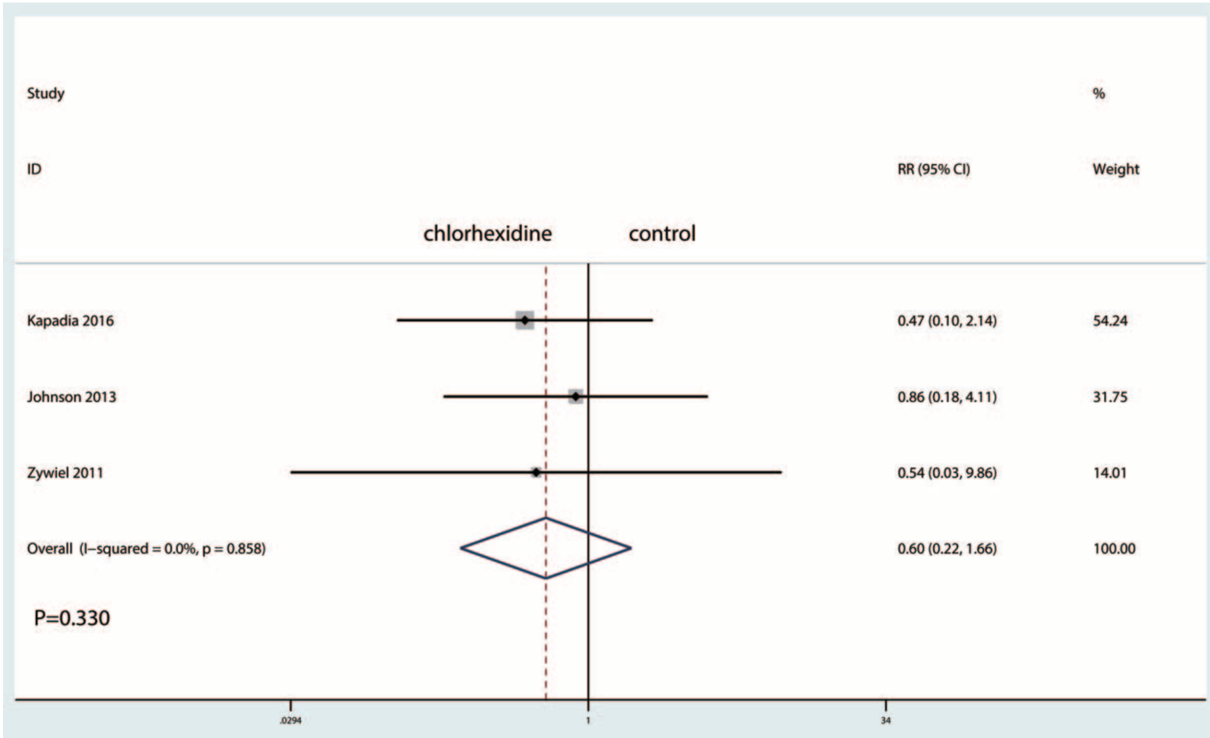

Figure 3. Forest plot comparing the incidence of infection in the low-risk category patients.

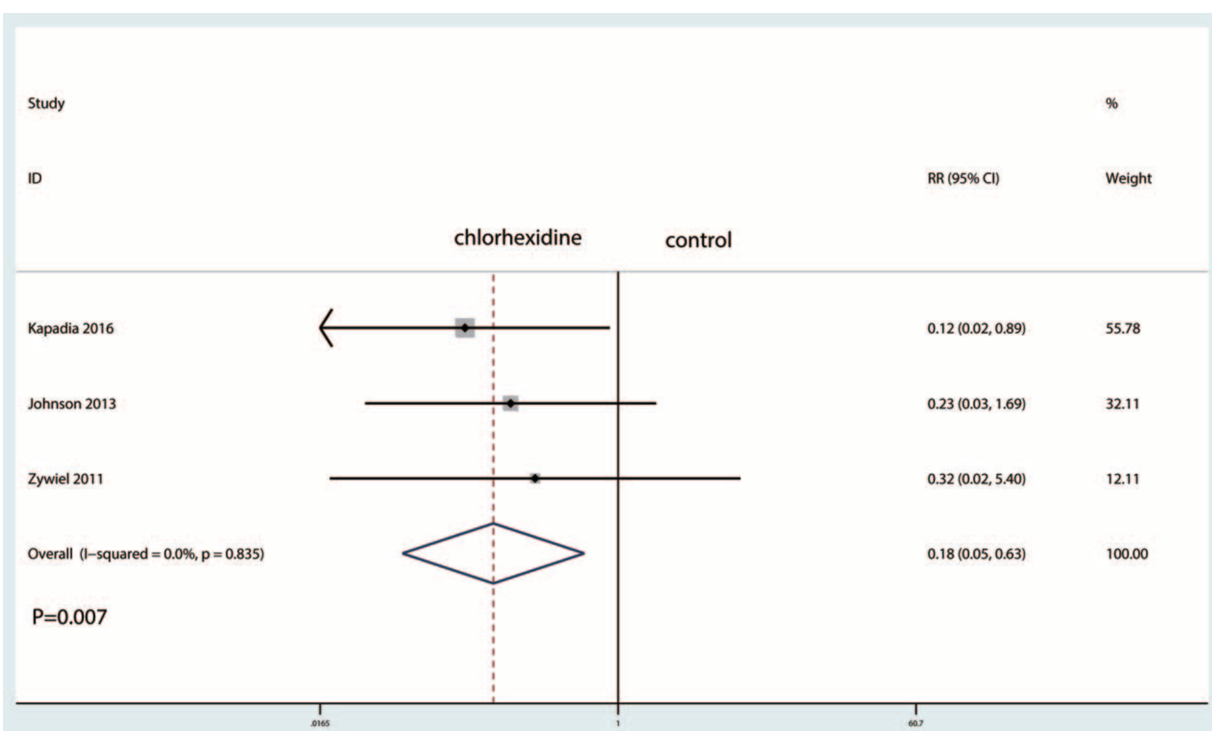

Figure 4. Forest plot comparing the incidence of infection in the moderate-risk category patients.

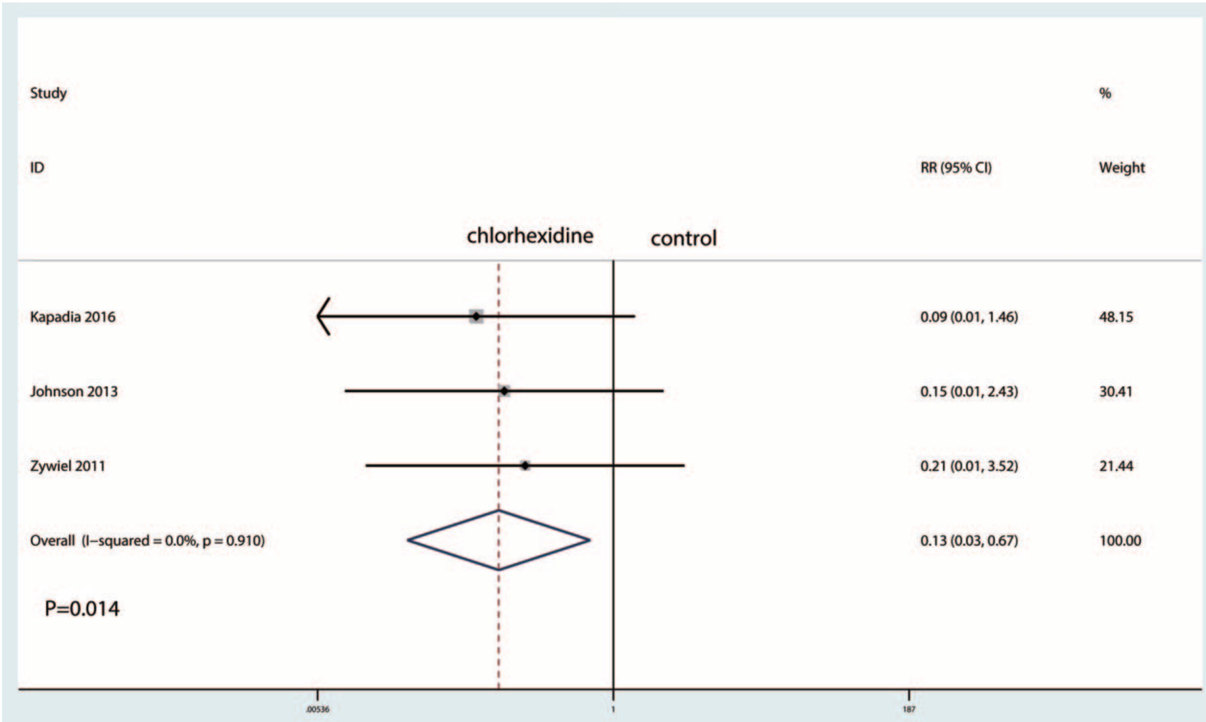

Figure 5. Forest plot comparing the incidence of infection in the high-risk category patients.

patients. The pooled RR for all patients revealed no significant heterogeneity (I^2 = 0.0%, P = .910). The results showed that the preoperative use of chlorhexidine could reduce the incidence of infection among high-risk category patients by 4.15% (RR, 0.13; 95% CI, 0.03–0.67; P = .014, Fig. 5).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis regarding the efficacy of the preoperative use of chlorhexidine for reducing the incidence of site infections after TKA. All included studies were RCS. The pooled results indicated that the preoperative use of chlorhexidine is effective for the prevention of surgical site infection and that the use of chlorhexidine could reduce the incidence of infection among moderate-risk and high-risk category patients. There was no significant difference in the incidence of infection among low-risk category patients with or without chlorhexidine use. The effect of chlorhexidine on the incidence of infection for the different infection risk category was further analyzed. There was no significant difference in the incidence of infection with or without chlorhexidine use in low-risk category patients (P > .05). The low-risk category included clean or clean-contaminated wounds, and the surgical cut time was always less than 2 hours. The final results indicated that the preoperative use of chlorhexidine could reduce the incidence of infection among moderate-risk and high-risk category patients by 1.95% and 4.15%, respectively. Thus, the antibiosis effects of chlorhexidine were most obvious in the high-risk category patients.

Although the benefit was conclusive, the level of evidence, which was undermined by the risk of bias and/or publication bias, was classified as "low," indicating that the degree of benefit of chlorhexidine in preventing surgical site infections must be further studied. RCS may have potential selection risk of bias and cause large heterogeneity for the final outcomes. A major strength of the current analysis is the use of a comprehensive search with strict statistical calculations. Furthermore, number need to treat (NNT) was used to analyze the benefit of chlorhexidine for reducing the infection rate, and a quality of evidence assessment was performed to assess the quality of present evidence for the use of chlorhexidine to reduce the incidence of surgical site infection.

A considerable number of studies have addressed the accurate diagnosis and effective treatments for surgical site infections after TKA. Current strategies include showering or bathing the night before surgery, and washing the incision site before antiseptic skin preparation to prevent the peri-prosthetic infections.[4,14–16] However, there was inconclusive evidence regarding the optimal preoperative preparation.[4,14,16] Chlorhexidine's bactericidal effect results from the binding of cationic molecules found in the solution to the anionic molecules of the bacterial cell wall. The current meta-analysis indicated that the preoperative use of chlorhexidine could reduce the total infection rate by 1.69%. Eiselt [21] revealed that the rate of surgical site infections was 3.19% with the use of a povidone-iodine wash, and this rate decreased to 1.59% with the use of chlorhexidine cloths in orthopedic surgeries. Webster and Osborne[22] conducted a meta-analysis that found no clear evidence of benefit for preoperative showering or bathing with chlorhexidine over other the use of other wash products for reducing the incidence of surgical site infections. In 2015, an updated meta-analysis found similar results.[23] The conclusion of these meta-analyses is in opposition to the findings of the present meta-analysis, possibly due to differences in infection risk categories. Previous studies included all types of surgeries and did not differentiate between infection risk categories in determining the benefit of chlorhexidine.

One issue that should be considered when examining the use of chlorhexidine is the mean chlorhexidine skin concentration. Edmiston et al[24] revealed that using 4% chlorhexidine soap or a 2% chlorhexidine cloth is the optimal concentration on this skin. What is more, Kapadia et al[15] reported that the cost–benefit analysis of using chlorhexidine at their institution, per 1000 TKA patients, showed a net savings of approximately $2.1 million due to the costs of treating surgical site infections. However, only 1 study reported this outcome; thus, more clinical trials are needed to identify the economic savings of using chlorhexidine.

There were several limitations in this meta-analysis: only 4 RCS were included, which might have a selective risk of bias; the follow-up period was relatively short in the included studies, and the infection rate may have been thus underestimated; and publication bias may have existed due to the limited number of included studies.

5. Conclusion

The preoperative use of chlorhexidine could reduce the total incidence of infection and the incidence of infection in moderate-risk and high-risk category patients. In addition, chlorhexidine possesses greater economic-sparing effects than the washes used in the control group. The overall evidence and the number of included studies was limited; thus, more high-quality RCTs are still needed to further identify the efficacy of chlorhexidine for reducing the incidence of infection after TKA.

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