International Journal of Surgery 44 (2017) 176–184

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Preoperative chlorhexidine versus povidone-iodine antisepsis for preventing surgical site infection: A meta-analysis and trial sequential analysis of randomized controlled trials

Dan Zhang, M.M [a, b], Xi-Chen Wang, M.M [a, b], Zeng-Xi Yang, M.M [a, b], Jian-Xin Gan, M.M [a, b], Jie-Bin Pan, M.M [a, b], Lan-Ning Yin, PhD [a, b, *]

[a] Department of General Surgery, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China
[b] Key Laboratory of Digestive System Tumors of Gansu Province, Lanzhou 730030, Gansu Province, China

HIGHLIGHTS

- To clarify the superiority of CH or PVI for prevention of SSIs in clean and clean-contaminated surgery.
- CH should be more preferentially recommended for preoperative skin preparation as compared with PVI in clean and clean-contaminated surgery.
- Preoperative CH antisepsis was associated with lower incidence of SSIs versus PVI.

ARTICLE INFO

Article history:
Received 16 April 2017
Accepted 1 June 2017
Available online 3 June 2017

Keywords:
Chlorhexidine
Povidone-iodine
Surgical wound infection

ABSTRACT

Backgrounds: Updated guidelines for surgical site infections (SSIs) suggested that chlorhexidine (CH) or povidone-iodine (PVI) product was equally appropriate to be applied in preoperative disinfection, but which one was optimal remained ambiguous. Moreover, recent studies reported inconsistent results. Thus, an updated meta-analysis was conducted to clarify the superiority of CH or PVI for prevention of SSIs in clean and clean-contaminated surgery.

Methods: From the inception to November 2016, Pubmed, Embase, and the Cochrane library were systematically searched for randomized controlled trials (RCTs) which explored preoperative antisepsis schemes (CH or PVI) for prevention of SSIs in clean and clean-contaminated surgery. Relative risks (RRs) with 95% confidence interval (CI) were calculated using random effects model. Furthermore, subgroup analysis, sensitive analysis, and trial sequential analysis (TSA) were applied to estimate whether overall pooled effect was enough credible and robust.

Results: Thirteen RCTs involving 6997 patients (3352 in CH and 3645 in PVI group) undergoing clean and clean-contaminated surgeries were included in our meta-analysis. Compared with PVI, preoperative CH antisepsis was associated with lower incidence of SSIs (RR, 0.70; 95%CI, 0.60–0.83, $I^2 = 0$). Additionally, subgroup analysis, sensitive analysis, and TSA indicated that the current available evidence was reliable and robust.

Conclusions: CH should be more preferentially recommended for preoperative skin preparation as compared with PVI in clean and clean-contaminated surgery.

1. Introduction

Surgical site infection (SSI), a frequent hospital-acquired infection, is associated with prolonged hospitalized time [1], unplanned readmission [2], and excessive clinical and economic burden in particular [1,3]. Preoperative skin disinfection can significantly eliminate skin microflora and further prevent the occurrence of SSI, which should be routinely performed before operation, according to the Centers for Disease Control and Prevention (CDC) and Association of periOperative Registered Nurses (AORN) guidelines [4,5].

Chlorhexidine (CH) and povidone-iodine (PVI), as the most

* Corresponding author. Department of General Surgery, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China.
E-mail address: dryinln@163.com (L.-N. Yin).

http://dx.doi.org/10.1016/j.ijsu.2017.06.001
1743-9191/

common preoperative skin antisepsis, are frequently used in surgical settings. Updated recommendations stated that CH or PVI product was equally appropriate to be applied in operation site disinfection, but which one was the optimal remained ambiguous [6]. Published systematic review and meta-analyses showed that skin preparation with CH had potential superiority over PVI in reducing the rate of SSI after clean or clean-contaminated surgery [7–10]. However, they included limited studies, which may be underpowered to reach enough credible conclusions when considering possible random error and subsequent false positive. Most importantly, whether different concentrations of CH products based on different solvent (alcoholic or aqueous) were also associated with similar superiority was unclear. Besides, previous studies seldom assessed the safety related with these disinfection products. Moreover, recently-published clinical studies reported inconsistent results. Two prospective studies reported that no difference was found between CH and PVI in reducing the risk of SSIs following clean-contaminated surgery [11,12]. Also, two retrospective studies reported similar results in patients undergoing breast, vascular, and colorectal surgery [13,14]. Paradoxically, a latest randomized controlled trial (RCT) totaling 1147 patients indicated that CH can be linked with a lower incidence of SSI in patients undergoing cesarean delivery when compared with PVI [15].

Considering the controversial situation, therefore, an updated systematic review and meta-analysis of RCTs was undertaken to clarify the superiority of CH or PVI in preventing preoperative SSIs in clean and clean-contaminated surgery, including the safety associated with skin antisepsis. Moreover, subgroup analysis, sensitive analysis, and trial sequential analysis (TSA) were undertaken to estimate whether the current available evidence was enough credible and conclusive.

2. Materials and methods

Our meta-analysis was consistently undertaken following the Cochrane Handbook [16] for Systematic Reviews of Interventions and PRISMA guidelines (Table S1 supporting information) [17]. Literature retrieval, date extraction, and quality assessment were separately conducted by two reviewers, with inconsistency solved by the chief reviewer. Specially, a statistician (Dan Zhang) in our group performed and reviewed the statistical section.

2.1. Inclusion criteria and data extraction

We merely included RCTs comparing CH with PVI products, whether alcoholic or aqueous solution, for preoperative skin antisepsis in adult patients (>18y) undergoing any clean and clean-contaminated surgeries. The primary outcome was SSI, with the second outcomes consisted of adverse effects associated with CH or PVI. Generally, SSI was defined based on the CDC criterion, which involving wound infections within 30 days postoperatively [5]. We also included studies with self-defined SSI and studies which did not report the primary outcome were excluded. A detailed inclusion and exclusion criteria was present in Table 1. Pubmed, Embase, and The Cochrane library were systematically searched without language limitation from the inception to November 2016. Additionally, references of included studies, previous meta-analyses [7–9,18], and relevant reviews were carefully checked for any possible inclusion. Detailed search strategies were attached to Appendix S1.

Characteristics of individual study were extracted into a predesigned Excel table, including demographic data, type of operations, skin disinfection protocols of two groups, outcomes of interest, and so on. In addition, the extraction of outcomes data was on the basis of intention-to–treat analysis. If more than two intervention groups (e.g. CH versus PVI versus CH + PVI) were compared in the include studies, we just divided targeted group (CH group) into two or more groups with equal sample size to maintain randomization, according to the Cochrane handbook guideline (**16.5.4**) [16].

2.2. Quality assessment and trial sequential analysis

The Cochrane Collaboration's tools were used for assessing the quality of included studies, which encompassing six domains, that is, random sequence generation; allocation concealment; blinding of patients, personnel, outcome assessors; incomplete outcome data; selective reporting [19]. Individual study with six domains of low risk of bias is deemed as low risk of bias, or else, unclear or high risk of bias. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was also employed to evaluate the whole quality of evidence for SSIs, which was classified as very low, low, moderate, or high [20]. We based the quality of the evidence on a specific outcome on five domains: limitations of the study design, inconsistency, indirectness, imprecision of results and publication bias across all studies that measured that particular outcome.

Generally, small sample size and repetitive testing of accumulating data may lead to the risk of random error, subsequently ending up with type I error or type II error in updated meta-analyses [21,22]. Just like interim analysis in some trials, trial sequential analysis (TSA) is introduced into meta-analyses to supervise the possibility of random error and estimate whether current available evidence is enough credible and conclusive [22,23]. When cumulative Z-curve crosses trial sequential monitoring boundary or futility boundary, the current available evidence for the targeted intervention effect may be enough sufficient and further studies cannot reverse pooled effect estimate in updated meta-analyses [23]. In the current meta-analysis, required information size (RIS) which is similar to sample size calculation in a single trial, was also estimated based on an anticipated effect size of 20% relative risk reduction, type I error of 5%, and power of 80%. TSA version 0.9 beta (http://www.ctu.dk/tsa) was applied to all these analyses.

2.3. Statistical analysis and publication bias

Relative risk (RR) with 95% CI was pooled using Mantel-Haenszel method. More conservatively, random effects model was used to estimate overall pooled effect when considering possible clinical and methodological heterogeneity across included studies. Q statistic with its P value and I^2 statistic were applied to evaluate the level of heterogeneity and $I^2 < 50\%$ was regarded as accepted heterogeneity [24]. To investigate underlying source of heterogeneity, we performed pre-defined subgroup analyses including clean and clean-contaminated, single-center and multi-center, low and high or unclear risk of bias, sample size >200 and < 200, CDC criteria and self-defined criteria, and alcoholic PVI and Aqueous PVI. Additionally, the 'leave-one-out' influence analyses were performed to explore the influence of a single study on overall pooled effect estimate by omitting a study each time. Furthermore, we also conducted sensitive analyses to explore the credibility of the pooled effect based on different inclusion criterion in varied clinical scenarios (Low risk of bias, Clean-contaminated surgery, Sample size > 100, Varied CH products; Duration of follow-up > 30 days). A two-tailed P value of less than 0.05 was thought statistically significant.

Publication bias was identified though funnel plot of visual inspection as well as Begg and Egger test [25,26]. If potential