Global *Journal of Microbiology*
2020; 1(1): 2-10.
ISSN Online: 0000-0000; ISSN Print: 0000-0000
Website: http://natureschol ars.com
Email: Glo_J_Mic@126.com
Publisher: Scholars Publishing, LLC

Research Article

Effect of Oral Administration of Chlorhexidine Gargle Combined with Toothbrushing on The Prevention of Ventilator-Associated Pneumonia: A Meta-Analysis of Randomized Controlled Trials

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Received: July 9, 2019; Accepted: November 6, 2019; Published online: June 7, 2020.
Cite this paper: Zheng, P.P., Zhang, L., Sun, R., and Peng, X.Y. (2020) Effect of oral administration of chlorhexidine gargle combined with toothbrushing on the prevention of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. *Global Journal of Microbiology*, 1(1): 2-10. http://natureschol ars.com/gjmic.010102. https://doi.org/10.46633/gjmic.010102.

Abstract

Objective: To evaluate the effect of oral administration of chlorhexidine gargle combined with toothbrushing scrubbing on the prevention of ventilator-associated pneumonia in mechanically ventilated patients. **Methods:** Randomized controlled clinical trials about the effect of chlorhexidine combined with toothbrushing on the incidence of ventilator-associated pneumonia (VAP) were retrieved from the databases including PubMed, Cochrane Library, Web of Science, CNKI, CMB, Wan Fang and VIP, et al. After data extraction and methodological quality evaluation, RevMan5.3 software was used for data analysis. **Results:** A total of 1370 patients were included in 6 studies, and the results of meta-analysis showed that the application of chlorhexidine gargling solution combined with toothbrushing can significantly reduce the incidence of VAP, shorten the time of mechanical ventilation, shorten the length of ICU stay and reduce the mortality of patients (all $P<0.05$). **Conclusion:** The oral nursing plan of chlorhexidine gargling combined with toothbrushing can significantly reduce the incidence of VAP, shorten the time of mechanical ventilation, shorten the length of ICU stay and reduce the mortality of patients. Due to the differences in specific implementation schemes, rigorous and high-quality research are still needed to confirm the application advantages of this scheme.

Key words: Oral nursing; Toothbrushing; Mechanical ventilation; Ventilator-associated pneumonia; Meta-analysis

Introduction

Ventilator-associated pneumonia refers to pneumonia that occurs on patients with tracheal intubation or tracheotomy within 48 hours after mechanical ventilation or extubation, which is the most common hospital-acquired infection in China (1). According to statistics, the incidence of ventilator-associated pneumonia in the intensive care unit (ICU) is 6% to 52%, and the mortality rate is 14% to 50% (2). Studies have shown that about 30% of ICU deaths are associated with VAP. American scholars also found that 70% of common pathogenic bacteria come from the mouth, so good oral nursing is an important measure to reduce the incidence of VAP (3,4). Studies have pointed out that the occurrence of VAP can extend the average hospitalization day by 7 days, which leads to increase of treatment costs. Therefore, prevention of VAP has become the focus of modern medical circles (5).

At present, there are big differences in oral nursing programs for critically ill patients. Foreign oral nursing tends to use the brushing method, and the chlorhexidine has been the most used oral gargle. The mechanism of action is mainly to increase the friction between the toothbrush and the teeth, gums and tongue by mechanical force, so that plaque, oral secretions and tongue coating are easy to fall off, thereby removing most of the dirt in the mouth. Then the repeated washing with chlorhexidine can better remove the residual bacteria, sputum and blood stasis in the mouth, so that the bacterial colonization of the mucosal surface and oropharynx is greatly reduced, thereby reducing the occurrence of VAP (6). More studies have shown that brushing could reduce the incidence of VAP (7-13). In the study of Camargo shown that when using chlorhexidine for oral nursing in mechanically ventilated patients, brushing does not seem to reduce the incidence of VAP compared to brush or gauze cleaning (14). There were also some studies have shown that chlorhexidine combined with toothbrush scrubbing does not reduce the incidence of VAP (10,12). In order to confirm the effect of brushing on the prevention of VAP in patients with mechanical ventilation, this study collected relevant trials on the prevention of VAP in the domestic and international, using meta-analysis to conduct comprehensive analysis to evaluate the effect of chlorhexidine gargle combined with toothbrushing scrubbing, and provide a basis for the optimal selection of clinical oral care methods.

1. Materials and Methods

1.1 Inclusion Criteria

1) Study Design: RCTs or other clinical controlled trials; 2) Participants: patients undergoing tracheal intubation or tracheotomy with ventilator-assisted ventilation and receive oral care in ICU. 3) Interventions: the experimental group received oral nursing with chlorhexidine combined with toothbrushing, the control group receive routine oral nursing with cotton ball. 4) Outcome indicators: the main outcome indicator was the incidence of VAP, and the secondary outcome indicators were mechanical ventilation time, length of stay in ICU, and mortality.

1.2 Exclusion Criteria

1) The types of literature are reviews, storytelling, expert opinion articles;2) Studies that are republished or with incomplete data.

1.3 Search Strategy

We tried to plan, perform, and report this meta-analysis in comply with PRISMA guideline (15). Foreign language databases and Chinese databases were searched from their inception until May 2019 for randomized controlled trials about the effect of oral administration of chlorhexidine gargle combined with toothbrushing on the prevention of ventilator-associated pneumonia, included PubMed, Cochrane Library, Web of Science, China National Knowledge Infrastructure(CNKI), Chinese Biomedical Literature Database (CBM), Wan Fang database and VIP database, etc. Search terms: “oral nursing/ oral care/ oral hygiene”, “toothbrush/ toothbrushing”，“ventilator associated pneumonia/

VAP" and "randomized controlled trial/RCT". In addition, the references of the retrieval studies and previous reviews were reviewed, computer retrieval is the main method, supplemented by the secondary literature traceability method to expand the retrieval, so as to avoid missing the studies not captured by electronic searches.

1.4 Study Selection and Quality Evaluation

The literature quality evaluation was completed by two researchers independently. Firstly, the reviewers evaluated the quality of the included literatures according to the RCT quality evaluation criteria published in Cochrane handbook 5.1.0. When there is any disagreement, the third researcher was consulted. After screening, it will be finally included in the literature for data extraction and drawing.

1.5 Statistical Analysis

Meta-analysis was performed with RevMan5.3 software. The incidence of VAP is described by Relative Risk (RR) and its 95% Confidence Interval (CI). Chi-square (χ^2) was used to confirm whether there was heterogeneity among the studies. If there was no significant statistical heterogeneity ($P > 0.1$, $I^2 < 50\%$), the fixed effect model was adopted. If there was heterogeneity ($P < 0.1$, $I^2 \geq 50\%$), the random effect model was used to combine with the effect size. Descriptive analysis was adopted if heterogeneity was too obvious and cannot be judged. Subgroup analysis was used to observe the effect of evaluation contents are as follows: 1) Whether the generation of a random order is reported; 2) Whether to hide the allocation of random schemes; 3) Whether study subjects and intervention practitioners were blinded; 4) Whether the outcome evaluators are blind;5) Whether the outcome indicator data are complete; 6) Whether there is selective reporting bias; 7) Whether there are other sources of bias (7). After the independent evaluation was completed, the two researchers discussed and reached a consensus on the evaluation results. If there

clinical heterogeneity on the results of the study.

2 Results

2.1 Study Selection and Study Characteristics

A total of 968 related trials were searched. After de-duplication with literature management software, reading the abstracts and full text, 468 duplicates were excluded, 395 trials were not related to the literature, and the subjects, experimental design, intervention measures and outcome indicators were inconsistent. Finally included 6 trials. The flow of study identification is shown in **Figure 1**. **Table 1** shows the characteristics of the included studies.

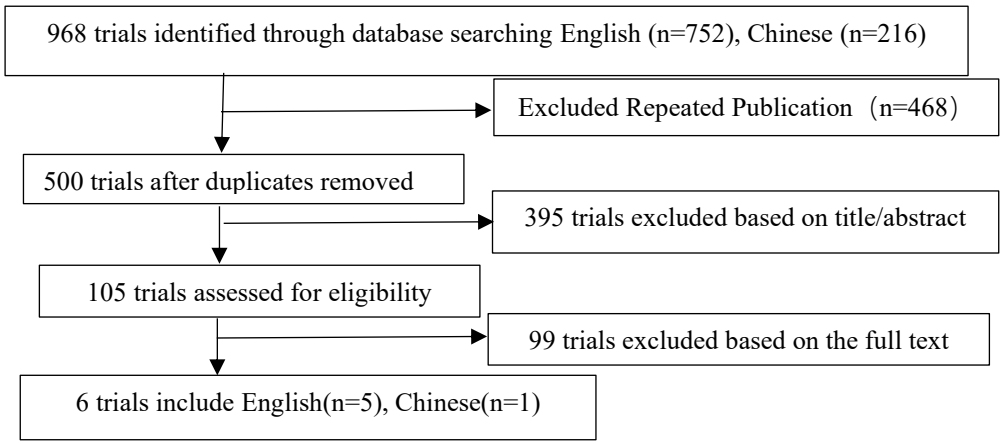

Figure 1. Literature screening flow chart.

Table 1. Characteristics of the included studies.

Included study	Nation	Type	Simple size (Intervention /control)	Intervention group	Control group	Outcome indicator
Liu 2014 (8)	China	RCT	33/35	Wash with 0.12% chlorhexidine solution and brush with negative pressure toothbrush	0.12% chlorhexidine solution rinse, supplemented by cotton ball scrub	①
Chacko 2017 (9)	India	RCT	104/102	Wash with 0.12% chlorhexidine solution and brush with negative pressure toothbrush	0.12% chlorhexidine solution rinse, supplemented by cotton ball scrub	①
Vidal 2017 (10)	Brazil	RCT	105/108	0.12% chlorhexidine solution assisted by toothbrush brushing	Wash with 0.12% chlorhexidine solution	①②③④
Lorente 2012 (11)	Spain	RCT	217/219	Rinse and attract 0.12% chlorhexidine solution, assisted by toothbrush brushing.	Rinse and suction of 0.12% chlorhexidine solution	①③④
Pobo 2009 (12)	Spain	RCT	74/73	0.12% chlorhexidine solution rinse and suction, supplemented by electric toothbrush scrub	Rinse and suction of 0.12% chlorhexidine solution	①②③④
Nicolosi 2014 (13)	Argentina	Experimental study	150/150	Rinse with chlorhexadine gluconate solution and brush with toothbrushing	Rinse with chlorhexadine gluconate solution	①②

Note: ①VAP incidence；②Mechanical ventilation time; ③Length of stay in ICU; ④Mortality

2.2 Methodological Quality Evaluation of the Literature

Therefore 6 trials, including 1370 patients were analyzed, of which 5 trials were in English and 1 in Chinese. The methodological quality of the study was evaluated in **Table 2**. It showed the qualities of the 1study were grade A and 5 studies were grade B.

Table 2. Assessment of risk bias.

Inclusion study	Random grouping	Assignment hiding	Implementation bias	Measurement bias	Report bias	Other bias	Quality grade
Liu 2014 (8)	low	unclear	unclear	unclear	low	low	B
Chacko 2017 (9)	unclear	unclear	unclear	low	low	low	B
Vidal 2017 (10)	low	low	low	low	low	low	A
Lorente 2012 (11)	unclear	unclear	unclear	low	low	low	B
Pobo 2009 (12)	low	low	unclear	low	low	low	B
Nicolosi 2014 (13)	unclear	unclear	unclear	low	low	low	B

2.3 Results of Systematic Reviews

2.3.1 Effects of Chlorhexidine Combined with Toothbrushing on the Incidence of VAP

6 studies reported the effect of chlorhexidine combined with toothbrushing on the incidence of VAP (8,9,10,11,12,13). After analysis, there was no homogeneity among the studies (P=0.37, I^2=8%), so fixed effect model was used for meta-analysis. Meta-analysis showed that the incidence of VAP in the experimental group was lower than that in the control group [RR=0.65, 95% CI(0.49, 0.87), Z=2.87，P<0.01], as shown in **Figure 2**.

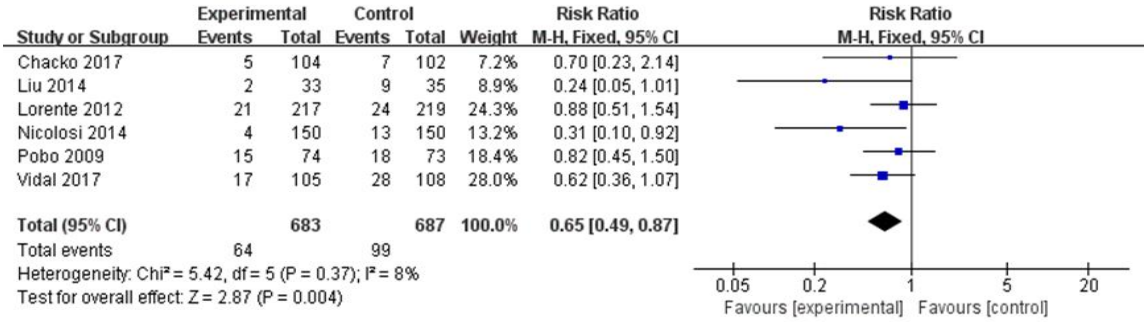

Figure 2. Effect of chlorhexidine combined with toothbrush brushing on the incidence of VAP.

2.3.2 Effects of Chlorhexidine Combined with Toothbrushing on Mechanical Ventilation Time

3 studies reported the effect of chlorhexidine combined with toothbrushing on mechanical ventilation time (10,12,13). There was no heterogeneity among the three studies(P=0.22，I^2=34%), so fixed effect model was adopted for meta-analysis. The results showed that Chlorhexidine combined with toothbrushing can effectively shorten the mechanical ventilation time of ICU patients, and the difference was statistically significant [SMD=-018, 95% CI(-0.33,-0.03), Z=2.29, P＜0.05],as shown in **Figure 3**.

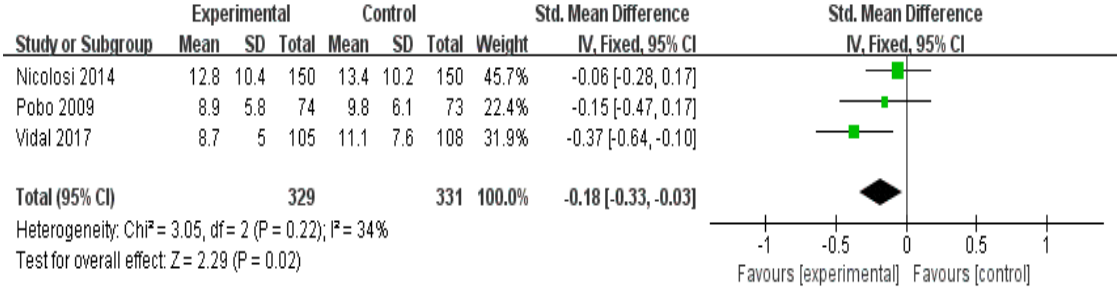

Figure 3. Effect of chlorhexidine combined with toothbrush on duration of mechanical ventilation.

2.3.3 Effects of Chlorhexidine Combined with Toothbrushing on ICU Length of Stay

3 studies reported the effect of chlorhexidine combined with toothbrushing on ICU length of stay (10,11,12). There was no heterogeneity among the three studies (P=0.37，I^2=0%), so fixed effect model was adopted for meta-analysis. The results showed that chlorhexidine combined with toothbrushing can significantly shorten ICU length of stay, and the difference was statistically significant [SMD=-0.15, 95% CI (-0.29,-0.01), Z=2.10, P＜0.05], as shown in **Figure 4**.

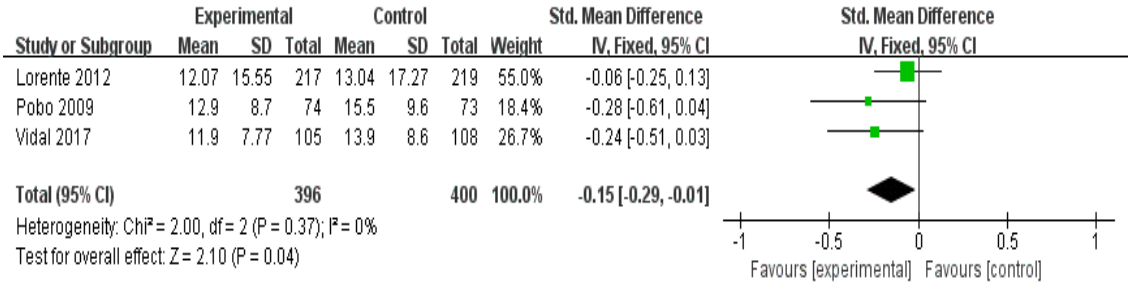

Figure 4. Effect of chlorhexidine combined with toothbrushing on ICU length of stay.

2.3.4 Effects of Chlorhexidine Combined with Toothbrushing on Mortality

4 studies reported the effect of chlorhexidine combined with toothbrushing on mortality (10,11,12,13). There was no heterogeneity among the three studies (P=0.18，I^2=41%), therefore, the fixed effect model was used. The results showed that Chlorhexidine combined with toothbrushing can reduce mortality of ICU patients, and the difference was also statistically significant[RR=0.78, 95%CI(0.63, 0.96), Z=2.33，P<0.05], as shown in **Figure 5**.

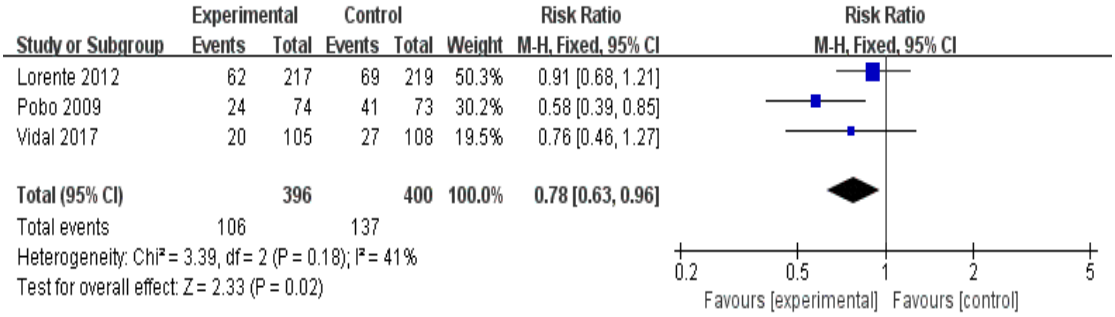

Figure 5. Effect of chlorhexidine combined with toothbrushing on mortality.

3 Discussion

3.1 Methodological Quality of the Included Studies

6 trials were included in this study and only 3 trials (8,10,12) reported specific randomized grouping methods, so there is a possibility of large selection bias. Only 2 trials (10,12). reported the implementation of allocation concealment, and one trial [10] reported the implementation of the blind method, so there is the possibility of larger implementation and measurement bias. one of the included trials quality grade evaluation results is A, and the other 5 studies are all B, 5 are RCT, and one trial is an experimental study.

3.2 Effects of chlorhexidine combined with toothbrushing on the outcome indicators

Most patients with mechanical ventilation are critically ill, cough reflexes and swallowing reflexes are reduced or even disappeared, normal physiological dysfunction, and oral self-cleaning effect is reduced. In addition, endotracheal intubation or regular suction, damage to the oral mucosa, so that the natural barrier of the mouth is weakened. If effective oral care is not performed, the secretions in the mouth will descend with the respiratory airflow along the tracheal intubation leading to VAP. Studies have shown that oral brushing combined with flushing can delay the occurrence of VAP, and effectively reduce the incidence of VAP by 40% to 90% in critically ill patients and reduce the proliferation of oropharyngeal bacteria (17).

This study shows that chlorhexidine gargling combined with toothbrushing can significantly

reduce the incidence of VAP, which is consistent with the results of meta-analysis by Ren et al (18). Study (19) showed that chlorhexidine gargling combined with toothbrushing can shorten the time of mechanical ventilation and the length of ICU stay. Study (20). showed that toothbrushing can significantly reduce the incidence of VAP and improve oral odor and mouth ulcers compared to traditional cotton ball wiping. Oral nursing with toothbrushing combined with chlorhexidine solution shows superiority compared with traditional cotton ball scrubbing method, but this oral care solution has not been widely applied in clinical practice, mainly for the following reasons. Due to the low immune function of critically ill patients, the mechanical force may damage the gums or mucous membranes of the patients during brushing, which may cause bacteremia or shock caused by bacteria in the blood. Especially for patients with coagulopathy, it is recommended that nurses should be adequate before oral care to evaluate the security (21). Chlorhexidine solutions are irritating and expensive and are not easily accepted by patients. Studies have shown that as an inexpensive alternative to existing solutions, brushing twice daily with pure water can reduce VAP and improve oral health and hygiene. Some patients are unable to use a toothbrush for oral nursing due to tooth loss (22-24). In short, whether to apply a toothbrush and which mouthwash to use depends on the individual.

3.3 Research limitations and implications for future research

This meta-analysis was limited to the research level and objective conditions, and only Chinese and English literature published at home and abroad were searched, which may lead to missing references. Although most of the included literatures are RCTs, the random grouping method, allocation concealment and blind method implementation are rarely explicitly reported. Therefore, it is necessary to conduct more extensive retrieval and include higher-level literatures for further analysis. This study did not consider other interventions that might reduce the incidence of VAP, so there are some limitations, suggesting that researchers should include more rigorous design in future studies, so as to improve the stability and reliability of research conclusions.

4 Conclusion

The results of this Meta-analysis showed that chlorhexidine combined with toothbrushing can significantly reduce the incidence of VAP compared with traditional oral regimen. In addition, mechanical ventilation time, length of stay in ICU and mortality rate were reduced. However, considering the limitations of this study, large sample and multi-center randomized controlled trials are still needed to be widely promoted in clinical practice. It is suggested that more rigorous design methods should be adopted in future studies to provide stronger evidence support for the formulation of more effective oral care plans for ICU patients with mechanical ventilation.

Declarations

1) ***Consent to publication***
We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2) ***Ethical approval and consent to participants***
Not applicable.
3) ***Disclosure of conflict of interests***
We declare that no conflict of interest exists.
4) ***Funding***
None
5) ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article.
6) ***Authors' Contributions***
Authors contributed to this paper with the design (Pan-Pan Zheng and Ling Zhang), literature search (Pan-Pan Zheng and Rui Sun), drafting (Pan-Pan Zheng and Rui Sun), revision (Pan-Pan Zheng and Xiao-Yan Peng), editing (Pan-Pan Zheng, Ling Zhang and Rui Sun) and final approval (Ling Zhang).
7) ***Acknowledgement***
None

8) Authors' biography

None

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