Research Article

Meta-Analysis of the Efficacy and Safety of Chlorhexidine for Ventilator-Associated Pneumonia Prevention in Mechanically Ventilated Patients

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Objective. To explore the efficacy and safety of chlorhexidine oral care in the prevention of ventilator-associated pneumonia (VAP) by means of meta-analysis. Methods. Randomized controlled trials on the effect of chlorhexidine oral care on the incidence of VAP in patients on mechanical ventilation were searched in PubMed, Scopus, Cochrane Library, and Embase from May 1, 2022. Two researchers independently screened and included the study, extracted the data, and evaluated the literature quality. RevMan5.3 software was used for meta-analysis. Results. Meta-analysis of 13 included literature studies involving 1533 patients showed that oral care with chlorhexidine solution could reduce the incidence of VAP in patients with mechanical ventilation and the difference was statistically significant (RR = 0.61, 95% CI (0.46, 0.82), \( P = 0.04 \)). However, the results showed that the incidence of VAP of low concentration (0.02%, 0.12%, and 0.2%) and high concentration (2%) of chlorhexidine in the intervention group was lower than that in the control group and the difference was statistically significant (RR = 0.70, 95% CI (0.51, 0.96), \( P = 0.03 \); RR = 0.41, 95% CI (0.27, 0.62)). There was no significant difference in mortality between the two groups (RR = 1.01, 95% CI (0.85, 1.21), \( P = 0.87 \)). There was no statistical significance in days ventilated or days in ICU between the two groups (RR = −0.02, 95% CI (−0.19, 0.16), \( P = 0.84 \); RR = 0.01, 95% CI (−0.11, 0.14), \( P = 0.85 \)). Conclusion. Existing evidence shows that chlorhexidine used for oral care of patients with mechanical ventilation can reduce the incidence of VAP, and high concentration of chlorhexidine (2%) or low concentration of chlorhexidine (0.02%, 0.12%, 0.2%) has a significant effect on the prevention of VAP. Considering the safety of clinical application, it is recommended to use 0.02%, 0.12%, and 0.2% chlorhexidine solution for oral care.

1. Introduction

Mechanical ventilation can provide essential oxygen supply for patients with respiratory failure due to serious cardiovascular infections and brain trauma, maintain smooth airways of patients, relieve respiratory failure, and provide adequate conditions for patients’ treatment [1]. Mechanical ventilation is a treatment technology that improves patient ventilation and oxygenation and prevents hypoxia and carbon dioxide accumulation with the help of mechanical devices [2]. Ventilator-associated pneumonia (VAP) is a nosocomial infection that occurs at least 48 hours after intubation in mechanically ventilated patients, with an incidence of 15%–60%. The common clinical symptoms of VAP are fever and purulent respiratory secretions. This includes refractory pneumonia with a high mortality rate [3]. The occurrence of VAP increases the risk of death of patients on mechanical ventilation by 8 times [4] and is an important cause of death in patients in intensive care. Proper prevention and control can not only effectively reduce the incidence of VAP and reduce the length of hospital stay of patients but also effectively reduce the mortality of patients and ensure the life safety of patients [5–7]. At present, several studies have discussed the effect of changing the application of oral care solutions to prevent VAP in patients with mechanical ventilation. Patients with mechanical
2.1.1. Inclusion Criteria. Study type: RCT was done with unlimited sample size and limited English literature. Intervention: oral care was performed with chlorhexidine solution in the intervention group, and oral care was performed with normal saline or placebo in the control group. Outcome indicators: the main outcome indicators were mortality, bacterial colonization (oral, oropharyngeal, tracheal), pulmonary infection score, mechanical ventilation time, length of hospital stay, oral ulcer, patient satisfaction, etc.

2.1.2. Exclusion Criteria. The exclusion criteria were as follows: (1) unable to obtain the full text; (2) data cannot be obtained or converted; (3) reviews, single-arm studies, and other non-RCTs; (4) repeated publications; (5) the intervention measures were chlorhexidine combined with other interventions or not used in the oral care literature; (6) infants- and children-based studies.

2.2. Search Strategy. The literature published in PubMed, the Cochrane Library, Scopus, and Embase was systematically searched from the establishment of the database to May 1st, 2022. Meanwhile, literature including conference papers and the references included in the studies was manually searched. The search terms were determined by the combination of mesh terms and entry terms. Terms include endotracheal intubation, dichlorobenzene biguanide hexane, chlorhexidine, VAP, and ventilator-associated pneumonia.

2.3. Literature Screening and Data Extraction. Literature screening was completed by 2 researchers independently. First, the literature data were imported into the database using Endnote software to remove duplicate literature. Then, the title and abstract were preliminarily screened by reading. Finally, the full text was read to determine whether the bibliography was included or not. Subsequently, data were extracted by two researchers alone, and the extracted information included the following: (1) the basic information of the literature, such as author, publication year, and country; (2) intervention frequency and intervention measures of the two groups; (3) outcome indicators.

2.4. Methodological Quality Evaluation of Included Studies. The authenticity of RCTs was evaluated by 2 researchers according to the Cochrane Collaboration System Evaluation Manual (version 5.1.0), including selection bias, implementation bias, measurement bias, loss of follow-up bias, reporting bias, and other biases. If there is any dispute between two researchers, the dispute should be settled through negotiation.

2.5. Statistical Methods. RevMan 5.3 software was used for statistical analysis. Hazard ratio (RR) and 95% confidence interval (CI) were used as statistics for categorical variables, and standard mean difference and 95% confidence interval (CI) were used as statistics for continuous variables. The heterogeneity was evaluated. When the heterogeneity test is $P < 0.1$ and $I^2 > 50\%$, the reasons for heterogeneity should be analyzed first, such as whether the design scheme and measurement method are the same. If there is still heterogeneity in the results, the random effect model can be used to calculate the pooled results.

3. Results

3.1. Literature Search Results. 485 related literature studies were obtained through preliminary retrieval. After the screening, 13 literature studies were finally included [19–31]. Figure 1 shows the literature screening process and results.

3.2. Basic Information of Included Studies. The 13 included literature studies [19–31] were published in 2005 and 2019, all of which were RCT studies involving 1533 patients with 786 in the intervention group and 747 in the control group (Table 1). The risk of bias for included studies is presented in Figure 2.
3.3. Meta-Analysis

3.3.1. The Incidence of VAP. Thirteen pieces of literature reported the incidence of VAP, involving 1533 patients with mechanical ventilation, with 786 in the intervention group and 747 in the control group. Heterogeneity test results showed that there was heterogeneity between studies ($F = 0.03, I^2 = 45\%$), so a fixed-effect model was adopted for analysis. The results showed that oral care with chlorhexidine can reduce the incidence of VAP in patients with mechanical ventilation, with a statistically significant difference (RR $= 0.61, 95\%$ CI $(0.46,0.82), P = 0.04$).

Further subgroup analysis found no source of heterogeneity, but the results showed that the incidence of low-concentration (0.02%, 0.12%, and 0.2%) and high-concentration (2%) chlorhexidine VAP in the intervention group was lower than that in the control group. Difference was statistically significant (RR $= 0.70, 95\%$ CI $(0.51, 0.96), P = 0.03$; RR $= 0.41, 95\%$ CI $(0.27, 0.62), F < 0.001$) (Figure 3).

Sensitivity analysis showed that Meinberg et al.’s [26] study was the main source of heterogeneity, heterogeneity among studies decreased after excluding this study ($P = 0.24, I^2 = 21\%$), and the results were still statistically significant (RR $= 0.55, 95\%$ CI $(0.45,0.68), F < 0.001$) (Figure 4).

3.3.2. Mortality Rate. Five studies [21,23,28,29,31] reported mortality, involving a total of 771 patients with mechanical ventilation, with 407 in the intervention group and 364 in the control group. Heterogeneity test results showed that there was no heterogeneity among studies ($P = 0.52, I^2 = 0\%$). There was no significant difference in mortality between the two groups (RR $= 1.06, 95\%$ CI $(0.87, 1.30), P = 0.54$) (Figure 5).

3.3.3. Days Ventilated. Eight studies [21–23, 25, 26, 28, 29, 31] reported the days ventilated, involving a total of 1205 patients with mechanical ventilation, including 625 in the intervention group and 580 in the control group. Heterogeneity test results showed that heterogeneity existed among studies ($P = 0.004, I^2 = 53\%$), so the random effect model was used for analysis, and the results showed that there was no significant difference in mortality between the two groups (RR $= −0.02, 95\%$ CI $(-0.19, 0.16), P = 0.84$) (Figure 6).

3.3.4. Hospitalization in ICU. Six studies [14–16, 18, 19, 21] reported the days in ICU, involving a total of 999 patients with mechanical ventilation, including 498 in the intervention group and 501 in the control group. Heterogeneity test results showed that heterogeneity existed among studies
Table 1: Basic information of the included study.

| Study            | Country   | Departments       | Frequency | Sample size, T/C | Intervention (solution and usage)                  | Outcomes |
|------------------|-----------|-------------------|-----------|-----------------|----------------------------------------------------|----------|
| Xia Shen, 2018   | China     | Respiratory medicine | Bid       | 37/37           | 0.12% chlorhexidine solution swab Normal saline swab scrub | 1        |
| Bellissimo-      | Brazil    | ICU                | —         | 64/69           | Rinse with 0.12% chlorhexidine solution 0.2% chlorhexidine gel scrub Rinse with placebo flushing | 1, 2, 3, 4 |
| Rodrigues, 2009  |           |                    |           |                 |                                                    |          |
| Cabov, 2010      | Croatia   | ICU                | Tid       | 17/23           | 0.2% gel wipe Placebo gel scrub | 1, 4 |
| Fourrie, 2005    | France    | ICU                | Tid       | 114/114         | 0.2% chlorhexidine solution rinse + scrub Comfort gel scrub | 1, 2 |
| Huanhuan Wang,   | China     | ICU                | Tid       | 30/30           | 0.2% chlorhexidine solution swab Normal saline rinse + scrub Normal saline swab scrub | 1        |
| 2013             |           |                    |           |                 |                                                    |          |
| Jie Gao, 2019    | China     | ICU                | Qid       | 45/45           | 0.12% chlorhexidine solution swab Normal saline swab scrub |          |
| Koeman 2006      | Netherlands | ICU              | Qid       | 127/13          | 2% chlorhexidine gel scrub Saline scrub | 1        |
| Meinberg, 2012   | Brazil    | CSICU              | —         | 28/24           | Brush with 0.2% chlorhexidine solution Brush with placebo | 1, 3, 4 |
| Ming Liu, 2008   | China     | ICU                | —         | 32/32           | Rinse with 0.12% chlorhexidine solution Normal saline rinse + scrub | 1        |
| Scannapieco, 2009| USA       | ICU                | Bid       | 97/49           | Brush with 0.2% chlorhexidine solution Brush with placebo Brush with placebo | 1, 2, 3, 4 |
| Tantipong, 2008  | Thailand  | ICU                | Qid       | 58/52           | Brush with 0.2% chlorhexidine solution Brush with placebo Normal saline rinse + scrub | 1        |
| Zoning Wei, 2014 | China     | ICU                | Tid       | 108/110         | Brush with 0.2% chlorhexidine solution Brush with placebo Normal saline rinse + scrub | 1        |
| Özçaka, 2012     | Turkey    | Respiratory ICU    | Qid       | 29/32           | 0.12% chlorhexidine solution swab Normal saline swab scrub | 1, 2, 3, 4 |
| Scannapieco, 2009| USA       | ICU                | —         | 32/32           | Brush with 0.12% chlorhexidine solution Normal saline rinse + scrub | 1        |

T: chlorhexidine group; C: control group; ICU: intensive care unit; Bid: 2 times per day; Tid: 3 times a day; Qid: 4 times a day; Qd: once a day. 1: the incidence of VAP; 2: mortality; 3: days ventilated; 4: days in ICU.

Figure 2: Risk of bias for included studies.
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### Figure 3: Meta-analysis of the incidence of ventilator-associated pneumonia between two groups (subgroup analysis).

| Study or Subgroup               | chlorhexidine Events | Control Events | Weight (%) | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|--------------------------------|----------------------|----------------|------------|--------------------------------|--------------------------------|
| Bellissimo-Rodrigues 2009      | 16 64 17 69         | 108 110 11 36 | 9.1        | 0.53 [0.28, 1.03]              |                                |
| Cabov 2010                     | 1 17 6 23           | 10 36 12 52  | 2.7        | 0.23 [0.03, 1.70]              |                                |
| Fourrier 2005                  | 13 114 12 114       | 32 45 12 49  | 6.4        | 1.08 [0.52, 2.27]              |                                |
| Huanhuan Wang 2013             | 5 30 12 30          | 97 108 12 49 | 6.4        | 0.42 [0.17, 1.04]              |                                |
| Jie Gao 2018                   | 2 45 9 45           | 10 36 12 52  | 4.8        | 0.22 [0.05, 0.97]              |                                |
| Koeman 2006                    | 12 127 23 130       | 114 127 12 114 | 9.1 | 0.59 [0.30, 1.18]              |                                |
| Ming Liu 2008                  | 11 32 17 32         | 110 127 12 114 | 2.7 | 0.65 [0.36, 1.15]              |                                |
| Scannapieco 2009               | 14 97 12 49         | 108 110 12 49 | 6.4        | 0.59 [0.30, 1.18]              |                                |
| Tantipong 2008                 | 11 108 36 110       | 32 45 12 49  | 6.4        | 0.45 [0.16, 1.23]              |                                |
| Xia Shen 2018                  | 4 37 9 37           | 108 110 12 49 | 4.8        | 0.44 [0.15, 1.32]              |                                |
| Ozcak 2012                     | 12 29 22 32         | 114 127 12 114 | 9.1 | 0.31 [0.17, 0.58]              |                                |
| Subtotal (95% CI)              | 786 747 100.0       | 124 196        | 0.61 [0.46, 0.82] |                                |                                |

(P = 0.82, I² = 0%), so a fixed-effect model was adopted for analysis. There was no significant difference in the length of ICU stay between the two groups (RR = 0.01, 95% CI (−0.11, 0.14), P = 0.85). (Figure 7).

### Figure 4: Meta-analysis of the incidence of ventilator-associated pneumonia between two groups (sensitivity analysis).

| Study or Subgroup               | chlorhexidine Events | Control Events | Weight (%) | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|--------------------------------|----------------------|----------------|------------|--------------------------------|--------------------------------|
| Bellissimo-Rodrigues 2009      | 16 64 17 69         | 108 110 11 36 | 9.1        | 0.53 [0.28, 1.03]              |                                |
| Cabov 2010                     | 1 17 6 23           | 10 36 12 52  | 2.7        | 0.23 [0.03, 1.70]              |                                |
| Fourrier 2005                  | 13 114 12 114       | 32 45 12 49  | 6.4        | 1.08 [0.52, 2.27]              |                                |
| Huanhuan Wang 2013             | 5 30 12 30          | 97 108 12 49 | 6.4        | 0.42 [0.17, 1.04]              |                                |
| Jie Gao 2018                   | 2 45 9 45           | 10 36 12 52  | 4.8        | 0.22 [0.05, 0.97]              |                                |
| Koeman 2006                    | 12 127 23 130       | 114 127 12 114 | 9.1 | 0.59 [0.30, 1.18]              |                                |
| Ming Liu 2008                  | 11 32 17 32         | 110 127 12 114 | 2.7 | 0.65 [0.36, 1.15]              |                                |
| Scannapieco 2009               | 14 97 12 49         | 108 110 12 49 | 6.4        | 0.59 [0.30, 1.18]              |                                |
| Tantipong 2008                 | 5 58 10 52          | 32 45 12 49  | 5.7        | 0.45 [0.16, 1.23]              |                                |
| Xia Shen 2018                  | 4 37 9 37           | 108 110 12 49 | 4.8        | 0.44 [0.15, 1.32]              |                                |
| Zongting Wei 2014              | 11 108 36 110       | 32 45 12 49  | 5.7        | 0.45 [0.16, 1.23]              |                                |
| Ozcak 2012                     | 12 29 22 32         | 114 127 12 114 | 9.1 | 0.31 [0.17, 0.58]              |                                |
| Subtotal (95% CI)              | 758 723 100.0       | 106 185        | 0.55 [0.45, 0.68] |                                |                                |

(P = 0.82, I² = 0%), so a fixed-effect model was adopted for analysis. There was no significant difference in the length of ICU stay between the two groups (RR = 0.01, 95% CI (−0.11, 0.14), P = 0.85). (Figure 7).

#### 3.4. Publication Bias and Sensitivity Analyses.

The funnel plot was drawn using VAP incidence as an outcome indicator, and the results showed asymmetry of the funnel plot, suggesting possible publication bias. Then, we performed the sensitivity analysis, Figure 8 shows the elimination of all studies included in the meta-analysis one by one. The results did not change, suggesting good stability of the results.

### 4. Discussion

As an important means of life support, mechanical ventilation is widely used in the treatment of respiratory diseases, which can relieve hypoxia and carbon dioxide retention. However, mechanical ventilation can lead to a variety of
complications such as VAP sepsis, bleeding, and digestive dysfunction, among which VAP is the most common [32, 33]. The causes of VAP are mainly due to the following two aspects: On the one hand, patients on mechanical ventilation are in critical condition and lie in bed for a long time, their body immunity is weak, and they are vulnerable to bacterial invasion and inflammation. On the other hand, long-term intubation and placement of a gastric tube in mechanically ventilated patients may easily lead to oral colonization bacteria flowing into the lung tissue with airway secretions or reflux of gastric contents, increasing the chance of lung infection [34]. Therefore, strengthening oral care to reduce oral colonization is one of the important nursing measures to prevent the occurrence of VAP. As an antibacterial agent commonly used in clinical practice, chloramidine has a broad antibacterial spectrum and a long residual effect [35], which can be used to kill most oral colonization bacteria to prevent the occurrence of VAP in patients with mechanical ventilation. There have been a large number of studies on chlorhexidine as oral care solution to prevent the occurrence of VAP in patients with mechanical ventilation. This study systematically evaluated relevant studies and provided reliable evidence-based medical evidence for clinical nursing.

The results of this study show that the oral care of mechanical ventilation patients with chlorhexidine can significantly reduce the incidence of VAP, and a high concentration of chlorhexidine (2%) or low concentration of chlorhexidine (0.02%, 0.12%, 0.2%) has a significant effect on the prevention of VAP and there is no significant difference in mortality between the two groups, ventilation time, and ICU stay time. However, studies have shown that long-term use of high concentrations of chlorhexidine may cause some adverse reactions, such as oral mucosa exfoliation, taste change, and tongue coloring [36]. Therefore, doses of 0.02%, 0.12%, and 0.2% are recommended under the premise of the

| Study or Subgroup | chlorhrxidine | Control | Weight (%) | Risk Ratio | Risk Ratio |
|-------------------|---------------|---------|------------|------------|------------|
|                   | Events Total  | Events Total |            | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Bellissimo-Rodrigues 2009 | 34 64 | 32 69 | 29.5 | 1.15 [0.81, 1.61] | |
| Fourrier 2005 | 31 114 | 24 114 | 23.0 | 1.29 [0.81, 2.06] | |
| Scannapieco 2009 | 16 97 | 8 49 | 10.2 | 1.01 [0.46, 2.20] | |
| Tantipong 2008 | 36 58 | 37 52 | 37.4 | 0.87 [0.67, 1.14] | |
| Ozczak 2012 | 1 29 | 9 0 | Not estimable | | |

Total (95% CI) 362 284 100.0 1.06 [0.87, 1.30]

Test for overall effect: Z = 0.61 (P = 0.19)

Figure 5: Meta-analysis of mortality rate between two groups.

| Study or Subgroup | chlorhrxidine | Control | Weight (%) | Std. Mean Difference |
|-------------------|---------------|---------|------------|---------------------|
|                   | Mean SD Total  | Mean SD Total |            | IV, Random, 95% CI |
| Bellissimo-Rodrigues 2009 | 11.1 4.7 98 | 11 4.8 96 | 15.3 | 0.02 [-0.26, 0.30] |
| Cabov 2010 | 17 11.9 30 | 23 12.1 30 | 7.9 | -0.49 [-1.01, 0.02] |
| Fourrier 2005 | 11.7 8.7 114 | 10.6 8.7 114 | 16.2 | 0.13 [-0.13, 0.39] |
| Koeman 2006 | 9.16 12 127 | 6.95 8.1 130 | 16.9 | 0.22 [-0.03, 0.46] |
| Meineberg 2012 | 8.5 5 28 | 6 4.8 24 | 7.1 | 0.50 [-0.05, 1.06] |
| Scannapieco 2009 | 8.9 5.1 97 | 9.7 6.3 49 | 12.8 | -0.14 [-0.49, 0.20] |
| Tantipong 2008 | 4.5 3.4 102 | 5.2 3.6 105 | 15.6 | -0.20 [-0.47, 0.07] |
| Ozczak 2012 | 9 8.3 29 | 12.28 11.9 32 | 8.1 | -0.31 [-0.82, 0.19] |

Total (95% CI) 625 580 100.0 -0.02 [-0.19, 0.16]

Heterogeneity: $I^2 = 14.76$, $d = 7$ ($P = 0.04$); $I^2 = 53$

Test for overall effect: Z = 0.20 ($P = 0.84$)

Figure 6: Meta-analysis of days ventilated between two groups.

| Study or Subgroup | chlorhrxidine | Control | Weight (%) | Std. Mean Difference |
|-------------------|---------------|---------|------------|---------------------|
|                   | Mean SD Total  | Mean SD Total |            | IV, Fixed, 95% CI |
| Bellissimo-Rodrigues 2009 | 9.7 8.2 98 | 10.4 8 96 | 19.4 | -0.09 [-0.37, 0.20] |
| Fourrier 2005 | 14 8.5 114 | 13.3 8.8 114 | 22.8 | 0.08 [-0.18, 0.34] |
| Koeman 2006 | 13.71 17.4 127 | 12.48 12.9 130 | 25.7 | 0.08 [-0.16, 0.32] |
| Meineberg 2012 | 12 10.8 28 | 11 8.9 24 | 5.2 | 0.10 [-0.45, 0.64] |
| Tantipong 2008 | 12 11.8 102 | 12 11.4 105 | 20.8 | 0.00 [-0.27, 0.27] |
| Ozczak 2012 | 12.17 11.3 29 | 15.44 13.5 32 | 6.0 | -0.26 [-0.76, 0.25] |

Total (95% CI) 498 501 100.0 0.01 [-0.11, 0.14]

Heterogeneity: $I^2 = 2.24$, $d = 5$ ($P = 0.82$); $I^2 = 0$

Test for overall effect: Z = 0.19 ($P = 0.85$)

Figure 7: Meta-analysis of days in ICU between two groups.
same preventive effect and considering the safety of the clinical application.

Limitations of this study: the languages included in the study were limited, only English, and there may be some included parts of publication bias. The literature quality is not high. Among the 13 included studies, only 7 reported allocation hiding, 8 introduced the random grouping method in detail, 7 mentioned the implementation of interventional blindness, and the other studies did not mention or implement interventional blindness, which may be interfered with by interventional subjective factors. The homogeneity of the included studies was not high. Factors such as frequency and method of oral care (such as washing, scrubbing, and brushing), the concentration of chlorhexidine in the intervention measures, and physical fitness and cultural environment caused by different countries and regions of subjects may affect the results.

5. Conclusion

Existing evidence shows that chlorhexidine used for oral care of patients with mechanical ventilation can reduce the incidence of VAP, and high concentration of chlorhexidine (2%) or low concentration of chlorhexidine (0.02%, 0.12%, 0.2%) has a significant effect on the prevention of VAP. Considering the safety of clinical application, it is recommended to use 0.02%, 0.12%, and 0.2% chlorhexidine solution for oral care.

Data Availability

Data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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