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Research paper

Effect of different mouthwashes on ventilator-related outcomes and mortality in intensive care unit patients: A network meta-analysis

Qianqian He, BSc(Nurs) [a, d], Zengjin Peng, MSc(Nurs) [a, b, d], Caiyun He, RN [a, *], Chao Zhang, BSc(Nurs) [c], Rong Hu, BSc(Nurs) [a]

[a] Medical College, Hunan Normal University, No. 371 Tongzipo Road, Yuelu District, Changsha, Hunan, China; [b] Department of Internal Cardiovascular Medicine, The Second Xiangya Hospital of Central South University, No. 139 Middle Renmin Road, Furong District, Changsha, Hunan, China; [c] Nursing Department, School of Nursing, Shandong University of Traditional Chinese Medicine, 16369 Jingshi Road, Lixia District, Jinan, Shandong 250014, China

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ABSTRACT

Background: Ventilator-associated pneumonia is a common and life-threatening complication in intensive care unit (ICU) patients. Maintaining oral hygiene is crucial for reducing ventilator-associated pneumonia incidence. Various mouthwash solutions are used for oral care in ICU settings, but their comparative effectiveness remains unclear. This study aims to systematically evaluate and compare the efficacy and safety of commonly used mouthwashes for oral care in mechanically ventilated ICU patients.
Methods: We searched PubMed, Web of Science, Embase, and Cochrane Library for randomised controlled trials (RCTs) comparing saline, chlorhexidine, sodium bicarbonate, oxidising agents, herbal extracts, and povidone-iodine for oral care in ventilated ICU patients. Outcomes included ventilator-associated pneumonia incidence, ICU mortality, duration of ventilation, and *Escherichia coli* fixed value. A network meta-analysis (NMA) was conducted to synthesise direct and indirect evidence. This study is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols, 2023120028.
Results: FourteenRCTs with 1644 participants were included. Oxidising agents showed a trend towards reducing the incidence of VAP compared to the control group (risk ratio: 0.24, 95% confidence interval: 0.05−1.10). Administration of saline was associated with a notable reduction in ICU mortality (risk ratio: 0.18, 95% confidence interval: 0.04−0.88) versus no mouthwash. No significant differences were observed in the duration of mechanical ventilation between chlorhexidine, povidone-iodine, and the control group.
Conclusions: Antimicrobial mouthwashes, especially chlorhexidine, pose potential risks in ICU patients; oxidising solutions demonstrate relative safety. Saline solution emerges as a promising alternative, associated with a significant reduction in mortality rates. However, the need for large, high-quality RCTs remains paramount to substantiate these findings and establish evidence-based oral-care protocols in ICU settings.
Registration: This study is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols, 2023120028.

1. Introduction

Critically ill patients in intensive care units (ICUs) are susceptible to various complications, among which ventilator-associated pneumonia (VAP) is one of the most common and fatal nosocomial infections.[1–3] The inability to maintain oral hygiene due to endotracheal intubation and mechanical ventilation is a major risk factor for VAP, which occurs in 9−28% of ventilated patients and leads to mortality in 24−50% of cases.[1,4]

Interventions to prevent VAP aim either to prevent repeated microaspiration, colonisation of the upper airway and gastrointenstinal tract with potentially pathogenic organisms, or contamination of ventilator/respiratory equipment.[5,6] Aspiration of contaminated oropharyngeal secretions or stomach contents

* Corresponding author.
E-mail addresses: heqian1023@163.com (Q. He), pengzengjin@163.com (Z. Peng), hecaiyunhnu@126.com (C. He), zhchao97@163.com (C. Zhang), 1135898838@qq.com (R. Hu).
[d] Qianqian He, Zengjin Peng made equal contributions to this manuscript.

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refluxing into the oropharynx and then into the airways plays a paramount role in VAP pathogenesis and likely represents one of the most preventable factors that should be factored into the design of VAP prevention strategies.[7] Since aspiration of oropharyngeal secretions appears to be the primary mechanism for the development of VAP, a number of approaches attempting to inhibit pathogenic colonisation of the oropharynx have been tested. These include everything from brushing your teeth to using a variety of topical/oral antibacterial mouthwashes such as sodium bicarbonate, chlorhexidine (CHX) and povidone-iodine (PI), and non-antibacterial mouthwashes.

Various mouthwash solutions have been used for oral hygiene care in ICU settings, including saline, CHX, PI, sodium bicarbonate, oxidising agents (ozone water, hydrogen peroxide), and herbal extracts.[8–13] As the gold standard, CHX exhibits broad antimicrobial activities against pathogens causing oral diseases and has low risks of inducing resistance.[13,14] However, CHX is also associated with side-effects such as tooth discolouration and taste disturbance.[15,16] PI has been suggested as one of the best antimicrobial agents in reducing the incidence ofrespiratory infections such as VAP. Nevertheless, the available evidence regarding the efficacy of PI oral care in VAP prevention is notably scant and occasionally discordant.[17] Saline often serves as placebo or control. Sodium bicarbonate softens oral mucosa but increases dental plaque.[18] Oxidising agents have antibacterial and antiviral properties but certain adverse reactions.[10,19] Herbal extracts are increasingly used for their antimicrobial, antiviral, and antifungal effects, with fewer side-effects.[20,21]

Previous meta-analyses have evaluated the anti-inflammatory and antimicrobial effects of various mouthwashes or the efficacy of CHX in preventing VAP.[22–24] However, there is no consensus on the optimal oral-care regimen tailored for individual ICU patients based on evidence.[23–25] Therefore, this study aims to systematically compare the efficacy and safety of the six commonly used mouthwash solutions for oral care in ventilated ICU patients using a network meta-analysis, in order to guide evidence-based standardised oral assessment and nursing practices.

2. Methods

The NMA protocol used in this study was registered in International Platform of Registered Systematic Review and Meta-analysis Protocols (2023120028.). This network meta-analysis was conducted following the guidelines in the preferred reporting items for systematic reviews and meta-analyses report, with modifications for network meta-analyses.[26]

2.1. Literature search strategy

We systematically searched PubMed, Web of Science, Embase, and Cochrane Library for relevant randomised controlled trials (RCTs) from database inception to July 2023. The following keywords and their synonyms were used: “oral care”, “intensive care”, and “ventilator-associated pneumonia”. Reference lists of relevant studies were hand-searched for additional eligible trials.

2.2. Selection criteria

RCTs pertinent to our research question were included. The inclusion criteria were as follows: (i) conducted in endotracheal tubes or mechanically ventilated ICU patients; (ii) the intervention group(s) should use mouthwashes by liquids, sprays, or with a swab. Application of different mouthwash solutions, including saline, CHX, sodium bicarbonate, oxidising agents, herbal extracts, and PI; (iii) reporting at least one outcome of our interest, including VAP incidence, ICU mortality, duration of ventilation, *Escherichia coli* colonisation of bacteria; (iv) studies written in English. Non-randomised studies and those with incomplete data were excluded.

2.3. Data extraction and risk-of-bias assessment

Two reviewers independently extracted the following information: first author, publication year, study design, participant characteristics, interventions in each group, and main outcome measures. The Cochrane risk-of-bias tool was used by two reviewers to assess the risk of bias in terms of random sequence generation, allocation concealment, blinding, incomplete data, and selective reporting. Disagreements were resolved by discussion or consulting a third reviewer.

2.4. Statistical analysis

A network meta-analysis was performed using the R software. Conventional pairwise meta-analysis was first conducted. The I^2 test was used to assess heterogeneity across studies, with $I^2 > 50\%$ indicating significant heterogeneity. The network meta-analysis was then performed to synthesise direct and indirect evidence. The model fit was evaluated by comparing coefficient function values. The probability of superiority for each intervention was estimated based on surface under the cumulative ranking curves (SUCRA). Inconsistency between direct and indirect sources of evidence was assessed by node-splitting analysis.

3. Results

3.1. Literature search and selection

The initial search yielded 1053 records. After removing duplicates and obviously irrelevant studies, 14 RCTs[9–13,27–35] were finally included through title/abstract and full-text screening. All were two-arm trials comparing different mouthwash solutions including saline, CHX, PI, sodium bicarbonate, hydrogen peroxide, and herbal extracts for oral care in ICU patients. The screening process is outlined in Fig. 1.

3.2. Baseline characteristics

The 14 RCTs enrolled 1644 ventilated ICU patients, with a mean age of 57.86 years, and 58.73% were male. The interventions and control arms varied across studies. Table 1 summarises the basic characteristics of the included trials.

3.3. Ventilator-associated pneumonia incidence

Network meta-analysis (Fig. 3) showed the use of oxidising agents demonstrated a trend towards reducing the incidence of VAP compared to the control group (risk ratio [RR]: 0.24, 95% confidence interval [CI]: 0.05–1.10). Conversely, sodium bicarbonate (RR: 0.96, 95% CI: 0.23–4.40), CHX (RR: 0.57, 95% CI: 0.25–1.38), PI (RR: 0.54, 95% CI: 0.15–1.63), herbal extracts (RR: 0.46, 95% CI: 0.13–1.87), and the control group did not exhibit statistically significant differences in VAP incidence. There was no evidence of heterogeneity ($P = 0.0150$, $I^2 = 54.6\%$).

3.4. ICU mortality

According to the data presented in Fig. 4, no significant differences were observed in ICU mortality between sodium bicarbonate (RR: 5.51, 95% CI: 1.14–28.39), CHX (RR: 1.15, 95% CI: 0.43–3.33), PI (RR: 1.01, 95% CI: 0.37–2.49), and the control group. However, the

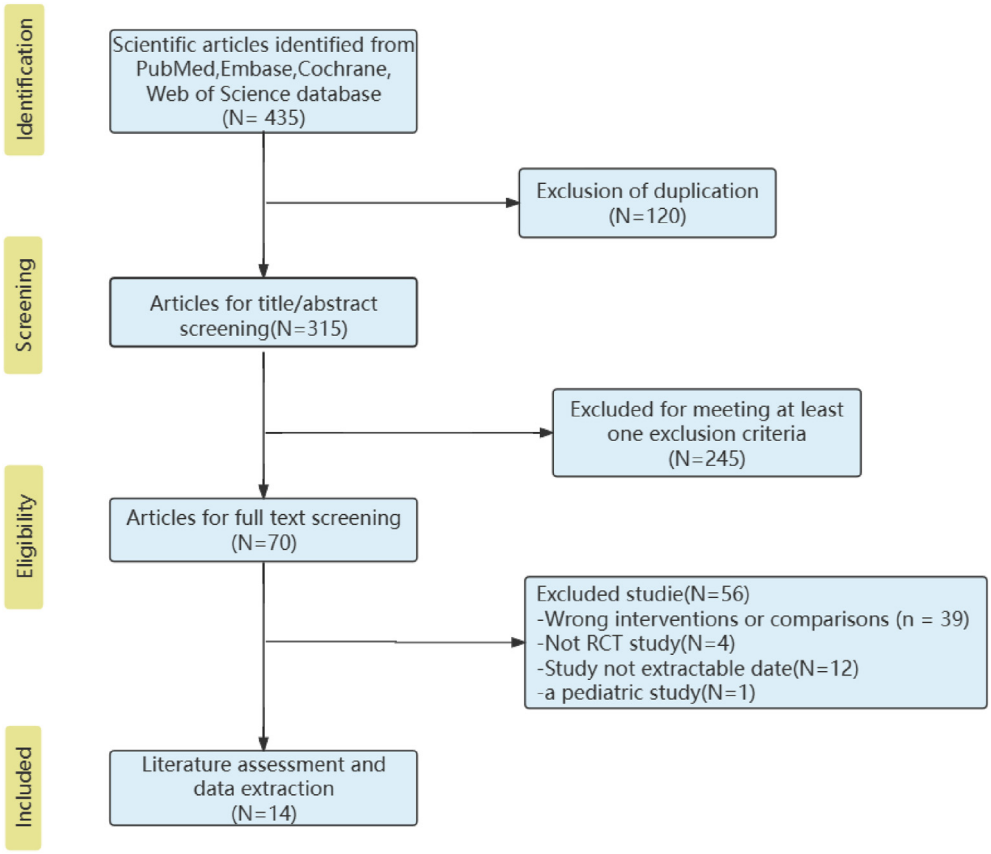

Fig. 1. Flow diagram of study selection.

administration of saline (RR: 0.18, 95% CI: 0.04–0.88) was associated with a notable reduction in ICU mortality, as shown in Fig. 4. There was no evidence of heterogeneity ($P = 0.4398$, $I^2 = 0\%$).

3.5. Duration of mechanical ventilation

No significant differences were observed in the duration of mechanical ventilation between CHX (RR: −1.49, 95% CI: −8.52 to −4.86), PI (RR: −0.70, 95% CI: −9.52 to −8.50) and control. Fig. 5. There was no evidence of heterogeneity ($P = 0.7250$, $I^2 = 0\ \%$).

3.6. Escherichia coli fixed value

In our network meta-analysis, as depicted in Fig. 6, we investigated the efficacy of various interventions in addressing *Escherichia coli* infections, aiming to elucidate their comparative effectiveness. The results revealed no statistically significant differences in the efficacy of sodium bicarbonate (RR: 1.12, 95% CI: 0.35–3.47), CHX (RR: 0.96, 95% CI: 0.25–3.42), PI (RR: 0.29, 95% CI: 0.03–1.79), herbal extracts (RR: 2.23, 95% CI: 0.19–32.38), and the control group. There was no evidence of heterogeneity ($P = 0.9908$, $I^2 = 0\ \%$).

3.7. Quality assessment

Fig. 2 summarises the risk of bias assessed for RCTs. Although all studies involved randomisation, nine trials used appropriate randomisation techniques. Ten articles reported information on hidden allocation. Regarding contamination between treatment groups, nine trials had a low risk of bias, and five trials had a low risk of bias due to selective reporting of results. Fig. 2 shows the Cochrane risk-of-bias assessment of the included studies.

4. Discussion

Through undertaking a meta-analysis, we systematically compared saline, CHX, sodium bicarbonate, oxidising agents, and herbal extracts for oral care in ventilated ICU patients regarding effects on VAP incidence, ICU mortality, duration of ventilation, and *Escherichia coli* fixed value. The results demonstrated that mouthwash may have no effect on the incidence of VAP, duration of mechanical ventilation, or colonisation with pathogenic bacteria in critically ill patients, but saline may significantly reduce mortality.

Research findings suggest that compared to the control group and CHX mouthwash, the use of oxidants has shown a positive effect on reducing the incidence of VAP in critically ill patients. Currently, the use of CHX mouthwash in ICUs to regulate oral colonisation of respiratory pathogens and microaspiration, thereby preventing VAP, seems to have become a widely accepted practice. However, in the current meta-analysis, CHX mouthwash did not significantly affect the incidence of VAP, which may be attributed to the fact that the positive effects of CHX are only effective for post–cardiac surgery patients and only with high doses of noncommercial 2% CHX gel.[36] The benefit of CHX in reducing VAP by approximately 27% mainly comes from studies involving cardiac surgery patients, For noncardiac patients, the use of CHX may increase the risk of death for these patients.[7]

Some studies[38,39] suggest a correlation between the use of antimicrobial mouthwash and increased risk of mortality. Addressing this issue, Blot et al.[36,37] proposed a hypothesis suggesting that a disturbance in nitric oxide homoeostasis by antiseptic mouthwashes may be responsible for the observed increase in mortality risk; this increased mortality risk might be linked to the eradication of oral bacterial communities by antimicrobial mouthwash, resulting in reduced nitric oxide (NO) bioavailability and potential life-

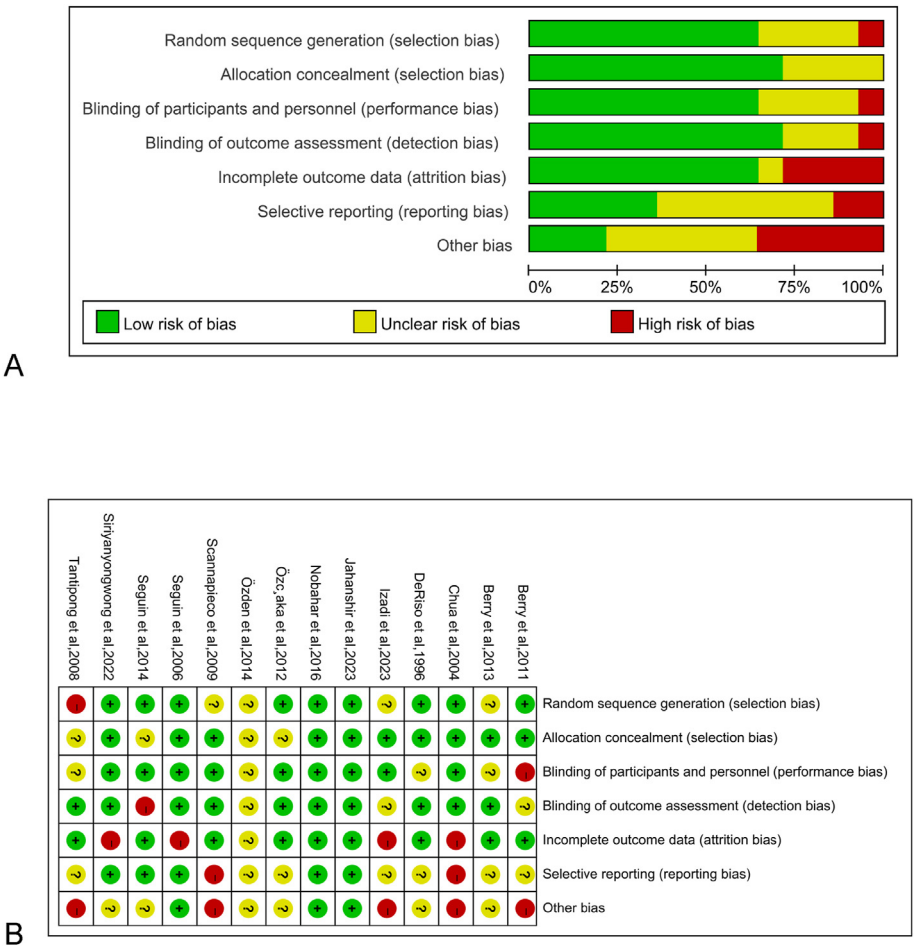

Fig. 2. Risk-of-bias analysis. (A) Review authors' judgements on each risk-of-bias items presented as percentages across all included studies. (B) Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study.

Table 1
Baseline characteristics of the included trials in 14 RCTs.

Study	Country	Design	meal	Age,y		Sample		Mouthwash		Follow-up assessments
				Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	
Jahanshir et al., 2023	Iran	RCT	109 (64.9%)	55.21 (9.7)	59.7 (21.4)	84	84	Herbal ingredients	CHX	5 days
Izadi et al., 2023	Iran	RCT	37 (50.8%)	60.3 (16.7)	63.7 (15.8)	36	37	Peroxide-type	CHX	5 days
Siriyanyongwong et al., 2022	Thailand	RCT	16 (53.3%)	68 (56–75)	63 (56–75)	15	15	Herbal ingredients	CHX	7days
Nobahar et al., 2016	Iran	RCT	34 (50%)	66 (15.5)	63.4 (20.5)	34	34	Peroxide-type	NS	5 days
Özden et al.,2014	Turkey	RCT	22 (55%)	61.6% were over 66 years old		20	20	Sodium bicarbonate	CHX	4 days
Seguin et al., 2014	France	RCT	60 (71%)	64 (78%)		85	82	PVP-I	NS	7 days
Berry et al., 2013	Australia	RCT	154 (59.2%)	54.93 (19.5)	59.96 (18.0)	133	127	Sodium bicarbonate	Herbal ingredients	4 days
Özcaka et al., 2012	Turkey	RCT	NR	56.0 (18.2)	60.5 (14.7)	32	29	NS	CHX	14 days
Berry et al., 2011	Australia	RCT	35 (53%)	60.4 (17.5)	58.2 (19.4)	33	33	Sodium bicarbonate	CHX	4 days
Scannapieco et al., 2009	USA	RCT	104 (71.2%)	50.0 (22.5)	48.0 (20.8)	42	97	NS	CHX	21 days
Tantipong et al., 2008	Thailand.	RCT	101 (48%)	56.5 (20.1)	60.3 (19.1)	52	58	NS	CHX	2 days
Seguin et al., 2006	France	RCT	52 (78%)	38 (17)	38 (16)	36	31	PVP-I	NS	7 days
Chua et al., 2004	Philippine	RCT	17 (40.5%)	51.4 (15.8)	55.2 (16.5)	22	20	PVP-I	NS	7 days
DeRiso et al., 1996	USA	RCT	242 (68.6%)	63.5 (0.84)	64.1 (0.86)	180	173	NS	CHX	NR

Abbreviations: CHX: chlorhexidine; NR: Not Reported; NS: Normal Saline; PVP: Polyvinylpyrrolidone-Iodine (also known as Povidone-Iodine); RCT: randomised controlled trial.

threatening complications such as ischaemic cardiac events or sepsis. The impact of other mouthwashes besides CHX on NO bioavailability remains unknown; however, it is possible that each mouthwash with preservative properties targeting the reduction of oral nitrates should be able to decrease NO bioavailability and trigger adverse events.[36] The results of this study demonstrate that, compared to other mouthwashes, saline solution significantly reduces mortality rates. Thus, it is evident that nonantimicrobial mouthwash (saline

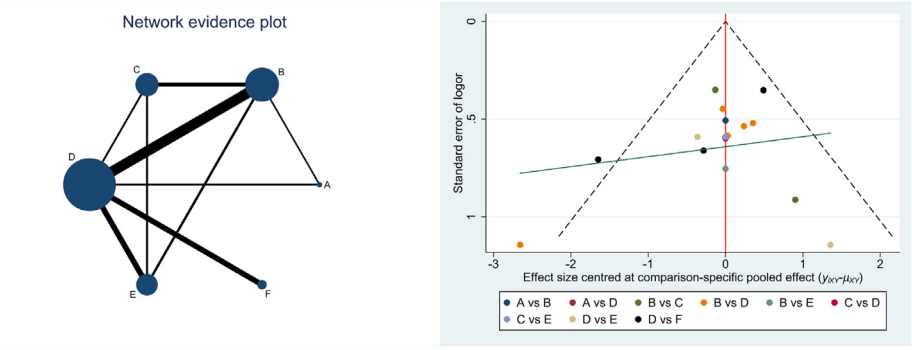

Fig. 3. Ventilator-associated pneumonia incidence network plot and funnel plot. A: peroxide-type; B: chlorhexidine; C: herbal ingredients; D: normal saline; E: sodium bicarbonate; F: povidone-iodine.

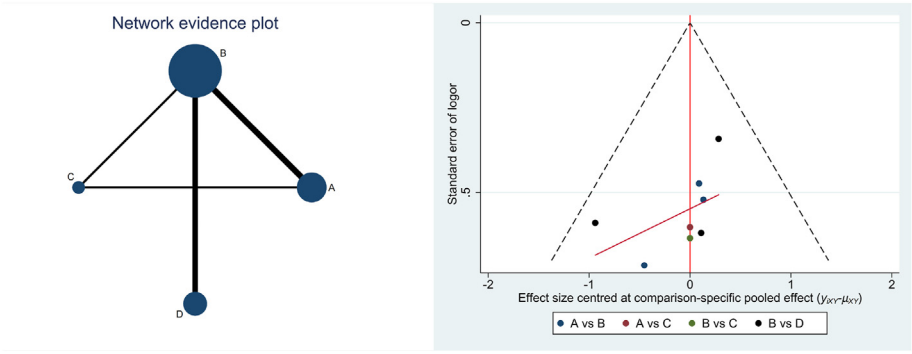

Fig. 4. Intensive care unit fatality-rate network chart and funnel chart. A: chlorhexidine; B: normal saline; C: sodium bicarbonate; D: povidone-iodine.

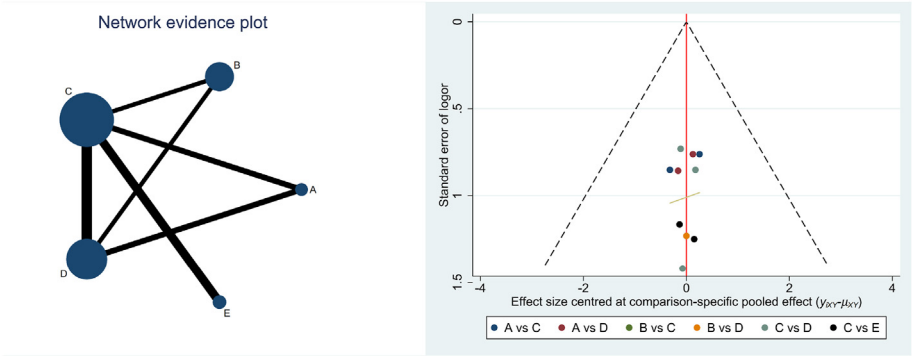

Fig. 5. *Escherichia coli* 1fixed value network chart and funnel chart. A: chlorhexidine; B: herbal ingredients; C: normal saline; D: sodium bicarbonate; E: povidone-iodine.

solution) can reduce the risk of mortality in ICU patients compared to antimicrobial mouthwashes represented by CHX.

CHX and oxidising agents, especially the latter, conferred optimal VAP prevention.[9,40,41] This could be attributable to their potent antimicrobial and disinfectant properties.[40] As a well-known aminoglycoside antiseptic, CHX rapidly disrupts cell membranes of pathogenic bacteria and suppresses their growth and reproduction, effectively reducing oral bacterial load and migration into respiratory tract.[42] On the other hand, oxidising agents such as hydrogen peroxide exert microbicidal effects via free-radical formation during oxidation, degrading bacterial biofilms and killing various pathogens.[19,43] Therefore, CHX and oxidising mouthwashes may effectively control pathogenic oral flora in ICU patients, mitigating risks of respiratory infections and thereby VAP incidence. Additionally, CHX mouthwash effectively prevents nosocomial pneumonia in ICU patients, especially among those in cardiac surgery.[44] Using hydrogen peroxide together with CHX may alleviate side effects of the latter such as unpleasant taste and tooth discolouration, improving patient compliance.[45]

Compared to other oral-care regimens, the duration of mechanical ventilation and ICU stay was markedly shorter in the oxidising-agent group. By maintaining oral hygiene and reducing risks of respiratory infections, oxidising agents may contribute to expedited recovery and shortened ICU stay.[9]

Similar to CHX, herbal extracts also exhibit antibacterial activities. The two mouthwash solutions had comparable efficacy in suppressing growth of *Staphylococcus aureus* and *Streptococcus pneumoniae*. Given the increasing threat of pathogen resistance, herbal mouthwashes are considered effective alternatives.[46,47] Especially regarding safety, herbal extracts were

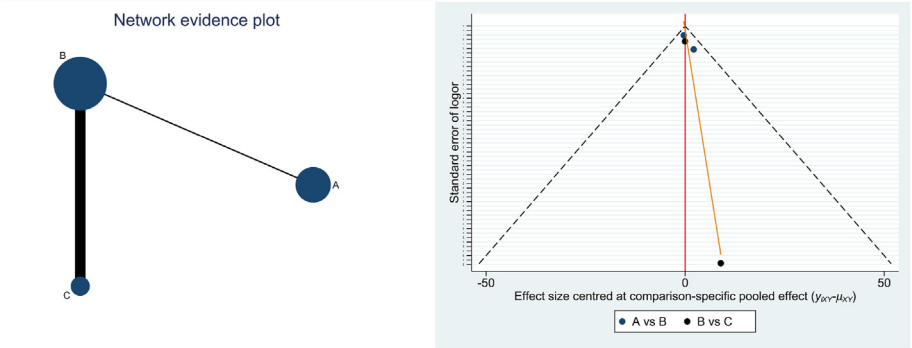

Fig. 6. Duration of mechanical ventilation network plot and funnel plot. A: chlorhexidine;B: normal saline; C: povidone-iodine.

associated with the least adverse reactions, attributable to the natural ingredients and synergistic actions of medicinal herbs. CHX did show slightly more side-effects, which clinicians should monitor for.

A recent national point prevalence study on oral health care in adult ICUs across the UK[48] concluded that good oral hygiene helps lower risks of VAP, but there is lack of standardised protocols and written consensus guiding oral-care practices for intubated ICU patients with tailored interventions. Proper and effective oral care is of paramount importance for ICU patients with endotracheal tubes. In addition to mouthwashes, oral care encompasses various modalities. Some studies focussed not only on the VAP preventive effects of mouthwashes but also on different combinations of oral-care techniques. For example, toothbrushing plus mouthwash showed superior VAP prevention compared to either intervention alone in ventilated ICU patients. Toothbrushing is easier to perform regardless of the method (manual or electric toothbrush, swab).[49–51]

Previously published meta-analyses have evaluated the effectiveness of CHX mouthwash and oral hygiene measures in preventing VAP in mechanically ventilated ICU patients.[15,52] However, conclusions remain inconclusive regarding optimal CHX concentrations and formulations.[53] In contrast, this network meta-analysis integrates evidence across multiple RCTs assessing different mouthwash solutions used in oral care of critically ill patients. By synthesising data across mouthwash categories, the analysis enables both direct and indirect comparisons to evaluate their relative effects on patient outcomes.

Potential advantages of this approach include the ability to assess a wider range of mouthwash formulations beyond just CHX, facilitate comparisons between different mouthwash categories in terms of their efficacy, and potentially provide more definitive conclusions to guide the selection of optimal mouthwash regimens for this patient population. However, some limitations should be noted when interpreting the results. These include reliance on published RCTs with inherent biases, caution when drawing inferences from indirect comparisons, and the inability to account for all factors that may moderate effectiveness such as frequency and consistency of mouthwash application. Clearly, further high-quality RCTs directly comparing different mouthwash protocols are still required to consolidate the evidence base, but this network meta-analysis represents an important advance in making better use of existing data.

5. Limitations

This study incorporated high-quality RCT evidence published recently. The efficacy and safety of different oral-care regimens were systematically evaluated to provide hierarchical evidence guiding standardised practices for ICU patients. However, there are some limitations, such as between-study heterogeneity, lack of subgroup analyses by frequency of application, and risk of selective reporting bias. Future research should adopt standardised outcome measures, assess the effects of varying frequencies and dosages of interventions, and report cost-effectiveness data, in order to furnish more solid evidence supporting standardised oral-care protocols tailored for ICU patients.

6. Conclusion(s)

In summary, while the effectiveness of different mouthwash types on VAP incidence, duration of mechanical ventilation, and bacterial colonisation remains inconclusive, there is evidence suggesting potential risks associated with the use of antimicrobial mouthwash, particularly CHX, in ICU patients. Oxidising solutions appear relatively safe. Saline solution emerges as a promising alternative, showing a significant reduction in mortality rates. However, large, high-quality RCTs are warranted to verify our findings and provide more robust evidence to inform evidence-based oral care in ICU settings.

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Credit authorship contribution statement

Qianqian He: conceptualisation, methodology, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, project administration. **Zengjin Peng:** conceptualisation, methodology, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, project administration. **Caiyun He:** conceptualisation, methodology, validation, formal analysis, investigation, writing—original draft, writing—review and editing, supervision. **Chao Zhang:** conceptualisation, methodology, validation, investigation, writing—review and editing. **Rong Hu:** methodology, validation, formal analysis, writing—review and editing.

Conflict of interest

The authors declare that they have no competing interests.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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References

[1] Rezaei S, Rezaei K, Mahboubi M, Jarahzadeh MH, Momeni E, Bagherinasab M, et al. Comparison the efficacy of herbal mouthwash with chlorhexidine on gingival index of intubated patients in Intensive Care Unit. J Indian Soc Periodontol 2016;20(4):404–8.
[2] Sayegh A, Dini EL, Holt RD, Bedi R. Oral health, sociodemographic factors, dietary and oral hygiene practices in Jordanian children. J Dent 2005;33(5):379–88.
[3] Hua F, Xie H, Worthington HV, Furness S, Zhang Q, Li C. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. Cochrane Database Syst Rev 2016;10(10):Cd008367.
[4] Aslam MT, Kanpurwala MA, Arshad R. Application of CDC standards for prevention of ventilator associated pneumonia (VAP) by paramedical personnel working in tertiary care hospitals of karachi, Pakistan. 2016.
[5] Blot SI, Poelaert J, Kollef M. How to avoid microaspiration? A key element for the prevention of ventilator-associated pneumonia in intubated ICU patients. BMC Infect Dis 2014;14:1–6.
[6] Hellyer TP, Ewan V, Wilson P, Simpson AJ. The Intensive Care Society recommended bundle of interventions for the prevention of ventilator-associated pneumonia. J Intensive Care Soc 2016;17(3):238–43.
[7] Guillamet CV, Kollef MH. Is zero ventilator-associated pneumonia achievable? Updated practical approaches to ventilator-associated pneumonia prevention. Infectious Disease Clinics 2024;38(1):65–86.
[8] Enwere EN, Elofson KA, Forbes RC, Gerlach AT. Impact of chlorhexidine mouthwash prophylaxis on probable ventilator-associated pneumonia in a surgical intensive care unit. International Journal of Critical Illness and Injury Science 2016;6(1):3.
[9] Nobahar M, Razavi MR, Malek F, Ghorbani R. Effects of hydrogen peroxide mouthwash on preventing ventilator-associated pneumonia in patients admitted to the intensive care unit. Braz J Infect Dis 2016;20:444–50.
[10] Izadi M, Bagheri M, Far AB, Bagheri-Baghdasht MS, Ghasemzadeh G, Sureda A, et al. Reduce the risk of ventilator-associated pneumonia in ICU patients by Ozonated water mouthwash: a double-blind randomized clinical trial. Am J Infect Control 2023;51(7):779–85.
[11] Özden D, Türk G, Düger C, Güler EK, Tok F, Gülsoy Z. Effects of oral care solutions on mucous membrane integrity and bacterial colonization. Nurs Crit Care 2014;19(2):78–86.
[12] Berry A. A comparison of Listerine® and sodium bicarbonate oral cleansing solutions on dental plaque colonisation and incidence of ventilator associated pneumonia in mechanically ventilated patients: a randomised control trial. Intensive Crit Care Nurs 2013;29(5):275–81.
[13] Jahanshir M, Nobahar M, Ghorbani R, Malek F. Effect of clove mouthwash on the incidence of ventilator-associated pneumonia in intensive care unit patients: a comparative randomized triple-blind clinical trial. Clin Oral Invest 2023:1–12.
[14] Zhang Q, Li C, Worthington HV, Hua F. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. Cochrane Database Syst Rev 2020;(12).
[15] Pinto ACdS, Silva BMd, Santiago-Junior JF, Sales-Peres SHdC. Efficiency of different protocols for oral hygiene combined with the use of chlorhexidine in the prevention of ventilator-associated pneumonia. J Bras Pneumol 2021;47.
[16] Pałka Ł, Nowakowska-Toporowska A, Dalewski B. Is chlorhexidine in dentistry an ally or a foe? A narrative review. Healthcare 2022;10(5):764.
[17] Zeydi AE, Parvizi A, Haddadi S, Karkhah S, Hosseini SJ, Mollaei A, et al. Effect of oral care with povidone-iodine in the prevention of ventilator-associated pneumonia; a systematic Review and meta-analysis. Archives of Academic Emergency Medicine 2023;11(1).
[18] Li L, Ai Z, Li L, Zheng X, Jie L. Can routine oral care with antiseptics prevent ventilator-associated pneumonia in patients receiving mechanical ventilation? An update meta-analysis from 17 randomized controlled trials. Int J Clin Exp Med 2015;8(2):1645.
[19] Ortega KL, Rech BdO, El Haje G, Gallo CdB, Pérez-Sayáns M, Braz-Silva PH. Do hydrogen peroxide mouthwashes have a virucidal effect? A systematic review. J Hosp Infect 2020;106(4):657–62.
[20] Stoeken JE, Paraskevas S, van der Weijden GA. The long-term effect of a mouthrinse containing essential oils on dental plaque and gingivitis: a systematic review. J Periodontol 2007;78(7):1218–28.
[21] Batiha GE-S, Alkazmi LM, Wasef LG, Beshbishy AM, Nadwa EH, Rashwan EK. Syzygium aromaticum L.(Myrtaceae): traditional uses, bioactive chemical constituents, pharmacological and toxicological activities. Biomolecules 2020;10(2).
[22] Sarrami N, Pemberton M, Thornhill M, Theaker E. Adverse reactions associated with the use of eugenol in dentistry. Br Dent J 2002;193(5):257–9.
[23] Xiang Y, Ren X, Xu Y, Cheng L, Cai H, Hu T. Anti-inflammatory and anti-bacterial effects of mouthwashes in intensive care units: a systematic review and meta-analysis. Int J Environ Res Publ Health 2022;20(1):733.
[24] Dale CM, Rose L, Carbone S, Pinto R, Smith OM, Burry L, et al. Effect of oral chlorhexidine de-adoption and implementation of an oral care bundle on mortality for mechanically ventilated patients in the intensive care unit (CHORAL): a multi-center stepped wedge cluster-randomized controlled trial. Intensive Care Med 2021;47:1295–302.
[25] Collins T, Plowright C, Gibson V, Stayt L, Clarke S, Caisley J, et al. British Association of Critical Care Nurses: evidence-based consensus paper for oral care within adult critical care units. Nurs Crit Care 2021;26(4):224–33.
[26] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162(11):777–84.
[27] Berry AM, Davidson PM, Masters J, Rolls K, Ollerton R. Effects of three approaches to standardized oral hygiene to reduce bacterial colonization and ventilator associated pneumonia in mechanically ventilated patients: a randomised control trial. Int J Nurs Stud 2011;48(6):681–8.
[28] DeRiso AJ, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996;109(6):1556–61.
[29] Seguin P, Laviolle B, Dahyot-Fizelier C, Dumont R, Veber B, Gergaud S, et al. Effect of oropharyngeal povidone-iodine preventive oral care on ventilator-associated pneumonia in severely brain-injured or cerebral hemorrhage patients: a multicenter, randomized controlled trial. Crit Care Med 2014;42(1):1–8.
[30] Seguin P, Tanguy M, Laviolle B, Tirel O, Mallédant Y. Effect of oropharyngeal decontamination by povidone-iodine on ventilator-associated pneumonia in patients with head trauma. Crit Care Med 2006;34(5):1514–9.
[31] Chua JV, Dominguez EA, Sison CMC, Berba RP. The efficacy of povidone-iodine oral rinse in preventing ventilator-associated pneumonia: a randomized, double-blind, placebo-controlled (VAPOR) trial: preliminary report. Philipp J Microbiol Infect Dis. 2004;33(153):e61.
[32] Özçaka Ö, Başoğlu ÖK, Buduneli N, Taşbakan MS, Bacakoğlu F, Kinane DF. Chlorhexidine decreases the risk of ventilator-associated pneumonia in intensive care unit patients: a randomized clinical trial. J Periodontal Res 2012;47(5):584–92.
[33] Scannapieco FA, Yu J, Raghavendran K, Vacanti A, Owens SI, Wood K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. Crit Care 2009;13(4).
[34] Siriyanyongwong P, Teanpaisan R, Pahumunto N, Uppanisakorn S, Vattanavanit V. Efficacy of Moraceae with chlorhexidine mouthwash on the microbial flora of critically ill intubated patients: a randomized controlled pilot study. Sci Rep 2022;12(1).
[35] Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008;29(2):131–6.
[36] Blot S, Labeau SO, Dale CM. Why it's time to abandon antiseptic mouthwashes. Intensive Crit Care Nurs 2022;70:103196.
[37] Blot S. Antiseptic mouthwash, the nitrate–nitrite–nitric oxide pathway, and hospital mortality: a hypothesis generating review. Intensive Care Med 2021;47(1):28–38.
[38] Sands KM, Twigg JA, Wise MP. Oral hygiene with chlorhexidine in critically ill patients. JAMA Intern Med 2015;175(2):316.
[39] Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ 2014;348.
[40] Vyas N, Mathur P, Jhawar S, Prabhune A, Vimal P. Effectiveness of Oral hygiene with chlorhexidine mouthwash with 0.12% and 0.2% concentration on incidence of ventilator associated pneumonia (VAP) in intubated patients–a parallel arm double blind randomized controlled trial. Ann Int Med Dent Res 2021;7(3):6.
[41] Dai W, Lin Y, Yang X, Huang P, Xia L, Ma J. Meta-analysis of the efficacy and safety of chlorhexidine for ventilator-associated pneumonia prevention in mechanically ventilated patients. Evid base Compl Alternative Med 2022;2022.
[42] Brookes ZLS, Belfield LA, Ashworth A, Casas-Agustench P, Raja M, Pollard AJ, et al. Effects of chlorhexidine mouthwash on the oral microbiome. J Dent 2021;113:103768.
[43] Cervantes Trejo A, Castañeda ID, Rodríguez AC, Andrade Carmona VR, Mercado M, Vale LS, et al. Hydrogen peroxide as an adjuvant therapy for COVID-19: a case series of patients and caregivers in the Mexico city metropolitan area. Evid base Compl Alternative Med 2021;2021.
[44] Cruz JC, Martins CK, Piassi JEV, Garcia Júnior IR, Santiago Junior JF, Faverani LP. Does chlorhexidine reduce the incidence of ventilator-associated pneumonia

in ICU patients? A systematic review and meta-analysis. Med Intensiva 2023;47(8):437–44.
[45] Mathurasai W, Thanyasrisung P, Sooampon S, Ayuthaya BIN. Hydrogen peroxide masks the bitterness of chlorhexidine mouthwash without affecting its antibacterial activity. J Indian Soc Periodontol 2019;23(2):119–23.
[46] Kiabi FH, Baradari AG, Kiasari AZ, Shahheidari M. The difference in mouthwash side effects of persica and chlorhexidine for preventing ventilator-induced pneumonia among patients admitted to the intensive care unit. Open Publ Health J 2023;16(1).
[47] Khezri HD, Gorji MH, Morad A, Gorji H. Comparison of the antibacterial effects of matrica & Persica™ and chlorhexidine gluconate mouthwashes in mechanically ventilated ICU patients: a double blind randomized clinical trial. Rev Chilena Infectol 2013;30(4):368–73.
[48] Kelly N, Blackwood B, Credland N, Stayt L, Causey C, Winning L, et al. Oral health care in adult intensive care units: a national point prevalence study. Nurs Crit Care 2023;28(5):773–80.
[49] Fu L-S, Zhu L-M, Yang Y-P, Lin L, Yao L-Q. Impact of oral care modalities on the incidence of ventilator-associated pneumonia in the intensive care unit: a meta-analysis. Medicine 2023;102(13).
[50] Gershonovitch R, Yarom N, Findler M. Preventing ventilator-associated pneumonia in intensive care unit by improved oral care: a review of randomized control trials. SN comprehensive clinical medicine 2020;2:727–33.
[51] de Lacerda Vidal CF, Vidal AKdL, Monteiro JGdM, Cavalcanti A, Henriques APdC, Oliveira M, et al. Impact of oral hygiene involving toothbrushing versus chlorhexidine in the prevention of ventilator-associated pneumonia: a randomized study. BMC Infect Dis 2017;17:1–9.
[52] Lee S, Lighvan NL, McCredie V, Pechlivanoglou P, Krahn M, Quiñonez C, et al. Chlorhexidine-related mortality rate in critically ill subjects in intensive care units: a systematic review and meta-analysis. Respir Care 2019;64(3):337–49.
[53] Tran K, Butcher R. Chlorhexidine for oral care: a review of clinical effectiveness and guidelines. 2019.