Chlorhexidine and prevention of ventilator-associated pneumonia: An integrative review of VAP incidence and mortality

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ABSTRACT

Ventilator-Associated Pneumonia (VAP) is a common infection in Intensive Care Units (ICUs), with high mortality rates. Maintaining adequate oral hygiene plays a crucial role in prevention, and chlorhexidine is the main substance used for this purpose. However, uncertainties persist regarding the effective use of this substance. Objectives: This study aims to evaluate the comparative effectiveness of chlorhexidine and inert substances in preventing VAP and mortality in patients under mechanical ventilation. Methodology: The search on Pubmed, from 2013 to 2023, resulted in 194 articles, and the manual 182, with 12 articles selected for inclusion in the integrative review. The Test Group (chlorhexidine) had 779 patients, the Control Group (inert substances) involved 302 patients. The comparative analysis focused on the incidence of VAP and mortality rate. Results: In the Test Group, 19.78% developed VAP, with a mortality rate of 8.22%. In the Control Group, the incidence of VAP was 18.54%, with a mortality rate of 8.61%. Conclusion: Despite the lack of conclusiveness in this study, the widespread use of chlorhexidine in all patients does not seem to be justified, as it did not show improvements in the incidence of VAP, although it also did not result in an increase in the mortality rate.

Keywords: Chlorhexidine, Ventilator-Associated Pneumonia, Oral Hygiene.

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INTRODUCTION

According to the World Health Organization, ventilator-associated pneumonia (VAP) is the most common infection in the intensive care unit, with a prevalence of 15 to 45%, and a higher incidence in countries with limited resources, being linked to high hospital mortality, lack of broad-spectrum antimicrobials, complementary tests (MEINBERG *et al*., 2012), increased mechanical ventilation time and expenses (COLLARD, SANJAY SANTO & MATTHAY, 2003); (VIEIRA, OLIVEIRA & SILVA MENDONÇA, 2022).

Pneumonia occurs when pathogens overcome human defense mechanisms, such as those of the respiratory system: cough reflex, glottic reflex and mucociliary system; humoral immunity (antibodies and B lymphocytes); and cellular immunity (polymorphonuclear leukocytes, macrophages, lymphocytes) (MEINBERG *et al*., 2012).

The considerable morbidity and mortality associated with VAP, the expensive treatment, and the considerable evidence that oral hygiene may be one of the means of reducing the risk of VAP suggest that oral hygiene for intubated patients should be a priority (Booker et al., 2013). An important feature is the decontamination of the oropharynx, associated with nasopharyngeal cleaning, since these have direct evidence of association with pulmonary infection (SEGERS *et al*., 2006).

Within 48 hours of admission to an ICU, patients present with changes in the oral flora, with a predominance of gram-negative organisms and other virulent organisms (KUSAHARA *et al*., 2012); (TUON *et al*., 2017). Biofilm can provide an environment for respiratory pathogens such as *Staphylococcus aureus* resistant to methicline and *Pseudomonasaeruginosa* (SEDWICK *et al*., 2012); (GREETINGS) *et al*., 2012); (TUON *et al*., 2017).

Chlorhexidine has a high combination with skin and mucous membranes, electrostatically binding to their surfaces and performing antimicrobial substantivity for up to 12 hours, against gram-positive and gram-negative bacteria, fungi and viruses (SEGERS *et al*., 2006). The routine use of antimicrobials is not encouraged, as they can create multidrug-resistant bacteria (SEGERS *et al*., 2006); (BOOKER *et al*., 2013).

Brazilian intensive care institutions and societies, including the Brazilian Association of Intensive Care Medicine and the National Health Surveillance Agency, recommend that oral hygiene in critically ill patients under mechanical ventilation should be performed with chlorhexidine, due to its possible benefits. However, recent meta-analysis has presented contradictory conclusions (VIEIRA, OLIVEIRA & SILVA MENDONÇA, 2022).

Some articles that compared the chemical removal of biofilm alone with 0.12% chlorhexidine and the removal associated with an electric and/or manual toothbrush obtained non-significant results for the prevention of MV-associated pneumonia when using a toothbrush. These studies concluded that the use of toothbrushing alone or the use of brushing with chlorhexidine had no impact on VAP,

when compared to the use of chlorhexidine alone (MEINBERG *et al*., 2012); (SHI *et al*., 2013); (VILELA *et al*., 2015); (TUON *et al*., 2017); (CAMARGO *et al*., 2019).

There is insufficient evidence to prove that brushing affects the duration of mechanical ventilation, length of ICU stay, use of antibiotic therapy, oral health indices, effects adverse events, cost, or outcome with increased mortality (HUA et al., 2016).

Oral hygiene is now seen by intensive care as an intervention that reduces hospital-acquired pneumonia in critically ill patients, not just a comfort measure. A meta-analysis shows us that oral hygiene is significantly linked to reduced rates of ventilator-associated pneumonia (FEIDER, MITCHELL & BRIDGES, 2010). Physicians, nurses and dentists should improve their knowledge of VAP, as a better practice of oral hygiene leads to positive attitudes about the importance of knowledge of VAP (JORDAN *et al*., 2014).

In a systematic review, other forms of oral hygiene to help prevent VAP were addressed, including: mouthwash; gel-antiseptic; cotton swab and toothbrush; toothpaste, aspiration probe, gauze, mouthwash (CAMARGO *et al*., 2019), which can be used alone or in association (TINGTING *et al*., 2020).

Research indicates that 60% to 70% of ICUs in Europe and North America use chlorhexidine to clean the oral cavity at least once a day in all patients on mechanical ventilation. In addition, continuous oral care with chlorhexidine becomes a regular practice for the prevention of Ventilator-Associated Pneumonia (KLOMPAS *et al*., 2014). However, caution is needed because, according to double-blind research, it may not prevent VAP (KLOMPAS *et al*., 2014), and may be related to a higher risk of death, but it is not yet clear. (KLOMPAS, 2016); (BOUADMA & KLOMPAS, 2018); (KLOMPAS *et al*., 2022).

As recomendações da Society for Health care Epidemiology, Infectious Diseases Society of America e da Association for Professionals in Infection Control and Epidemiology (KLOMPAS *et al*., 2022), place the practice of oral hygiene with chlorhexidine as not recommended in the prevention of VAP. This protocol was based on systematic reviews and meta-analyses (KLOMPAS *et al*., 2014; PRICE, MACLENNSN & GLEN, 2014; KLOMPAS *et al*., 2016; DESCHEPPER *et al*., 2018).

Vieira, Oliveira & Mendoça (2022) draw attention to the high mortality and events related to mechanical ventilation when chlorhexidine is used. And they inform that the potential harm of chlorhexidine may be due to a possible mechanism of pulmonary toxicity after its aspiration, generating lung injury, acute respiratory distress syndrome (ARDS), and some patients may present anaphylaxis as an allergic reaction (BOUADMA, 2018). In addition, chlorhexidine can cause hypersensitivity reactions, ulcers, and erosions in the oral cavity when its concentration is increased

(VIEIRA, OLIVEIRA & SILVA MENDONÇA, 2022), as well as plaques and bleeding in mucosal tissue when chlorhexidine is used (BOUADMA, 2018).

Despite its beneficial properties to the patient's treatment, chlorhexidine used continuously can lead to tooth staining and mucosal lesions. In addition, its use involves costs and procedures for administration and storage according to the U.S. Food and Drug Administration which classifies it as a drug (KLOMPAS *et al*., 2014).

Recent research shows that, at the moment, the best choice is to remove chlorhexidine from oral hygiene protocols and opt for brushing and oral hygiene with water sterile, as it is the most cautious choice (VIEIRA, OLIVEIRA & SILVA MENDONÇA, 2022).

Currently, there is no standard on national and international recommendations on oral hygiene to prevent VAP. In addition, there are methodological limitations and inconsistency in the results of some studies. On the other hand, there may appear to be no benefit to chlorhexidine in terms of reducing the incidence of VAP and there may be a potential increase in mortality. Therefore, the primary objective of this study is to compare the use of chlorhexidine with placebo (inert substances or no substances) in relation to VAP incidence and mortality rate.

METHODOLOGY

This study proposes an integrative review in order to investigate the efficacy of oral hygiene with chlorhexidine compared to inert solutions in adult patients admitted to Intensive Care Units (ICUs). The guiding question, formulated in the PICOT format, is as follows:

In adult patients admitted to ICUs (P), what is the efficacy of oral hygiene with chlorhexidine (I) compared to inert solutions (C) in preventing the development of Ventilator-Associated Pneumonia (O) and reducing mortality rates.

The search was initially conducted in Pubmed based on specific descriptors: ((prevention [Title/Abstract]) AND (ventilator-associated pneumonia [Title/Abstract])) OR (VAP [Title/Abstract])), limited to the period from 2013 to 2023. The "Clinical Trial" and "Randomized Controlled Trial" study types were selected, and only "Full Text" articles were considered. Articles containing an analysis of VAP incidence or mortality using chlorhexidine at any concentration or placebo were chosen.

INCLUSION CRITERIA:

- **Adult Patients Over the Age of 18 Years:**
  The research considered studies that exclusively involved adult patients, ensuring that the analysis was focused on the population of interest in Intensive Care Units (ICUs).
- **Full Text Articles:**

Only articles with available full texts were considered, ensuring a more comprehensive and accurate analysis.

- **Available methodological description:**

  Inclusion encompassed studies that provided a clear description of their methodology, including controlled clinical trials, observational studies, prognostic studies, randomized studies, incidence studies, qualitative research, and screening studies.

- **Studies in any language:**

  There were no restrictions on the language of the selected articles.

EXCLUSION CRITERIA:

- **Duplicate Articles:**

Duplicate articles were excluded to avoid redundancies and ensure the uniqueness of the data analyzed.

- **Inaccurate or Incomplete Results:**

  Articles with inaccurate or incomplete results were excluded to ensure the quality and reliability of the data analyzed.

  The careful selection of studies, based on the predefined criteria, was complemented by detailed data analysis. Table assembly and a flowchart have been incorporated to facilitate the interpretation and visualization of relevant information.

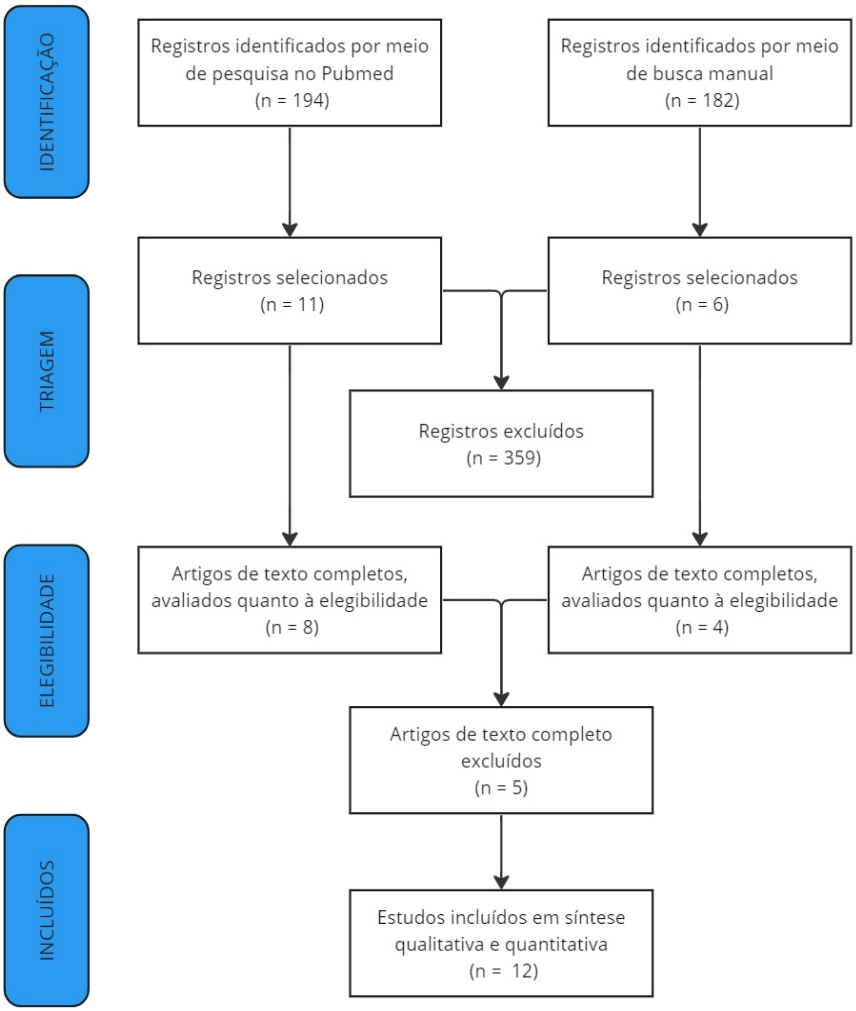
RESULTS

The initial objective of this study, using the specific descriptors in PubMed, was to identify studies that compared patients undergoing cleaning with chlorhexidine and inert substances, in order to evaluate the incidence of Ventilator-Associated Pneumonia (VAP) and the associated mortality rate. The initial search strategy resulted in 194 articles, of which 11 were selected based on the analysis of the abstracts. However, after a careful analysis, only 8 articles were considered for inclusion in the integrative review.

Given the scarcity of studies related to patients sanitized with inert substances, we undertook an additional manual search of 182 articles, based on the references of the article by Papazian et al. 2020. Initially, 6 articles were selected, however, after a more in-depth analysis, removal of duplicates, only 4 articles were definitively chosen to be part of the review.

In summary, a total of 369 articles were examined. After evaluation of the inclusion and exclusion criteria, removal of duplicates, incomplete and inaccessible articles, 12 were included in the integrative review. This process involved two distinct search strategies: one automated in PUBMED and the other manual (Figure 1).

Figure 1 – Flowchart with the search result



Source: prepared by the authors.

After the initial phase of article selection, the integrative review progressed to the organization of the data from the 12 chosen articles. This information was organized and presented in Table 1, where the authors were described and, for a better understanding, two distinct groups were delineated: the experimental group, which was cleaned with chlorhexidine, and the control group, which received care with inert solutions. This approach allowed a direct comparison of the effects of these hygiene practices on the incidence of Ventilator-Associated Pneumonia (VAP) and mortality.

Table 1 - Data from Studies on Ventilator-Associated Pneumonia (VAP) and Mortality Rate.

Author	Sample	Test Group (CHX)	Control Group (Subs. Inert)	Nº of cases of Pav experimental group	Number of VAP cases Control Group	Mortality Experimental Group	Mortality Control Group
CHACKO et al., 2017	206	206	-	12	-	-	-
VIDAL et al.,2017	213	213	-	45	-	47	-
KES et al., 2021	57	29	-	10	-	-	-
ZAND et al., 2017	114	114	-	16	-	16	-
JAHANSHIR et al., 2023	168	84	-	35	-	-	-
KHAKY et al., 2018	75	38	-	9	-	-	-
TUON et al., 2017	16	8	8	4	2	-	-
IZADI MD et AL., 2022	73	37	-	17	-	-	-
MEIDANI et al., 2018 *	150	50	50	6	15	4	5
SEGUIN et al.,2014 *	150	-	72	-	20	-	21
BERRY et al., 2013 *	398	-	138	-	6	-	-
NOBAHAR et al, 2016 *	68	-	34	-	13	-	-

* Manual search. Source: prepared by the authors.

By delimiting the Test Group, composed of patients submitted to the application of chlorhexidine, the 779 individuals analyzed revealed essential data on Ventilator-Associated Pneumonia (VAP) and the mortality rate. Among these participants, 154 developed VAP, representing approximately 19.78% of the total sample. Additionally, when examining the mortality rate within this specific group, we observed that 63 patients faced the fatal outcome, resulting in a mortality rate of 8.22% (Table 2).

In the comparative analysis conducted, the Control Group adopted inert solutions for oral hygiene, comprising an approach that involved the use of saline solutions, distilled water, saline solution, among others. This group consisted of 302 patients on mechanical ventilation (MV). The results revealed an incidence of Ventilator-Associated Pneumonia (VAP) of approximately 18.54%, reflected in 56 diagnosed cases, accompanied by a mortality rate of 8.61%, involving 26 patients who died (Table 2).

Table 2 - Consolidated Results of Ventilator-Associated Pneumonia (VAP) and Mortality Rates in the Test and Control Groups.

Group	Sample	Patients diagnosed with VAP	Patients who died (Mortality Rate)
Test	779	154 (≈19.78%)	63 (≈8.22%)
Control	302	56 (≈18.54%)	26 (≈8.61%)

DISCUSSION

This integrative review provided a comprehensive compilation of evidence on oral hygiene care for hospitalized patients on mechanical ventilation . In particular, it explored the effects of using inert solutions, such as saline solutions, distilled water, and saline, compared to chlorhexidine. Given the inherent complexity of these clinical settings, it is imperative to conduct a critical analysis of the findings, considering not only the immediate practical implications, but also identifying gaps to guide future research in this vital area of clinical practice.

When analyzing the relatively small percentage difference between the groups, both in terms of pneumonia incidence and mortality rate, there seems to be numerical similarity between the two groups indicated. Therefore, in this study, the incidence of VAP was similar between chlorhexidine and placebo. Vieira, Oliveira & Mendoça (2022) offer a view in line with the findings of this study, highlighting, in a meta-analysis of double-blind randomized clinical trials, the absence of an association between oral chlorhexidine and lower VAP rates. However, comparing chlorhexidine with placebo, Hua *et al*. (2016) disagree with these results, showing in 18 Randomized Controlled Trials (RCTs) that chlorhexidine, either as a mouthwash or gel, reduced the incidence of VAP. Similarly, Lee *et al*., (2019), in their meta-analysis, found reductions in VAP incidence in the chlorhexidine groups. Shi *et al*., (2013) also disagree, presenting evidence that chlorhexidine, either as a mouthwash or gel, reduces the chances of developing VAP in adults by about 40%. De Riso et al. 1996 do not agree with the results of this study, emphasizing a significant reduction of 65% in the incidence of nosocomial respiratory infections in the group treated with chlorhexidine. As for Klompas *et al*., (2014), there is partial agreement, noting a decrease in lower respiratory tract infections in cardiac surgery patients treated with chlorhexidine, but finding no significant difference in VAP risk in double-blind studies with noncardiac patients. Villar *et al*., (2016) add that oral hygiene with chlorhexidine is effective in reducing the incidence of VAP in the adult population only if chlorhexidine is administered at 2%.

Regarding the mortality rate, we did not identify a significant difference between the chlorhexidine and inert groups of substances. Hua *et al*., (2016) corroborate our findings, highlighting the absence of evidence of difference between chlorhexidine and placebo/usual care in mortality outcomes. Similarly, the analysis by Lee *et al.*, (2019) on mortality did not identify a

significant difference in the incidence of mortality between the chlorhexidine and control groups, aligning with our conclusions. Shi *et al*., (2013) agree that chlorhexidine does not influence the number of patients who die in the ICU. However, Vieira, Oliveira & Mendoça (2022) disagree, associating oral care with chlorhexidine with an increase in mortality, ICU-associated infections, and risk of ventilator-related events. This conclusion was based on several meta-analyses of randomized controlled trials and observational analyses. Klompas *et al*., (2014) agree with our conclusions in observing no significant difference in mortality between chlorhexidine and placebo in cardiac surgery studies, but identify a non-significant increase in mortality in noncardiac studies. Price *et al*., (2014) diverge from our results, associating the use of chlorhexidine in the oropharynx with an increase in mortality in adults in intensive care units in general. De Riso *et al*., (1996), on the other hand, observed a reduction in mortality in patients treated with chlorhexidine. This uncertainty regarding chlorhexidine-related mortality persists because, as seen, studies with a higher level of evidence suggest an increase in chlorhexidine-related mortality, whereas the majority, including this study, do not find differences in mortality. In one way or another, recently the *Society for Healthcare Epidemiology* (KLOMPAS *et al.,* 2022) suggested removing chlorhexidine from VAP prevention packages.

When comparing our study with previous studies, we found discrepancies in relation to VAP incidence, while we observed greater agreement, especially with regard to mortality. These divergences highlight the complexity of the topic and indicate the importance of future research to provide a more comprehensive understanding of the role of chlorhexidine in the prevention of VAP in mechanically ventilated ICU patients. Adding to the discussion, it is relevant to mention that Bellissimo-Rodrigues *et al*., (2019) suggested that chlorhexidine should be used exclusively in patients with dental problems, such as periodontitis, a recommendation with which we reiterate. This perspective directed towards a specific group of patients underscores the need for a more personalized approach to the use of chlorhexidine, considering individual conditions and potential benefits in specific contexts, such as dental problems. This consideration adds important nuances to the debate on the use of chlorhexidine in VAP prevention and highlights the importance of taking into account different clinical contexts when evaluating study results. In addition, it draws attention to the need for dental surgeons to be part of the multidisciplinary ICU team.

This study has limitations, including the lack of consideration of the different chlorhexidine concentrations, the absence of statistical analysis, and the fact that most of the studies included in this study did not assess the risk of death of patients at the beginning of hospitalization, compromising the robustness of the conclusions related to this outcome. In addition, the omission of adjustment for risk factors, such as the APACHE or SAPS indexes, highlights the need for future studies to incorporate risk assessment indices for a more accurate analysis of the impact of the intervention on ICU patient

mortality. Still, in order to advance the research, it is imperative that future studies deepen the investigation of the different concentrations of chlorhexidine, considering variables such as hospitalization costs, antibiotic use, length of stay, and mortality. A more comprehensive approach in this regard will contribute to guiding more informed clinical practices and improving oral hygiene protocols in ICU settings.

CONCLUSION

The use of chlorhexidine in all patients does not seem to be sustainable, as it did not improve the incidence of VAP, although it did not increase mortality. Therefore, the use of this substance seems to be more correct in cases with dental indications, instead of having its use indiscriminately for all patients on mechanical ventilation aiming at preventing VAP.

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