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EFFECTIVENESS OF CHLOREXIDINE DIGLUCONATE CONCENTRATIONS IN REDUCING THE INCIDENCE OF VAP IN PATIENTS ADMITTED TO ICU: A CRITICAL REVIEW OF THE LITERATURE

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Abstract: The objective of this review was to identify and critically analyze the evidence in the scientific literature, through clinical trials, to compare the effectiveness of the various concentrations of chlorhexidine with the same solution and the one most frequently used in the oral hygiene of hospitalized patients. The authors conducted an electronic and manual search in several databases (Pubmed, Scielo, Lilacs, Cochrane) and the gray literature (Thesis Bank and Google Scholar). There was no limitation as to the year of publication or language. A total of 176 articles were selected and systematically analyzed according to the pre-defined inclusion criteria (clinical trials, randomized or not, in any language, conducted in sick patients, regardless of gender, age, or race, admitted to hospitals, whether in the ICU or other sectors). These articles were evaluated, the data considered relevant were extracted, and a classification was made according to the quality of the methodological evidence found, with level I if it met all the criteria or four (with only one B). Level II if it partially met the criteria (maximum two C assessments). Level III if it followed two criteria or less (more than two C's). The only study selected was classified as level of evidence III, as it did not include the information necessary for a good quality study and, therefore, was considered to have a high risk of bias. Regarding the treatment used, the chlorhexidine solution was compared to the same product in different concentrations in the control group. Given the great variability in the concentrations of this mouthwash, further research should be carried out in order to achieve greater certainty and standardization of which concentration is shown to be more effective in the prevention of aspiration pneumonia in hospitalized patients.
Keywords: Oral hygiene. Chlorhexidine. Intensive Care Unit.

INTRODUCTION

Most individuals who are hospitalized in Intensive Care Units (ICUs) are mostly frail and need intubation; they do not have adequate oral hygiene during hospitalization or have poor oral hygiene when there are no trained dental surgeons in the hospital environment (BATISTA, S. A. *et al*., 2014). Consequently, these individuals are vulnerable to some oral conditions related to systemic diseases, medications, or mechanical ventilation equipment. And, in the case of oral infections, most of the time there is a correlation concerning the emergence of systemic disorders such as, for example, nosocomial pneumonia (BATISTA, S. A. *et al*., 2014).

Pneumonia, an acute infection of the lungs, can cause various symptoms and local and systemic signs in the patient, such as rapid and shortened breathing, cough, fatigue, fever, the production of secretions, and chest pain. The main causes of this pulmonary pathology are bacteria, which, in turn, are the easiest to avoid and solve (SCANNAPIECO, F. A., 2006).

In this sense, and when it comes to hospital environments, the type of pneumonia that occurs in these places, in an interval between 48 and 72 hours after the patient's admission, is nosocomial. One of the risk factors for its appearance is the lack or failure of oral hygiene. Thus, one of the common causes of death among hospital-acquired infections (BARROS, J. N. P. *et al.*, 2022).

The bacterial colonization found in the oral cavity of hospitalized patients varies according to several factors, including the use of antimicrobials during hospitalization (BASSIN, A. S.; NIEDERMAN, M. S., 1995). As a result, means of prevention have been the target of several studies, one of which is the adoption of non-absorbable antibiotics for topical use (FARDIN, R. *et al*., 2005).

Oral hygiene in ICU patients is considered a basic factor for maintaining oral health. In addition to acting in the prevention of infections, it also has the role of providing convenience to the patient (BATISTA, S. A. *et al*., 2014). With oral hygiene action being performed frequently, there is a reduction in the occurrence of mechanical aspiration pneumonia or ventilator- associated pneumonia (VAP), since, with the maintenance of the patient's oral health, there is a decrease in the aspiration of microorganisms that may cause this problem (BATISTA, S. A. *et al*., 2014).

Among antiseptic mouthwashes, chlorhexidine, an antimicrobial agent, is highly effective and is generally used as the gold standard over others (ELDRIDGE, K. R. *et al.*, 1998). In this sense, it has several benefits: it can act against several pathogenic agents, such as gram-positive, gram-negative bacteria and yeasts, and therefore can reduce bacterial colonization (DAI, W. *et al*., 2022). It also has low rates of undesirable effects and low local and systemic toxicity (ELDRIDGE, K. R. et al., 1998). In addition, it has good effectiveness even after approximately 12 hours of application (ZAND, F. *et al*., 2017). When combined with salivary glycoprotein, chlorhexidine reduces the protein adsorption on the tooth surface and prevents plaque formation (DAI, W. *et al*., 2022). Chlorhexidine is also beneficial for the healing and regeneration of oral tissue. Its mechanism of action is its dissociation, with which chlorhexidine cations and anions are generated, and the combination of the bacterial cell wall with a negative charge produces a sterilization effect (DAI, W. *et al.,* 2022). In addition, chlorhexidine can also bind to the bacterial extracellular polysaccharide, which prevents bacteria from easily attaching to the cell membrane and thus helps to decrease bacterial proliferation (DAI, W. *et al*., 2022).

Being indicated for individuals with motor limitations and mental disabilities, it will play

a fundamental role in reducing pathologies and oral health problems (ELDRIDGE, K. R. *et al.*, 1998). In addition, the topical use of this mouthwash, when used in mechanically ventilated patients, seems to reduce the colonization of the oral cavity, and is precisely associated with a decrease in the occurrence of aspiration pneumonia due to mechanical ventilation (BERALDO, C. C.; ANDRADE, D. DE., 2008).

According to the results of Nascimento's (2018) research, there are several concentrations of chlorhexidine found in investigative studies, namely 0.02%, 0.05%, 0.1%, 0.12%, 0.2% and 2%, which hinders any discussion regarding the efficacy in the prevention of aspiration pneumonia in hospitalized patients. However, amid this variety, there is still no consensus regarding the ideal concentration of this mouthwash in the oral hygiene of hospitalized patients (BERALDO, C. C.; ANDRADE, D. DE., 2008). Given the above, the main objective of this study was to compare the effectiveness of the various concentrations of chlorhexidine and the most frequently used in the oral hygiene of hospitalized patients.

MATERIAL AND METHOD

The methodology was developed following the PICO Strategy. The clinical question was elaborated according to the acronym PICO: Population = patients, regardless of age or gender, hospitalized with VAP; Intervention = use of 0.12% chlorhexidine. Comparison/ Control = chlorhexidine in different concentrations. Outcomes = effectiveness of chlorhexidine in reducing VAP incidence. The question was: "What is the most effective concentration of chlorhexidine for mouthwash in hospitalized patients with VAP?"

The searches were carried out in the Pubmed, Scielo, Lilacs, Cochrane databases and in the gray literature (Thesis Bank and Google Scholar) with predetermined inclusion and exclusion criteria, with keywords obtained from DECS and MeSH, isolated or combined, in English "oral hygiene," "chlorhexidine," and "intensive care unit".

Clinical trials, randomized or not, in any language, conducted on sick patients, regardless of gender, age, or race, admitted to hospitals, whether in the ICU or other sectors, were included. The intervention of interest was the performance of oral hygiene using chlorhexidine comparing concentrations, and the outcome to be evaluated was the effectiveness of chlorhexidine in the oral hygiene of hospitalized patients.

A detailed and complete analysis of the articles of choice for the study was carried out, and several aspects were taken into account to carry out the final evaluation. These aspects were: author/year, study design, sample size, objectives, inclusion criteria, interventions, material used and its concentration, conclusions, and level of evidence.

The evaluation of the quality of the trials was carried out according to the CONSORT checklist (MOHER, D. *et al.* 2010) and based on the following criteria for the qualification of the methodology and classification of the levels of evidence: sample calculation, randomization, allocation concealment, masking, and follow-up losses (BELÉM, L. *et al.* 2021) (Table 1).

Table 1. Classification for Evaluation of the Quality of Clinical Trials

Criteria	A	B	C
Sample calculation	Adequate	Partially reported	Not mentioned
Randomization	Adequate	Partially reported	Not mentioned
Allocation concealment	Adequate	Partially reported	Not mentioned
Masking	Adequate	Partially reported	Not mentioned
Follow-up losses	Adequate	Partially reported	Not mentioned

Font: adapted from Belém, Ludmila M *et al.* 2021

The criterion was considered adequate as A when reported by the authors and explained; if it was only mentioned and not explained, it was established as B, and C if it was not even mentioned. If the trial met all or four criteria (with only one B), it was evaluated as level of evidence I, if it partially met the criteria (maximum two C evaluations) it was evaluated as level of evidence II, and if it followed two criteria or less (more than two C's), it was evaluated as level of evidence III (BELÉM, L. *et al.* 2021).

The research, reading of the articles, selection and critical evaluation of the selected studies were carried out by two previously trained evaluators (JHLB) and (RSC). In case of doubt, a third evaluator (ODF) was consulted to reach a consensus.

RESULTS

Initially, 176 articles were found, 155 by electronic search and 21 by manual search. After applying the eligibility criteria, 1 article was selected for full and critical reading, which is described on Table 2.

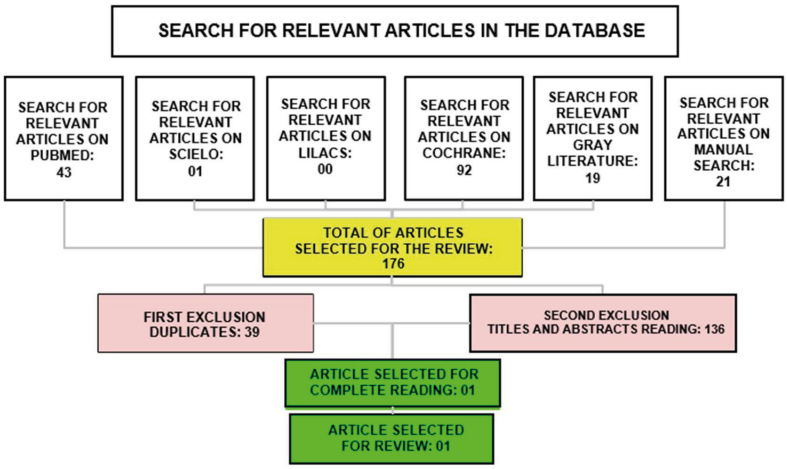
Table 2. Summary of the selected study

Author/ year	Study design	Sample size	Objective	Inclusioncriteria	Interventions	Conclusion
Zand et al.,2017	RCT	114 patients	To compare2 different concentrations of CHX on thereduction of oropharyngeal bacterial colonization and VAP in patients in ICU	Age ≥ 18 years- old, using tracheal tube, in mechanical ventilation for less than 48 hours, with no diagnostic of pneumonia at admission, no allergy to CHX,trauma or or oral inflammation, no immune disorders and first time at ICU	0.2% CHX versus 2% CHX every 12 hours.	2% CHX was more efficient in reducing oropharyngeal bacterial colonization and VAP incidence

Font: adapted from Belém et al., 2021. Abbreviations: CHX = Chlorexidine, RCT = Randomized Clinical Trial, VAP = Ventilator-Associated Pneumonia

Figure 1 shows the flowchart for identifying, tracking, and including articles for critical review.

Figure 1: Fluxogram



The only article that met the inclusion criteria of this study had evidence level III according to the criteria established to evaluate the quality of randomized clinical trials (Table 3).

Table 3. Methodological evaluation of the selected article

Author/year	Sample calculation	Randomization	Allocation concealment	Masking	Follow-uplosses	LE
Zand et al., 2017	NM = C	YES = A	NM = C	NM = C	PM = B	III

Font: Adapted from Belém et al., 2021. Abbreviations: NM = Not Mentioned, LE = Level of Evidence, PM = Partially Mentioned.

DISCUSSION

VAP is pneumonia that occurs in patients on mechanical ventilation through an endotracheal tube or tracheostomy for at least 48-72 hours. Several studies have also shown a relationship between dental plaque colonization and respiratory disease. Fortunately, the incidence of VAP can be reduced by identifying risk factors and improving prevention methods. Oral hygiene is a basic and special nursing care that helps to provide comfort to patients and prevent VAP, and may include mechanical and pharmacological interventions (ZAND, F. *et al.*, 2017).

When properly designed, conducted, and reported, the randomized clinical trial represents the gold standard study in the evaluation of health interventions. However, it can produce biased results if there is no methodological rigor (FLECHA, O. D. *et al.*, 2016). The study evaluated in this review may be at high risk of bias because it does not report sufficient information contained in a good-quality study.

In the selected article, the method of performing the sample calculation was not mentioned, which represents the possibility that the authors did not obtain an adequate number of participants. The sample size calculation is very important to determine the amount needed to compose the sample in order to obtain valid results (NASCIMENTO, N. P. G. DO *et al.*, 2018).

Randomization was rated A, since it was performed based on a computer-generated randomization table. However, allocation concealment and masking were also not mentioned as to how or if they were performed. Trials in which the allocation

sequence is inadequately concealed may yield higher estimates of treatment effects than trials in which the authors reported adequate concealment (SCHULZ, K. F., 1996).

The development of the study may be affected by the absences or losses of the participants, and to compensate for these deviations, one of the strategies commonly used is the Intention-to-Treat Analysis, using the last observation made or the worst possible result (FLECHA, O. D. *et al.*, 2016). In the study evaluated, 16 deaths were reported (9 in the 0.2% chlorhexidine group and 7 in the 2% chlorhexidine group). They are not even included in the flowchart, and it was also not explained how these losses were treated, which means that there is a possibility that the result of the study was not consistent with reality, as there is a chance of a decrease in the power of comparison (NASCIMENTO, N. P. G. DO *et al.*, 2018).

Some of the greatest difficulties in conducting clinical trials in ICU patients are due not only to the resistance to the acceptance, on the part of those responsible for the patients to undergo the studies, but also to the difficulty of evaluating various intraoral parameters due to the limitation imposed by the intubation devices.

In the study conducted by Keijser J. A. M. et al., (2003), where volunteer participants did not receive mechanical plaque removal, but only mouthwashes with CHX solutions twice a day for three days, the results revealed that the effectiveness of 30- second mouthwash with a 15 ml 0.12% solution was equivalent to that of mouthwash for 60 seconds with a 10 ml 0.2% solution. The authors concluded that the 30-second mouthwash time was sufficient for CHX in a 0.12% solution to be effective.

The most commonly used method was mouthwash, twice a day, using 10 ml of chlorhexidine at a concentration of 0.2%. Further research revealed that by reducing the concentration of the product and increasing the volume of solution, the amount of drug used was about the same, and the ability to fight plaque remained similar, resulting in fewer side effects. As a result, the concentration of 0.12% with 15 ml mouthwash became widely used, and the recommended time at this concentration would be 1 minute (FARDIN, R. *et al.*, 2011).

One of the strengths of the current study is the fact that it conducted a broad electronic and manual search of articles on clinical trials in several databases. In addition, the standardization of important items ensures a good level of evidence for the clinical trials found and their critical evaluation. On the other hand, the outcome of this review initially is that many studies were found according to the keywords, but excluded because they did not meet the inclusion criteria, since most of them compare chlorhexidine with several other solutions, such as saline solution, placebo, emulsions, among others. Unfortunately, the literature on the subject is scarce. Thus, this review study was limited, since only 01 article was included.

Long-term use of chlorhexidine in high concentrations can cause side effects such as changes in taste and peeling of the oral mucosa. In contrast, lower concentrations are preferred because they have the same preventive effect and greater clinical safety.

Due to the great variability of concentrations of this mouthwash, further research should be carried out in order to achieve greater certainty and standardization of which concentration is shown to be more effective in the prevention of aspiration pneumonia in hospitalized patients.

CONCLUSION

There is insufficient evidence to answer the study question due to low methodological quality and high risk of bias.

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