Uso de clorhexidine para higiene bucal en UCI: Revisión sistemática y metanálisis

Uso de clorexidina para higiene bucal em UTI: Revisão sistemática e metanálise

Use of chlorhexidine for oral hygiene in the ICU: Systematic review and meta-analysis

RESUMO

Objetivos: identificar as diferentes formas de utilização da clorexidina para higiene bucal de pacientes em ambiente de UTI e qual proporciona maior índice de redução da PAV. Métodos: foi realizada uma Revisão Sistemática, que teve como estratégia PICO, pacientes internados na UTI, submetidos à higiene bucal com clorexidina, avaliando o resultado na redução da PAV. Resultados: a solução de clorexidina 0,12% é a mais utilizada e gerou uma Metanálise com 5 estudos que mostraram que não há significância estatística no uso de clorexidina na higiene bucal nesses pacientes [RR 0,69 (IC 95% = 0,46 - 1,03)]. Conclusão: apesar da crescente utilização da higiene bucal com clorexidina na UTI, não há evidências científicas de que ela proporcione maior benefício na redução da PAV e, portanto, recomenda-se uma melhor avaliação do benefício em seu uso frequente.

DESCRITORES: Clorexidina; Higiene bucal em UTI; Pneumonia Associada à ventilação mecânica; Pneumonia; Unidade de Tratamento Intensivo.

ABSTRACT

Objectives: to identify the different ways of using chlorhexidine for oral hygiene of patients in an ICU environment and which one provides the highest rate of VAP reduction. Methods: a Systematic Review was carried out, which had as a PICO strategy, patients admitted to the ICU, subjected to oral hygiene with chlorhexidine, evaluating the result on the reduction of VAP. Results: 0.12% chlorhexidine solution is the most used and generated a meta-analysis with 5 studies that showed that there is no statistical significance in the use of chlorhexidine in oral hygiene in these patients [RR 0.69 (95% CI % = 0.46 - 1.03)]. Conclusion: despite the growing use of oral hygiene with chlorhexidine in the ICU, there is no scientific evidence that it provides greater benefit in reducing VAP and, therefore, a better evaluation of the benefit in its frequent use is recommended.

DESCRIPTORS: Chlorhexidine; Oral hygiene in ICU; Pneumonia Associated with mechanical ventilation; Pneumonia; Intensive care unit.

RESUMEN

Objetivos: identificar las diferentes formas de utilizar clorhexidina para la higiene bucal de los pacientes en un ambiente de UCI y cuál proporciona la mayor tasa de reducción de NAV. Métodos: se realizó una Revisión Sistemática, que tuvo como estrategia PICO, pacientes ingresados en UCI, sometidos a higiene bucal con clorhexidina, evaluando el resultado sobre la reducción de NAV. Resultados: la solución de clorhexidina al 0,12% es la más utilizada y generó un metaanálisis con 5 estudios que demostraron que no existe significación estadística en el uso de clorhexidina en la higiene bucal en estos pacientes [RR 0,69 (IC del 95% = 0,46 - 1,03)]. Conclusión: a pesar del creciente uso de la higiene bucal con clorhexidina en UCI, no existe evidencia científica de que aporte mayor beneficio en la reducción de la NAV y, por tanto, se recomienda una mejor valoración del beneficio en su uso frecuente.

DESCRIPTORES: Clorhexidina; Higiene bucal en UCI; Neumonía Asociada a la ventilación mecánica; Neumonía; Unidad de cuidados intensives.

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INTRODUCTION

During the patient's stay in the ICU, changes in the stomatognathic system are frequent, both originating from the maxillomandibular complex and with manifestations of systemic diseases, changes related to the use of medications or even related to the presence of equipment such as an artificial breathing tube. Associated with inadequate hygiene in hospitalized patients, these complications lead to infection of community or hospital origin, which is one of the main causes of mortality.

Other factors contribute to this risk, such as: breakdown of the natural barriers that separate the microorganism from the internal environment, invasion of the skin by catheters, drains, orotracheal tube and loss of the protective barrier of the glottis, urinary catheter, etc., the state of immunosuppression represented by the severity of the disease. [1]

Patients admitted to the ICU generally remain with their mouth open due to tracheal intubation, which allows dehydration of the oral mucosa and reduced salivary flow, which allows an increase in the lingual biofilm, causing, in addition to an unpleasant odor, colonization. [2]

Chlorhexidine is the most used compound for the control of oral biofilm, being considered the gold standard and is the most used for oral hygiene also in ICU patients.

The main objective of the systematic review was to identify the different ways of using chlorhexidine for oral hygiene of patients in the ICU environment and which one provides greater effectiveness and efficiency in reducing the rate of VAP. As specific objectives: to critically evaluate the research methodologies that study the use of chlorhexidine for oral hygiene as an antimicrobial agent in the ICU environment; determine which dose and frequency of use most effectively contribute to the reduction of VAP; identify the best course of action to reduce and control NAV.

In this article, we report the results of a systematic literature review on the use of chlorhexidine for oral hygiene in ICUs, considering the most used formulation and the result achieved in reducing the rate of VAP.

METHODS

A systematic review of the literature was carried out, guided by the recommendations of the Cochrane Collaboration and the Center for Review Dissemination (CRD), considering the similarities between the two. [3] The review protocol was registered with PROSPERO under registration number: CRD42019127930.

The acronym PICO was used to establish the research question, where the components are: P-participants; I- intervention; C- comparison or control; O- (results), which would be the clinical result.

For this, it was established that:

- P: patients admitted to the ICU on mechanical ventilation (MV);

- I: use of chlorhexidine digluconate for oral hygiene;

- OR: result of ventilator-associated pneumonia.

Thus, based on the acronym PICO, the following questions were established: What are the different ways of using chlorhexidine for oral hygiene in intensive care unit (ICU) environments? And, Which provides greater reduction in the NAV rate?

Studies could be in any language, between the years 2000 and 2019, published or from gray literature and ongoing clinical studies.

Thus, searches were carried out in 6 electronic databases: PubMed (Medline), Lilacs/Virtual Health Library (VHL), Scopus, Central, Clinical Trials and Wiley. The search started on April 29, 2019 and ended on May 5, 2019, from the training phase of DeCs and Mesh, to the search in selected databases. After searching the 6 databases, a total of 574 selected studies were obtained.

The descriptors of this research were constructed through a search on the Virtual Health Library (VHL) website in the specific query field by word or term, using writing in Portuguese and later in Spanish and also in English.

With the DeCS terms incorporated, in the three languages, the advanced search began, using the code "MH:" before the term, using quotation marks for terms with more than one word and parentheses for synonyms with two or more words, eliminating the comma when there is one.

In this construction, categories are also provided, which are what kind of science or subject the terms belong to. To search categories, the code "MH:" was used before the category and the code "$" after it. Among the terms, in each search line, the OR code was used between them.

At the time of the advanced search, to integrate the DeCS of each PICO proposal used, the Boolean AND operator was used. Thus, the search was developed according to PICO (ICU patients who received intervention with chlorhexidine to observe the reduction of nosocomial pneumonia), obtaining a complete and comprehensive strategy, as seen in chart 1.

The mesh was also searched in the PubMed database in the advanced search in the English language. For "P" the term intensive care units was used, for "I" the term chlorhexidine and for "O" pneumonia associated with mechanical ventilation, obtaining the strategy that can be seen in table 2.

After the search and selection of studies in the databases, the 574 articles were exported to the Rayyan QCRI program, which helps the researcher organize the search results on different platforms.

From this analysis, 127 were excluded, 16 were identified as non-duplicates, and 90 were discarded, leaving 341 studies for analysis.

Then, the title and abstract of each article were read and, based on the in-

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clusion/exclusion criteria, checking the correlation with the key question, the selection of those that would be included in the review began. This step was performed by two independent readers (reader A and reader B), in a blind and double-blind analysis, so that there was no interference in the selection. From these individual analyzes, 27 conflicts emerged, which generated the need to involve a third reader to correct cases of inconsistency between the articles examined by the two previous researchers, analyzing only cases of incompatibility/conflict. This resulted in the final inclusion of 64 articles for the study.

Each study was evaluated by its level of evidence and classified by the validity of the evidence on the interventions, according to their diagnostic, etiological, prognostic or therapeutic approach, being directly related to the research study model, for which the Level of Evidence Classification proposed by the Oxford Center for Evidence-Based Medicine, in a version adapted by Nobre. [4]

To facilitate the classification, the categories of Strong Evidence (Grade of Recommendation A), Moderate Evidence (Grade of Recommendation B), Weak Evidence (Grade of Recommendation B) were assigned. (Degree of Recommendation C) and Very Weak Evidence (Degree of Recommendation D), according to what was done by Santos. [5]

To perform the analysis of the quality of the selected studies, the Jadad Scale was used. The Jadad scale is a list of five questions that assesses three aspects of clinical trials: randomization, blinding and description of loss to follow-up, resulting in a score ranging from 0 to 5, studies with scores <= 3 being considered to have a high risk of bias. [6]

From these classifications and data extraction, it was also possible to arrive at candidate studies for a possible meta-analysis, based on randomization, control, population and intervention criteria. This extraction reached 5 studies, which were further classified by the practical implications of the therapeutic intervention, level of evidence, degree of recommendation and quality of the study.

In the studies selected for the meta-analysis, the GRADE - Grading of Recommendations Assessment, Development and Evaluation system was applied as a way to assess the quality of the evidence and the strength of the recommendation. [7]

The risk of bias in the papers selected for the meta-analysis was also classified as low, uncertain or high according to the criteria established by the Cochrane Collaboration tool, using the RevMan 5.4.1 software. [8]

The meta-analysis of the studies was performed using the RevMan 5.4.1 software, using the Mantel-Haenszel method and the random effects analysis model, measuring the effect through Relative Risk (RR) with a 95% confidence interval. Heterogeneity among studies included in the meta-analysis was measured by I2. For all analyses, a significance level of 5% was used.

Table 1: VHL research strategy .

MH:"Intensive Care Units" OR MH:"Unidades de Cuidados Intensivos" OR MH:"Unidades de Terapia Intensiva" OR (Centro de Terapia Intensiva) OR (Centros de Terapia Intensiva) OR (CTI) OR (Unidade de Terapia Intensive) OR (Unidade de Terapia Intensiva de Adulto) OR (Unidade de Terapia Intensiva Especializada) OR (Unidade de Terapia Intensiva do Tipo II) OR (UTI) OR (Care Unit Intensive) OR (Care Units Intensive) OR (Intensive Care Unit) OR (Unit Intensive Care) OR (Units, Intensive Care) OR (UCI) OR (Unidad de Cuidados Intensivos) OR (Unidad de Cuidados Intensivos) OR (Unidad de Terapia Intensiva) OR (Unidades de Terapia Intensiva) OR MH:N02.278.388.493$ OR MH:VS3.002.001.001.005$ AND MH:"Chlorhexidine" OR MH:"-Clorhexidina" OR MH:"Clorexidina" OR (Chlorhexidine Acetate) OR (Chlorhexidine Hydrochloride) OR MH:D02.078.370.141.100$ AND MH:"Oral Hygiene" OR "Higiene Bucal" OR "Higiene Bucal" OR (Higiene Dentária) OR MH:E02.547.600$ OR MH:E06.761.726$ AND MH:"Pneumonia Ventilator-Associated" OR "Neumonía Asociada al Ventilador" OR "Pneumonia Associada à Ventilação Mecânica" OR "Pneumonia" OR "Neumonía" OR "Respiration Artificial" OR "Respiración Artificial" OR "Respiração Artificial" OR (Pneumonia Associada ao Ventilador) OR (Pneumonia Associada ao uso de Ventiladores Pulmonares) a Respirador) OR (Pneumonia Associada a Respirador Mecânico) OR (Inflamação Experimental dos Pulmões) OR (Inflamação do Pulmão) OR (Pneumonia Lobar) OR (Pneumonite) OR (Inflamação Pulmonar) OR (Pulmonia) OR (Inflamación Experimental del Pulmón) OR (Inflamación del Pulmón) OR (Neumonía Lobar) OR (Neumonitis) OR (Inflamación Pulmonar) OR (Ventilación Mecánica) OR (Experimental Lung Inflammations) OR (Inflammation Experimental Lung) OR (Inflammation Lung) OR (Inflammation Pulmonary) OR (Inflammations Lung) OR (Inflammations Pulmonary) OR (Lobar Pneumonias) OR (Lung Inflammation Experimental) OR (Lung Inflammations) OR (Lung Inflammations Experimental) OR (Pneumonias) OR (Pneumonias Lobar) OR (Pneumonitides) OR (Pulmonary Inflammations) OR (Experimental Lung Inflammation) OR (Lobar Pneumonia) OR (Lung Inflammation) OR (Pneumonitis) OR (Pulmonary Inflammation) MH:C01.539.248.500$ OR MH:C08.381.520.750.750$ OR MH:C08.381.677.800$ OR MH:C08.730.610.750$ OR MH:C08.381.677$ OR MH:C08.730.610$ OR MH:E02.041.625$ OR MH:E02.365.647.729$ OR MH:E02.880.820$

Source: prepared by the author.

Table 1: PubMed research strategy .

((("Intensive Care Units"[Mesh])) OR "Intensive Care Units, Pediatric"[Mesh]) OR "Intensive Care Units, Neonatal"[Mesh] AND "chlorhexidine"[MeSH Terms] OR chlorhexidine [Text Word] AND ("pneumonia"[MeSH Terms] OR pneumonia [Text Word]) AND ("ventilators, mechanical"[MeSH Terms] OR ventilator [Text Word]) AND associated [All Fields]

Source: prepared by the author.

RESULTS

The complete selection of studies can be seen in Figure 1.

The most used chlorhexidine concentration, with 44.06% of the studies [(26)], is 0.12%; followed by a concentration of

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0.2%, with 20.33% [12]; 2% chlorhexidine in 8.47% [8] of the studies; Chlorhexidine 1% in 3.38% [3] and 1.69% with concentrations of 0.5% [1] and 0.1% [1] each.

Regarding the use of chlorhexidine in the different selected studies, 45.76% [27] used it in the form of a liquid rinse solution or swab and 22.03% [13] in the form of a gel. It did not specify the concentration and/or wording used, which totaled 30.50% [18] and those that were not included because 1 was editorial and 1 could not be translated from Persian (3.38%).

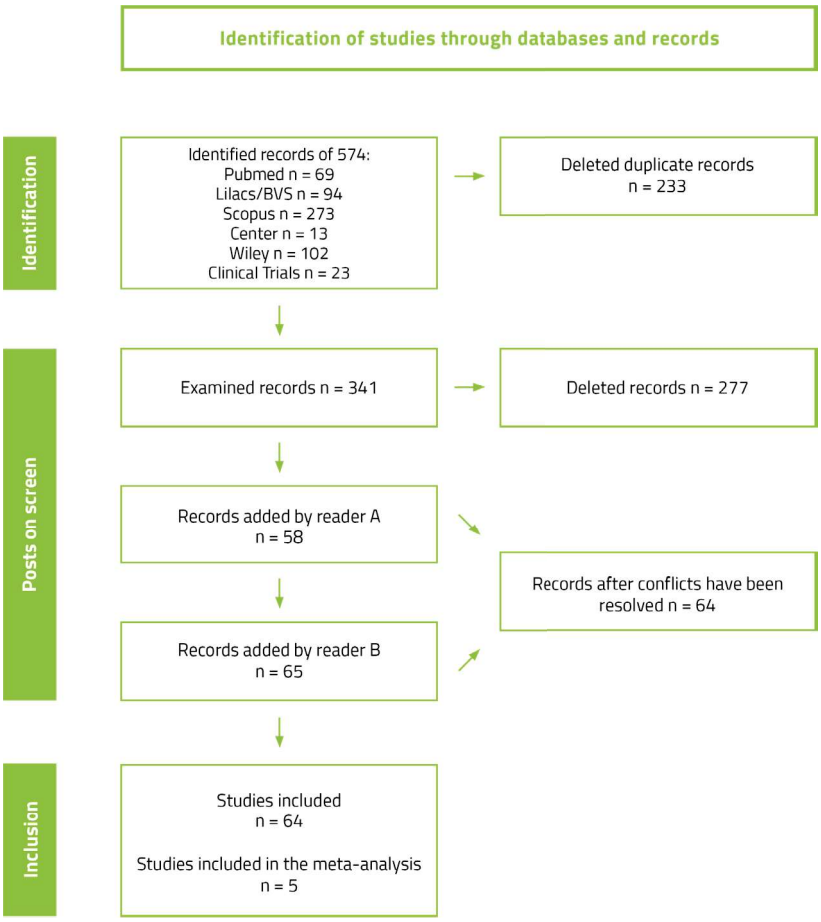
Indicating the level of evidence, the degree of recommendation and classification according to the Jadad scale, as well as the result obtained and the conclusions of the researchers, it is possible to have a quality analysis of each one regarding its methodology and possible selection for meta-analysis that was carried out and 5 studies were classified with grade of recommendation A and 3 points or more on the Jadad scale, which presupposes their quality and relevance.

These studies were loaded into RevMan5.4.1, so that the GRADE (Grading of Recommendations Assessment, Development and Evaluation) could be built, thus achieving an assessment of the risks of bias in each study and, thus, having evidence of its quality in a general panorama, as shown in graph 1.

The analysis of the effects of each study, using the RevMan5.4.1 program, allowed the construction of the Relative Risk (RR). The process of grouping the effect observed during the evaluation of the eligible studies selected for the meta-analysis was carried out by extracting the dichotomous outcome measure linked to the population of interest (intervention group = CHX; control group = placebo) by the number of participants who had the VAP result.

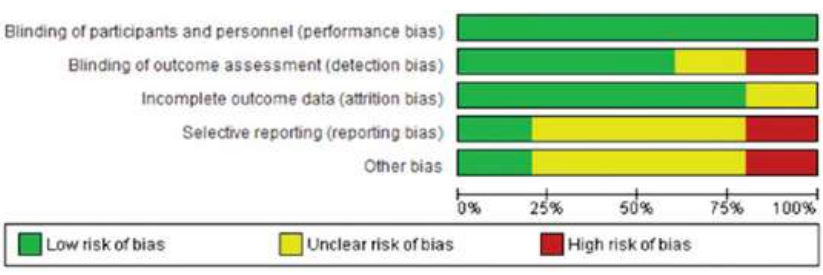
Figure 2 shows the Forest plot graph showing the total number of participants who had the VAP result where the relative risk (RR) corresponding to each study can be observed and combined at the end, as well as its confidence interval (CI), which is defined as 95% (95% CI), that is, means that if the study is repeated infinitely and in each case a CI calculated at 95%, then there is a 95% probability that your result will be inserted in

Figure 1: Flow diagram of articles obtained by searching the databases and adopting the inclusion and exclusion criteria.



Source: prepared by the author.

Gráfico 1:Riesgo de sesgo según el juicio de los jueces de la metodología de cada estudio eccionado para el metaanálisis.



Fuente: elaborado por el autor em programa RevMan 5.4.1.

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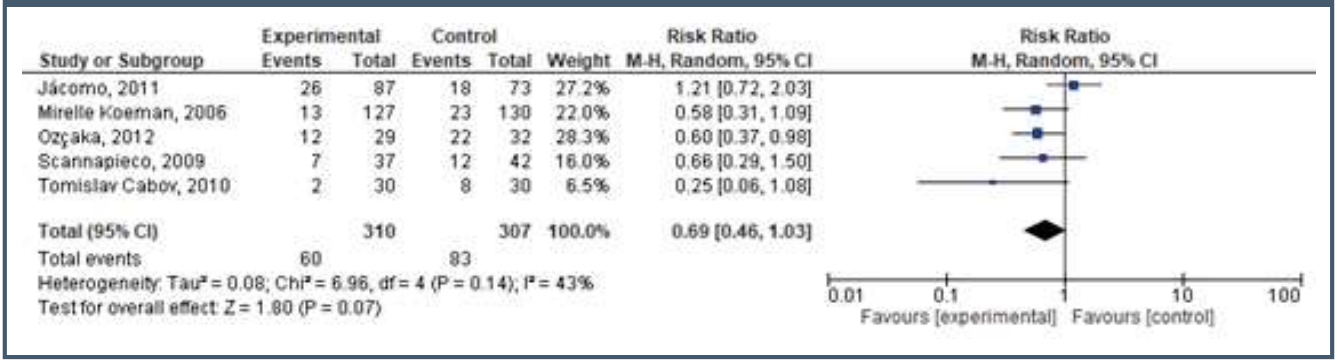
Figura 2: Diagrama de bosque de comparação Risco relativo: Clorhexidina versus placebo, resultado: VAP[10,11,12,13,14].



Fonte: Elaborado pelo autor em programa RevMan 5.4.1

the values established by the CI.

In the graph of figure 2, the Q test that presented a p value = 0.15 from which the null hypothesis of homogeneity cannot be rejected (p> 0.05), that is, there is no evidence to affirm that the studies are heterogeneous, with heterogeneity attributed to 43%, considered moderate (I2 between 30 and 60%), however, the random effects model was chosen, considering the different realities in which the different studies are inserted and taking into account the different concentrations of CHX evaluated.

Regarding the 95% CI of each study, when the horizontal line touches or crosses the vertical line of the graph (RR = 1), indicates that there is no statistical difference between the groups in relation to the risk-benefit of the treatment, and only the study by Ozçaka (2012) did not demonstrate this behavior. The other studies, considering that the horizontal line crosses the vertical line of the graph (RR = 1), are considered without statistical significance, despite being located on the left side of the graph.

The size of the central point on each horizontal line that represents the 95% CI interval, refers to the weight that each study had in the final result, based on the number of participants in each group.

The dark diamond (diamond) located at the bottom of the graph is the final result of combining the studies (meta-analysis), in which the central point represents the 95% CI. For the meta-analysis carried out in the present study, the final RR value of the study composition was 0.69 (95% CI = 0.46 - 1.03), which means that the probability of outcome (NAV) with the use of chlorhexidine is 1.44 times lower with the use of chlorhexidine compared with the non-use. The 95% CI does not include 1. Thus, it can be seen that the diamond in this diagram in Figure 2 touches the vertical line and, therefore, the statistical difference between the evaluated groups regarding the incidence of the result is no longer statistically significant.

DISCUSSION

In this systematic review, it became clear that more and more researchers and ICU services have been concerned with the patient's oral hygiene and, as can be seen, have tried to include this action in the so-called care packages, highlighting the 22 studies that showed interest in having or experimenting with a protocol that includes oral hygiene performed by the intensive care team, with or without the supervision of a dentist.

Studies have shown a relationship between poor oral hygiene, periodontal disease and nosocomial infections in ICU patients, since the presence of dental biofilm and a compromised periodontium serve as potential reservoirs of microorganisms responsible for causing infections, including NAV.[9]

The most common formulation was in solution, with 27 studies (45.76%), which can be evidenced by the ease of application and less impact on the oral cavity, because of the 13 studies that used chlorhexidine gel, after application there was no need to remove the excess.

The most common concentration was 0.12%, present in 26 analyzed studies, including those that used both solution and gel.

The action of chlorhexidine on the biofilm is due to its adsorption on the dental surface, which hinders its formation. If the concentration of chlorhexidine is low, it causes damage to the bacterial cell membrane, however, if a high concentration is used, it leads to precipitation and coagulation of proteins in the bacterial cytoplasm. [10]

VAP is associated with a longer length of stay for patients admitted to the ICU, in addition to increasing the risk of morbidity and mortality. [11] In this investigation, they included 14 randomized clinical trials (12 investigating the effect of CHX and two, povidone-iodine), and the results indicated that the application of CHX proved to be very effective [RR 0.72; 95% CI (0 to 55-094); p = 0.02].

Through the Jadad Scale, one can analyze the quality of the study and its methodology, obtaining a graduation of the study that ultimately determines

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the quality of its evidence. In this observation, we can say that, of the 39 studies with all eligible data, 7 of them (20.51%) were classified with a score > = 3, which is the score attributed to a quality study, the other 31 studies (79.48 %), scored <3, ranging from -2 to 2, which classifies them as lower quality.

The strengths of this systematic review are the comprehensive search strategy and assessment of the methodological quality of the included studies. Excluded studies are not suitable for meta-analysis due to variations in methodologies, including heterogeneity in patient populations, outcomes, and assessment methods.

To a greater or lesser extent, according to the studies included in the review, it seems fair to conclude that CHX has a beneficial effect in the management of VAP in mechanically ventilated patients. However, studies varied in terms of CHX concentration and frequency, sample design, and outcome measures. These variations were responsible for the choice of a random model in the construction of the Relative Risk (RR), because in the fixed effects model, what contributes to the variability (95% CI) of the combined result is that the internal variability is ignored within each study (within the errors of the study) and the variability between studies (between studies ≈ heterogeneity).

Bescos (2020), investigated the effect of using chlorhexidine mouthwash for 7 days on the salivary microbiome, as well as various saliva and plasma biomarkers in 36 healthy subjects, reporting that CHX disrupts the ability of oral bacteria to reduce nitrate from oral bacteria to nitrite, which may support lower circulatory bioavailability of nitrite and increased blood pressure, suggesting that the oral microbiome may regulate cardiovascular health in healthy individuals and hypertensive patients. [12]

The vasodilator effects of nitrite have been well described in previous studies using intra-arterial infusions or dietary supplements with this anion. [13]

Taking into account what was said above, it is considered that it is possible to question the use of chlorhexidine as the substance of choice, in general, in oral hygiene protocols in patients admitted to the ICU who present these characteristics and, even more recently, it could have a significant impact on ICU actions for the care of patients infected with COVID-19 (SARS-COV-2).

CONCLUSION

The systematic review carried out was able to answer the proposed questions and determined objectives. It is also possible to observe the indication of oral hygiene in hospitalized patients, through the inclusion of items in sets of procedures, which, although they vary in some items, include the frequency of cleaning, including more chlorhexidine as a selection support.

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