

Review Article

Oral hygiene with chlorhexidine in preventing pneumonia associated with mechanical ventilation*

Higiene bucal com clorexidina na prevenção de pneumonia associada à ventilação mecânica

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Abstract

Ventilator-associated pneumonia (VAP) is a common infection in intensive care units (ICUs), and oral antiseptic is used as a preventive measure. We reviewed meta-analyses and randomized clinical trials indexed in the Medical Literature Analysis and Retrieval System and Cumulative Index to Nursing and Allied Health Literature databases regarding the topical use of chlorhexidine in the prevention of VAP. Eight publications were analyzed. In seven (87.5%) chlorhexidine diminished the colonization of the oropharynx, and in four (50%) there was a reduction of VAP. Chlorhexidine seems to reduce colonization, thus reducing the incidence of VAP.

Keywords: Pneumonia, ventilator-associated; Oral hygiene; Chlorhexidine.

Resumo

A pneumonia associada à ventilação mecânica (PAVM) é uma infecção freqüente nas unidades de terapia intensiva (UTI), e anti-sépticos bucais são utilizados preventivamente. Revisamos metanálises e ensaios clínicos randomizados indexados no *Medical Literature Analysis and Retrieval System* e *Cumulative Index to Nursing and Allied Health Literature* sobre o uso tópico da clorexidina na prevenção da PAVM. Oito publicações foram avaliadas. Em sete (87,5%), a clorexidina diminuiu a colonização da orofaringe, e em quatro (50%) houve redução de PAVM. A clorexidina parece diminuir a colonização, podendo reduzir a incidência da PAVM.

Descritores: Pneumonia associada à ventilação mecânica; Higiene bucal; Clorexidina.

Introduction

Ventilator-associated pneumonia (VAP) is defined as that developing in the period from 48 h after initiation of mechanical ventilation to 48 h after extubation. It is one of the most common cross infections in intensive care units (ICUs), with rates that range from 9 to 40% of the infections acquired in these units, and is associated with an increase in length of hospitalization and in morbidity and mortality rates, which significantly affects costs.⁽¹⁻³⁾

The aspiration of microorganisms present in the oropharynx constitutes the most common means of acquiring the disease, and the principal risk factors are

those that favor the colonization of the oropharynx or the stomach, the aspiration of secretions into the lower respiratory tract or reflux of the gastrointestinal tract, and factors inherent in the host.^(2,4,5)

The bacterial agent found will depend on length of hospital stay, use of antimicrobial agents, host susceptibility, and ICU microbiota. Gram-negative bacilli (*Pseudomonas aeruginosa*, *Proteus* spp., *Acinetobacter* spp.) and *Staphylococcus aureus* are frequently isolated.^(6,7)

Considering that the microbiota of the oral cavity represents a threat to critical patients,^(2,4,8-12) some strate-

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gies to prevent colonization, such as administration of nonabsorbable topical antibiotics, have been studied. However, prolonged use of prophylactic antibiotics increases the risk of the induction and selection of resistant microorganisms and has therefore not been recommended.⁽¹⁾

The use of antiseptics in oral hygiene has also been the object of investigation.^(6,9-13) Among the products used is chlorhexidine, an antimicrobial agent with a broad spectrum of activity against gram-positive bacilli, including oxacillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* sp., and lower efficacy against gram-negative bacilli. It is absorbed by the tissues and has a residual effect over time, presenting activity even 5 h after administration.^(14,15)

Various aspects affect oral cavity hygiene and further favor microbial growth, such as difficulty in or impossibility of self-care, presence of tracheal tube, which makes access to the oral cavity difficult, and the consequent formation of dental plaque biofilm.^(10-12,16) The Centers for Disease Control and Prevention (CDC) recommends oral hygiene with chlorhexidine in patients in the perioperative period of cardiac surgery. However, regarding medical-surgical ICU patients, the theme is considered an unresolved question.⁽¹⁾

In view of these facts, we have sought theoretical references on which to base this study in evidence-based practice, since it makes it possible to systematically use the best scientific evidence available to evaluate options and make decisions regarding the holistic care of the patient.^(17,18)

In this sense, our objective was to critically analyze the evidence available on the topical use of chlorhexidine in the oral hygiene of adult ICU patients for the prevention of VAP.

Methods

We made an integrative review of the literature, which makes it possible to summarize previous studies and draw conclusions based on the design of the studies evaluated, allowing the synthesis and analysis of scientific knowledge on the theme investigated.⁽¹⁹⁾ Therefore, the steps taken were as follows: problem identification; sample selection; definition of the information to be extracted from the articles selected; analysis; presentation of and

discussion on the results; as well as presentation of the review.⁽¹⁹⁻²¹⁾

The following question was posed in order to guide the review: What is the scientific evidence on the topical use of chlorhexidine in the oral hygiene of adult ICU patients for the prevention of VAP?

The articles were selected using two major health care databases, accessed via the Internet: the Medical Literature Analysis and Retrieval System (Medline) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The following keywords, which are included in the Medical Subject Headings, were used in the search: pneumonia, ventilator-associated; oral hygiene; chlorhexidine; cross infection/prevention and control; critical care; and intensive care. In addition, a search was carried out in the references cited in the articles selected using the databases.

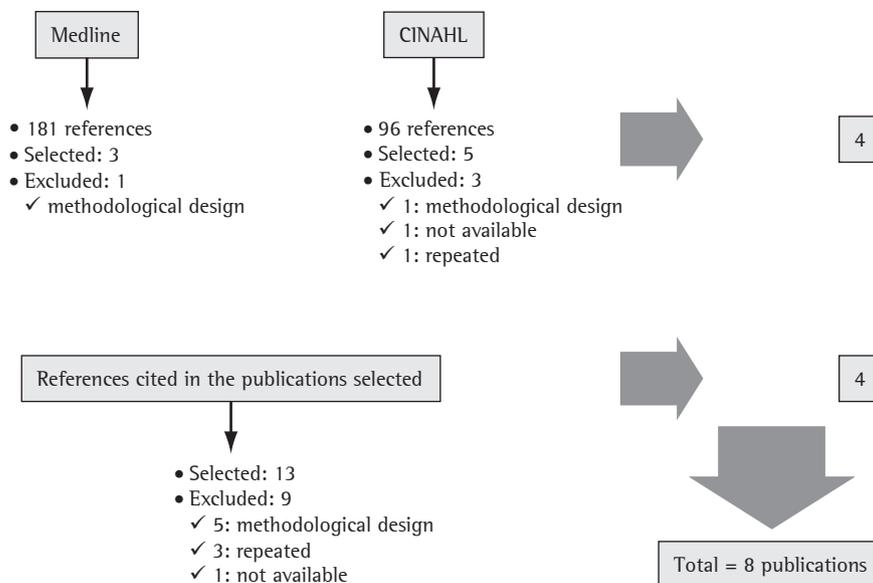
The inclusion criteria were as follows: full text being available; having addressed the topical use of chlorhexidine in the oral hygiene of adult ICU patients for the prevention of VAP; having been published in English, Spanish, or Portuguese between January of 1998 and August of 2007; and having been classified as level of evidence I and II, according to the classification system devised by Stetler et al.⁽²²⁾

It is important to emphasize that the aforementioned classification of scientific evidence is based on the study design, level I consisting of evidence from meta-analysis of multiple controlled studies, and level II comprising individual experimental studies.

In order to select the studies, each title and abstract were carefully read to determine whether they responded to the guide question. Furthermore, information about characteristics and methodological rigor, intervention studied, and main results were extracted. The extracted data were analyzed descriptively.

Results and discussion

In the search for evidence, 181 references were found in Medline, and 96 were found in CINAHL. These references were analyzed regarding the inclusion criteria, and 4 publications were selected. In those 4 publications, there were 13 articles listed in the reference lists, and, after being carefully read, 4 of the papers cited were included in the selection



Medline: Medical Literature Analysis and Retrieval System; and CINAHL: Cumulative Index to Nursing and Allied Health Literature.

Figure 1 - Selection of publications on the topical use of chlorhexidine in the prevention of ventilator-associated pneumonia (1998-2007), Ribeirão Preto, 2007.

of this review, the final sample therefore consisting of 8 publications (Figure 1).

Of the 8 articles on the use of chlorhexidine in the prevention of VAP, 5 (62.5%) were randomized controlled clinical trials (RCTs - level of evidence II), and 3 (37.5%) were meta-analyses (level of evidence I), all of them written in English and published between 2000 and 2007. Four (50%) of the studies were carried out in the United States, 2 (25%) were carried out in France, and the 2 remaining studies were carried out in Canada and in the Netherlands.

Chart 1 presents a synopsis of the critical analysis of the RCTs evaluated.^(13,16,23-25)

Regarding the methodological design, 2 (40%) of the 5 RCTs were double-blind, 1 (20%) was single-blind, and 2 (40%) were not blind. In addition, 4 (80%) involved patients admitted to medical-surgical ICUs, and 1 (20%) involved patients submitted to cardiac surgery. It is worthy of note that, in all of the studies evaluated, chlorhexidine was administered periodically, using a standard technique, during the period in which the patient remained on mechanical ventilation. However, in the study that evaluated patients in the perioperative period of

cardiac surgery,⁽²³⁾ the intervention was also administered in the preoperative period, that is, prior to orotracheal intubation, a procedure that was not performed in the remaining studies, in which non-elective intubation was performed.

Regarding the intervention administered, chlorhexidine was used at a concentration of 0.12% in 2 studies (40%), at a concentration of 0.2% in 2 studies (40%), and at a concentration of 2% in 1 study (20%). Koeman et al.⁽¹³⁾ evaluated two types of intervention: 2% chlorhexidine (group 1) and 2% chlorhexidine combined with colistin (group 2), which is an antibiotic polymyxin that is highly effective against gram-positive and gram-negative bacteria and has been topically administered with few reports of the induction of microbial resistance. The authors explain that the combination of these two substances provided better results against gram-negative bacteria, although both interventions had beneficial effects for the prevention of VAP.

Considering the control groups of the RCTs included, placebos, presenting characteristics similar to chlorhexidine in terms of presentation, color, odor, and taste, were used in 2 (40%) of the publications. In one study,⁽²³⁾ Listerine[®], which is a nonabsorbable

Chart 1 – Synopsis of the randomized controlled clinical trials (level of evidence II) regarding the use of chlorhexidine in the prevention of ventilator-associated pneumonia by authorship, objectives, method, population, intervention/control, main results, and complementary observations (1998 to 2007), Ribeirão Preto, 2007.

Authorship	Objective	Method	Population	Intervention	Control	Results	Observations
Fourrier et al., 2000 ⁽¹⁶⁾	To document the effect of decontamination of the oral cavity on the colonization of the dental plaque and the occurrence of CI in patients on MV.	Single-blind RCT	Medical-surgical ICU	0.2% chlorhexidine	Usual care (isotonic solution of bicarbonate)	<ul style="list-style-type: none"> higher overall rate of CI in controls (p = 0.018) higher ID of VAP in controls, with a 53% risk reduction (p < 0.05) higher frequency of positive dental plaque cultures in controls (days 5-7; p < 0.05) 	<ul style="list-style-type: none"> calculation of the sample not described standard measures for the prevention of VAP taken in both groups not described
Houston et al., 2002 ⁽²³⁾	To evaluate the efficacy of the oral use of 0.12% chlorhexidine in reducing the colonization of the respiratory tract and the incidence of nosocomial pneumonia in patients submitted to cardiac surgery.	RCT	Perioperative period of cardiac surgery	0.12% chlorhexidine	Listerine®	<ul style="list-style-type: none"> 58% lower rate of pneumonia in the experimental group (intubation > 24 h; p = 0.06) higher frequency of positive secretion cultures in the experimental group (NS) 	<ul style="list-style-type: none"> age bracket not described standard measures for the prevention of VAP not described low statistical power (66%)
Grap et al., 2004 ⁽²⁴⁾	To describe the effect of administration of a single dose of chlorhexidine in the oral cavity immediately after intubation on the oral microbiota and the incidence of VAP.	RCT	Medical-surgical ICU	0.12% chlorhexidine	Usual care	<ul style="list-style-type: none"> increase in diagnostic score for VAP greater in controls (from 4.7 at admission to 6.6 after 48 h) than in the experimental group (from 5.17 to 5.57) (NS) higher frequency of negative oropharyngeal cultures in the experimental group (NS) 	<ul style="list-style-type: none"> usual care performed in controls not described small sample (n = 34) diagnosis of VAP with score calculation of the sample not described
Fourrier et al., 2005 ⁽²⁵⁾	To document the effect of decontamination of the dental plaque and oral cavity with chlorhexidine on the incidence of nosocomial bacteremia and ICU-acquired respiratory infections.	Double-blind RCT	Medical-surgical ICU	0.2% chlorhexidine	Placebo	<ul style="list-style-type: none"> incidence of VAP, bacteremia, or bronchitis similar in both groups higher frequency of <i>Candida albicans</i> in the dental plaque of controls (p < 0.05) samples of dental plaque of controls remained positive longer (p < 0.05) 	<ul style="list-style-type: none"> no complementary observations
Koeman et al., 2006 ⁽¹³⁾	To determine the effect of decontamination of the oral cavity with chlorhexidine or chlorhexidine combined with colistin on the incidence of VAP.	Double-blind RCT	Medical-surgical ICU	2% chlorhexidine (1) and chlorhexidine + colistin (2)	Placebo	<ul style="list-style-type: none"> 65% lower risk of VAP in group 1 (p = 0.012) and 55% lower risk in group 2 (p = 0.03) than in controls lower colonization of the oral cavity in groups 1 and 2 (p < 0.001) 	<ul style="list-style-type: none"> length of the follow-up period not mentioned

CI: cross infection; MV: mechanical ventilation; RCT: randomized controlled clinical trial; ICU: intensive care unit; ID: incidence density; VAP: ventilator-associated pneumonia; and NS: not significant.

phenolic antiseptic agent and, therefore, has no residual effect like that of chlorhexidine, was used for comparison. However, 2 (40%) of the publications mentioned usual care as a control: in one study, the usual care employed was not described⁽²⁴⁾; and, in the other, an isotonic solution of sodium bicarbonate was used to rinse the oral cavity.⁽¹⁶⁾

Analyzing the results obtained, it was observed that, in 3 (60%) of the RCTs, the topical use of chlorhexidine in the oral hygiene of adult patients on mechanical ventilation reduced the incidence of VAP, with statistically significant results.^(13,16,23) Although Grap et al.⁽²⁴⁾ found no differences between the experimental and the control groups in terms of incidence of VAP, they considered their study sample small (34 subjects). It should be noted that, in that study, the diagnosis of VAP was determined by a score, based only on clinical and X-ray findings,

and did not consider the analysis of fluid cultures performed by standard methods (tracheal aspirate, bronchoalveolar lavage, and protected lavage) or blood culture for laboratory confirmation, which might have resulted in an over- or underestimation of the number of cases of infection listed.

Despite conducting a double-blind RCT that was well delineated in terms of methodology, Fourier et al.⁽²⁵⁾ attributed the absence of statistically significant results to the low incidence of VAP registered in the experimental and in the control groups, which implies an underestimated sample (insufficient to obtain statistically significant results).

Regarding the colonization of the oral cavity or dental plaque, 4 (80%) of the studies demonstrated that the use of chlorhexidine reduced the incidence of colonization in relation to that found in the control group. In only one study,⁽²³⁾ the number of

Chart 2 – Synopsis of the meta-analyses (level of evidence I) regarding the use of chlorhexidine in the prevention of ventilator-associated pneumonia by authorship, objectives, method, population, intervention/control, main results, and complementary observations (1998 to 2007), Ribeirão Preto, 2007.

Authorship	Objective	Studies included (n)	Results	Recommendations	Observations
Pineda et al., 2006 ⁽²⁶⁾	To evaluate the effect of oral administration of chlorhexidine on the incidence of VAP.	4	<ul style="list-style-type: none"> no statistically significant differences between controls and the experimental group in terms of incidence of VAP (random effect model) 	<ul style="list-style-type: none"> oral hygiene with chlorhexidine combined with other preventive measures recommended (oral hygiene with chlorhexidine in isolation does not prevent VAP) 	<ul style="list-style-type: none"> preoperative period of cardiac surgery versus medical surgical ICU use of different concentrations of chlorhexidine
Chan et al., 2007 ⁽²⁷⁾	To evaluate the effect of decontamination of the oral cavity with topical antibiotics or antiseptics on the incidence of VAP.	11	<ul style="list-style-type: none"> 44% reduction in the incidence of VAP in the experimental group/ antiseptics (random effect model; p = 0.002) decontamination of the oral cavity favored by combined meta-analysis of the articles (p < 0.001) 	<ul style="list-style-type: none"> prophylactic hygiene of the oral cavity with antiseptics recommended 	<ul style="list-style-type: none"> studies showing moderate heterogeneity
Chlebicki & Safdar, 2007 ⁽²⁸⁾	To evaluate the efficacy of the topical use of chlorhexidine in the prevention of VAP.	7	<ul style="list-style-type: none"> 30% reduction in the risk of acquiring VAP in the experimental group (random effect model; NS) 	<ul style="list-style-type: none"> use of chlorhexidine in the prevention of VAP in patients on mechanical ventilation recommended 	<ul style="list-style-type: none"> studies showing moderate heterogeneity

VAP: ventilator-associated pneumonia; ICU: intensive care unit; and NS: not significant. CINAHL: *Cumulative Index to Nursing and Allied Health Literature*.

positive cultures was greater in the experimental group, although the difference did not reach statistical significance.

Chart 2 presents a synopsis of the critical analysis of the meta-analyses evaluated.⁽²⁶⁻²⁸⁾

In the meta-analyses evaluated, differences were found in terms of the methods employed in the search for articles, inclusion/exclusion criteria, and objectives of the authors. However, there was concordance in the inclusion of some studies, which were also analyzed in the present review.

Pineda et al.⁽²⁶⁾ selected RCTs using various electronic databases, including Medline, Biosis Previews, PubMed, *Excerpta Medica*, and the Cochrane Library. Their objective was to analyze the effect of the use of chlorhexidine on the incidence of VAP, and the studies that combined mechanical removal and pharmacological treatment in the prevention of dental plaque formation were excluded. A total of 4 articles were analyzed, 2 of which involved patients who used 0.12% chlorhexidine in the preoperative period of cardiac surgery^(23,29) and 2 of which involved medical-surgical ICU patients who used 0.2% chlorhexidine.^(16,25) The differences between the target populations and the concentrations of chlorhexidine used made it difficult to compare the data.

The study conducted by Chan et al.⁽²⁷⁾ evaluated the efficacy of the use of antiseptics and antimicrobial agents in the prevention of VAP. Eleven RCTs, returned by a Medline, *Excerpta Medica* database, CINAHL, and Cochrane Library search, were analyzed. Four of those articles were related to the topical use of antimicrobial agents, and 7 were related to the use of oral antiseptics. Of those 7, 3 were discussed and analyzed in this review,^(13,16,25) 2 were unpublished studies, and 2 did not meet the inclusion criteria of our study (use of polyvinylpyrrolidone-iodine and year of publication prior to 1998). The results indicate that decontamination of the oral cavity reduced the incidence of VAP. However, the isolated analysis of the studies that used topical antimicrobial agents revealed no statistical significance in favor of the treatment. The use of oral antiseptics, in contrast, presented significant results, although discrepancies among the studies compared, such as different target populations, concentrations, and techniques of antiseptic use, should be pointed out.

Chlebicki and Safdar⁽²⁸⁾ analyzed 7 RCTs selected using PubMed, Medline, Current Contents, CINAHL, Database of Abstracts of Reviews of Effectiveness, and the Cochrane Library. Of those, 5 were the RCTs included in our study,^(13,16,23-25) and the remaining 2 were an unpublished article and an article published before 1998, which is outside the time period established the inclusion criteria of the present review. Due to the heterogeneity of the studies, no statistical significance was found, even though the use of chlorhexidine resulted in a 30% reduction in the relative risk of acquiring VAP.

Only one study⁽²⁶⁾ found statistically significant results favoring the use of chlorhexidine in the prevention of VAP. However, the 3 publications recommend that oral hygiene with chlorhexidine be performed as a preventive measure against VAP, although suggestions regarding concentrations, forms of presentation (gel, liquid, or paste), frequency, and administration techniques are not considered, due to the heterogeneity found in relation to these topics.

As previously mentioned, the CDC considers the use of chlorhexidine in the prevention of VAP in patients submitted to cardiac surgery as level of evidence II. The CDC recommendations are based on the following levels of evidence: IA, strongly recommended for implementation and based on good experimental, clinical, or epidemiological studies; IB, strongly recommended for implementation and based on some experimental, clinical, or epidemiological studies, as well as on strong theoretical models; IC, rules or standardizations of the federal regulations of the United States; II, suggested for implementation and based on suggestive clinical or epidemiological trials or on theoretical models; and unresolved question, when, according to the CDC, there is not enough evidence on which to base the recommendation.⁽¹⁾

Therefore, for level II, the measure is only suggested for implementation rather than being strongly recommended. Specifically in this case, this suggestion was based on only one double-blind RCT.⁽²⁹⁾

In Brazil, the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) recommends decontamination of the oral cavity with chlorhexidine, or with chlorhexidine combined with colistin, in the prevention of VAP in patients on mechanical ventilation.⁽³⁰⁾ This is a recommen-

dition with level of evidence B, that is, based on a limited database, which includes experimental studies and meta-analyses. However, the aforementioned recommendation is used when the number of studies is small, with a reduced sample, an inadequate population, or inconsistent data. The SBPT recommendation was based on 3 RCTs.^(13,16,29)

Although their level of evidence is not considered strong, the CDC and the SBPT recommendations on the use of chlorhexidine support a practice that is already routinely performed at some health care facilities. This review revealed that there is more evidence available to reinforce these recommendations and guide clinical practice.

Conclusion

In summary, of the 8 articles included in the present review, 3 RCTs and 2 meta-analyses (50% of the total sample) favored the use of chlorhexidine as a preventive measure against VAP. Regarding the colonization of the oral cavity, 4 (80%) of the 5 RCTs revealed preventive effects of chlorhexidine.

Based on the studies analyzed, we conclude that the topical use of chlorhexidine in the oral hygiene of patients on mechanical ventilation seems to reduce the colonization of the oral cavity, thereby reducing the incidence of VAP. In addition, this procedure is safe and quite tolerable, since no side effects were found in any of the studies. Furthermore, taking into account the increase in hospitalization costs caused by an episode of cross infection, it can be considered a low-cost measure.

However, further investigations are necessary to determine the ideal concentration, as well as the most suitable form of presentation, frequency, and administration technique.

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