Evidence on the best chlorhexidine concentration to perform oral hygiene: meta-analysis

Evidências sobre a melhor concentração de clorexidina para higiene bucal: metanálise

Juliana Rizzo Gnatta*
Isa Rodrigues da Silveira**
Rúbia Aparecida Lacerda***
Maria Clara Padoveze****

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Abstract

Although scientific literature has demonstrated the relevance of oral hygiene with chlorhexidine in preventing ventilation-associated pneumonia, there is a wide variation of concentrations, frequency and techniques when using the antiseptic. The aim of this research was to assess the best chlorhexidine concentration used to perform oral hygiene to prevent ventilation-associated pneumonia. A systematic review followed by four meta-analysis using chlorhexidine concentration as criterion was carried out. Articles in English, Spanish or Portuguese indexed in the Cochrane, Embase, Lilacs, PubMed/Medline and Ovid electronic databases were selected. The research was carried out from May to June 2011. The primary outcome measure of interest was ventilation-associated pneumonia. Ten primary studies were divided in four groups (G1-4), based on chlorhexidine concentration criterion. G1 (5 primary studies, chlorhexidine 0.12%) showed homogeneity among studies and the use of chlorhexidine represented a protective factor. G2 (3 primary studies, chlorhexidine 0.20%) showed heterogeneity among studies and chlorhexidine did not represent a protective factor. G3 (2 primary studies, chlorhexidine 2,00%) showed homogeneity among studies and the use of chlorhexidine was significant. G4 (10 primary studies with different chlorhexidine concentrations) showed homogeneity among studies and the common Relative Risk was significant. Statistic analyses showed a protective effect of oral hygiene with chlorhexidine in preventing ventilation-associated pneumonia. However, it was not possible to identify a standard to establish optimal chlorhexidine concentration.

Keywords: Oral Hygiene. Chlorhexidine. Pneumonia. Infection Control. Nursing.

Resumo

Embora a literatura científica tenha demonstrado a importância da higiene bucal com clorexidina na prevenção de pneumonia associada à ventilação, existe uma grande variação das concentrações, frequência e técnica de aplicação do antisséptico. O objetivo desta pesquisa foi avaliar a melhor concentração de clorexidina usada para realizar a higiene bucal na prevenção de pneumonia associada à ventilação mecânica. Foi realizada uma revisão sistemática seguida de quatro meta-análises usando como critério a concentração de clorexidina. Foram selecionados artigos em Inglês, Espanhol ou Português indexados nas bases de dados eletrônicas: Cochrane, Embase, Lilacs, PubMed / Medline e Ovid. A pesquisa foi realizada no período de maio a junho de 2011. O desfecho primário de interesse foi a pneumonia associada à ventilação mecânica. Dez estudos primários foram divididos em 4 grupos (G1-4), com base no critério de concentração de clorexidina. G1 (5 estudos primários, clorexidina 0,12%) apresentaram homogeneidade e o uso de clorexidina demonstrou efeito protetor; G2 (3 estudos primários, clorexidina 0,20%) houve heterogeneidade entre os estudos e clorexidina não representou um fator de proteção; G3 (2 estudos primários, clorexidina 2,00%) homogeneidade entre os estudos e a utilização de clorexidina foi significativa; G4 (10 estudos preliminares com diferentes concentrações de clorexidina) homogeneidade entre os estudos e o Risco Relativo comum foi significativo. A análise estatística mostrou um efeito protetor da higiene bucal com clorexidina na prevenção de pneumonia associada à ventilação mecânica. No entanto, não foi possível identificar um padrão para estabelecer a concentração ideal de clorexidina para realização de higiene bucal.

Palavras-chave: Higiene Bucal. Clorexidina. Pneumonia. Controle de Infecções. Enfermagem.

* PhD Student in Health Science. Surgical Nurse at University Hospital at University of São Paulo, São Paulo-SP, Brazil. E-mail: julianarg@hu.usp.br
** Master in Health Science. Nurse at Hospital Infection Control Committee of University Hospital of University of São Paulo, São Paulo-SP, Brazil.
*** Ph.D. Nurse. Professor at Medical-surgical Nursing Department, School of Nursing – University of São Paulo, São Paulo-SP, Brazil.
**** Ph.D. Nurse. Professor at Collective Health Nursing, School of Nursing – University of São Paulo, São Paulo-SP, Brazil.

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INTRODUCTION

The association between the oral cavity microbiota and pneumonia is well known, especially in critically-ill patients[1]. However, the acknowledgement of oral hygiene as a direct and relevant measure in preventing pneumonia in critically-ill patients is recent. Current guidelines for prevention of respiratory infections from the Center for Disease Control and Prevention of United States of America have recommended the implementation of a program that includes oral hygiene for these patients[2].

The colonization of the oropharynx, nasal cavity and teeth of critically-ill patients can change due to metabolic decompensations such as acidosis, uremia, uncontrolled diabetes mellitus, hypotension, and the use of antibiotics[3]. The oral cavity may also suffer invasion from exogenous microorganisms through the use of respiratory equipment and contact with healthcare workers[4]. It is known that microorganisms from the oral cavity can be present in more than 60% of both the respiratory secretions from ventilated-assisted patients and in respiratory equipment used by them[5].

Although the scientific literature has demonstrated the relevance of oral hygiene to prevent ventilator-associated pneumonia (VAP), there is no consensus on the use of chlorhexidine (CHX) as well as protocols to guide the indication, concentration, frequency, and technique used[6].

In a systematic review published in 2007[7], the authors concluded that it would not possible to carry out a meta-analysis due to variations in methods and interventions found in the primary studies. Similarly, an integrative review concluded that it is necessary to perform further studies to determine the best way to perform oral hygiene[8]. Trials that assessed oral hygiene with CHX in VAP prevention have several variations regarding the intervention, such as the concentration of the antiseptic agent, frequency of product use, CHX presentation (gel, solution or spray) and way of applying the product (swab, sterile gauze or not sterile gauze). Systematic reviews and meta-analyses have shown conflicting results on the importance of performing oral hygiene with CHX to prevent VAP[9,10,11,12]. In order to identify what is the best concentration of CHX to oral hygiene, we decided to perform a different meta-analysis, having as criterion the concentration of the antiseptic agent.

The aim of this systematic review and meta-analysis was to identify evidence on the best way to perform oral hygiene in ventilator-assisted critically-ill patients by means of a systematic review and meta-analysis using CHX concentration as the criterion.

METHOD

A systematic review and meta-analysis was performed based on the steps recommended in the online course of Systematic Review and Meta-analysis of the Cochrane Center of Brazil[13] seeking to answer the following question: *is there evidence on the best way to perform oral hygiene with CHX to prevent VAP in critically-ill patients?* Study selection was performed by two independent professionals that used the same search strategy to the ensure accuracy.

The Preferred Reporting Items for Systematic Reviews and Meta-analyses – PRISMA Statement[14] – 27-item checklist was followed during article selection and study performance.

Search methods

Descriptors indexed in databases were used according to PICO strategy[15], where P (Population) = *Respiration, Artificial OR Artificial Ventilation OR Critical Care OR Critical illness OR Intensive care OR Intensive care nursing OR Intensive care units*; I (Intervention) = *Oral hygiene OR Mouth hygiene OR Mouthwashes*; C (Comparison) = there was no descriptor to compare; O (Outcome) = *Ventilation-associated pneumonia OR Cross infection OR Infection control*.

The search was carried out from May to June 2011 in the following electronic databases: Cochrane Library, EMBASE, PubMed/MEDLINE, OVID and LILACS. The search included articles published in English, Spanish, and Portuguese with no time period limitation. References cited in included studies were also analyzed in order

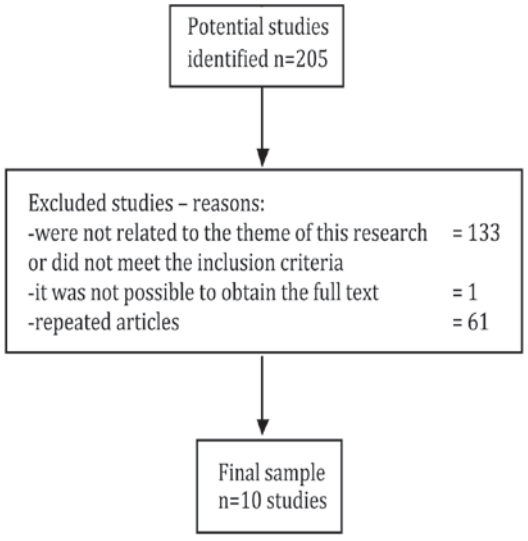
to identify other relevant studies that were not located by means of electronic search.

Population was defined as critically-ill patients aged 18 years or older, undergoing mechanical-assisted ventilation. Controlled randomized trials were included whenever they compared oral hygiene using CHX with placebo or usual care. Exclusion criteria were publications concerning letters to editor, duplicated studies, comments and opinions of experts that were not supported by research.

Search outcome

Initially, 205 publications were identified. After screening of titles, abstracts and reading of full-texts, 10 articles were selected for inclusion in the study. Seven studies that were reviews or meta-analyses were not included in the final sample of 10 studies (Figure 1), but had their literature references analyzed[6,7,8,9,10,11,12].

Figure 1. Flow diagram of studies selection process



Quality appraisal

The quality of studies was assessed according to the Oxford classification[16], Jadad score[17] and internal and external validity[18]. The first classifies the studies according to levels of evidence and selected only clinical trials. The second establishes the maximum value of five points, as follows: randomized (1 point), adequate randomization process (1 point), blinding (1 point), double-blind (1 point), and control of subject loss or exclusions (1 point). The studies included in this review have a classification > 3 according to Jadad score[17]. The third evaluates aspects related to control of confounding variables, stratification of the intervention and control groups and population. Two authors independently assessed the three criteria cited in all studies of this review in order to ensure that the included studies represented strong evidence.

Data abstraction

Data were extracted by one author using a instrument designed specifically to obtain the following details: age, sex, intervention details, and control groups, concentration of antiseptic agent, frequency of use of antiseptic agent and way of performing the oral hygiene. The main outcome evaluated by the studies was the development of ventilation-associated pneumonia.

Synthesis

The selected primary studies were grouped into 4 groups (G1 to G4). The groups were constituted as follows: G1 – five trials that used 0.12% CHX; G2 – three trials that used 0.20% CHX; G3 – two trials that used 2.00% CHX; G4 – comprised all 10 studies that evaluated the use of CHX in reducing VAP. The statistical methodology of the 98c EasyMA® package was applied to each group and a fixed-effects model was used to synthesize data Cochran's Q test was used to evaluate the homogeneity among studies.

RESULTS

Description of trials

The 10 clinical trials enrolled 2,471 patients: 1,237 receiving oral hygiene with CHX and 1,234 that constituted the control group (Table 1). Subjects from the control groups received placebo (483), usual care (35), electric toothbrush (73), mouthwash containing phenolic compounds - Listerine (291) or saline solution (352).

As shown in Table 1, studies with 0.12% CHX used liquid solution presentation; studies with 0.20% CHX used gel; and trials with 2.00% CHX used gel or solution.

Table 1. Number of subjects in the intervention (I) or control (C) group, frequency of use, chlorhexidine (CHX) presentation, type of use, volume, contact time, patients characteristics, blinding status, and outcome of Ventilation-Associated Pneumonia (VAP) reduction in 10 selected studies. Brazil, 2012

Study	Intervention group (I)		Control group (C)		Freq/ day	CHX presentation		Application	Quantity	Contact time	Type of patient (Intensive care unit)	Blinding	↓VAP
	N_I	VAP_I Yes	N_C	VAP_C Yes		Intervention	Control						
CHX 0.12%													
E1[19] (DeRiso, et al., 1996)	173	9	180	9	2x	solution	placebo solution	not cited	5 fl oz	30s	Cardiovascular	double-blind	Yes
E2[20] (Grap, et al., 2004)	7	4	5	3	2x	solution	usual care	spray or swab	2mL	Not cited	trauma and surgical	triple-blind	CHX use early in the post-intubation period may delay the development of VAP
E3[21] (Houston, et al., 2002)	270	4	291	9	2x	solution	Listerine®	swab	15mL	30s. No food or drink for 30 min after	cardiovascular	not cited	only in intubated patients > 24h
E4[22] (Scannapieco, et al., 2009)	116	14	59	12	2x	solution	placebo solution	swab	1 fl oz	1 min	trauma	double-blind	No
E5[23] (Pobo, et al., 2009)	74	15	73	18	3x	solution	electric toothbrush	gauze	20mL rubbing + injection 10mL	30s	medical-surgical	single-blind	No
CHX 0.20%													
E6[24] (Panchabhai, et al., 2009)	224	16	247	19	2x	solution	0.01% $KmnO_4$ solution	swab	10mL	Not cited. No food or drink for 1h after	general	not cited	No
E7[25] (Fourrier, et al., 2000)	30	5	30	18	3x	gel	usual care	sterile glove	Not cited	Gel was left until next time	medical-surgical	single-blind	Yes
E8[26] (Fourrier, et al., 2005)	114	13	114	12	3x	gel	placebo gel	sterile glove	Not cited	Gel was left until next time	6 ICUs (multicenter)	double-blind	No
CHX 2.00%													
E9[27] (Koeman, et al., 2006)	127	13	130	23	4x	vaseline FNA / colistin in vaseline FNA	placebo (vaseline FNA)	glove	0.5g	Product was left until next time	mixed & surgical	double-blind	Yes
E10[28] (Tantipong, et al., 2008)	102	5	105	12	4x	solution	saline solution	Not cited	15 mL	15 mL. Time not cited.	ICUs or general medical wards		Yes

Studies E2, E5, E7, E8 excluded edentulous patients and the last one also excluded patients with a tracheostomy tube. E2 justified that edentulous patients may have other potential pathogens and therefore a different risk level for VAP compared to patients with teeth. Nevertheless, this particular patient characteristic was not even mentioned in studies E1, E3, E6, E9, E10 and study E4 included edentulous subjects.

E8 is a multicenter study that took place in six French ICUs: three in university hospitals and three in general hospitals. E9 was multicenter and was performed in two university hospitals (two mixed and two surgical ICUs) and three general hospitals (all mixed ICUs) in the Netherlands. E10 was a singular study, as the authors carried out a randomized clinical trial with 207 patients in ICUs or general medical wards from a tertiary care university hospital (102 individuals in the Intervention group and 105 in the control group) and then performed a meta-analysis with a single study that also used 2.00% CHX (E9, in the present study). E10 used the patients' gender as a criterion for group composition. This means that intervention group was consisted of male patients and the control group of female patients.

Regarding the technique used, studies E5 and E9 did not refer whether the gauze or glove, respectively, which were used to apply CHX were sterile or not. In the E8 study, before CHX use, mouth-rinsing with water and oropharyngeal aspiration was performed. Tooth brushing was not allowed in the protocol of this study, aiming at eliminating bias regarding the CHX effect. E9 reports that before each intervention cleaning with gauze moistened with saline solution (NaCl 0.9%) was performed and E10 indicates that before patients received CHX or saline solution, teeth were brushed and oral secretions were aspirated.

E1 used a placebo that was similar to the base solution of CHX; this means that both intervention and placebo group had 3.2% ethyl alcohol as solvent. On the other hand, study E4 used a lower concentration of ethanol in the placebo (< 0.1%).

In the E7 study, usual care was defined and applied in the control group by means of a bicarbonate serum followed by oropharyngeal sterile aspiration four times a day.

Meta-analysis

Four meta-analyses were carried out according to CHX concentration groups as previously defined. Group 1 (G1) included studies that used 0.12% CHX; Group 2 (G2) studies with 0.20% CHX; Group 3 (G3) 2.00% CHX and Group 4 (G4) did not include the criterion of CHX concentration.

The meta-analysis of G1 (Figure 2) showed that the studies were homogeneous (Q Cochrane heterogeneity p = 0.67). We verified the occurrence of large confidence intervals in the studies, of which all crossed the line at 1.0 and can be seen as the possibility of no beneficial effect or a negative effect. However, after grouping these studies, oral hygiene with 0.12% CHX represented a protective factor (RR = 0.675; p = 0.039).

In the meta-analysis of G2 (Figure 3) there was heterogeneity among studies (Q Cochrane heterogeneity p = 0.037), indicating that this meta-analysis does not have good statistical power. It should be pointed out that only E7 did not cross the line at 1.0, so CHX represented a protective factor only in this study.

The meta-analysis of G3 (Figure 4) showed homogeneity among studies (Cochrane Q heterogeneity p = 0.62), which also had large confidence intervals and both studies E9 and E10 touch the line 1.0. This meta-analysis showed that the use of CHX was significant (p = 0.021) for the prevention of VAP and the RR = 0.53.

Finally, the meta-analysis of all 10 primary studies (Figure 5) showed homogeneity among the groups (Cochrane Q heterogeneity p = 0.35). The confidence interval did not cross the line at 1.0 and the Relative Risk was lower for patients using CHX (RR = 0.658; p < 0.001).

Figure 2. Meta-analysis of studies that used CHX 0.12% (Group 2) in oral hygiene to reduce the incidence of VAP. Brazil, 2012

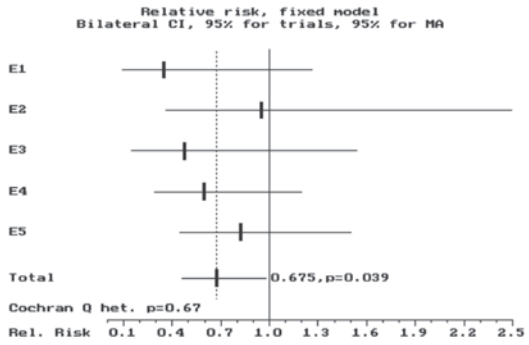


Figure 3. Meta-analysis of studies that used 0.20% CHX (Group 3) in oral hygiene to reduce the incidence of VAP. Brazil, 2012

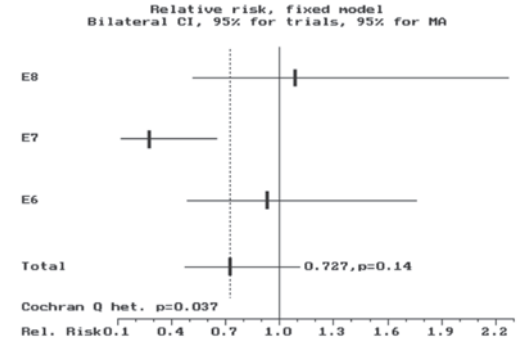


Figure 4. Meta-analysis of studies that used CHX 2.00% (Group 4) in oral hygiene to reduce the incidence of VAP. Brazil, 2012

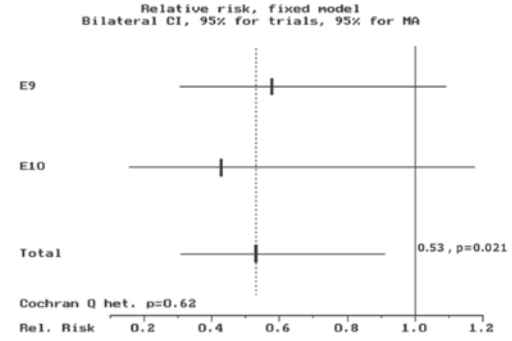
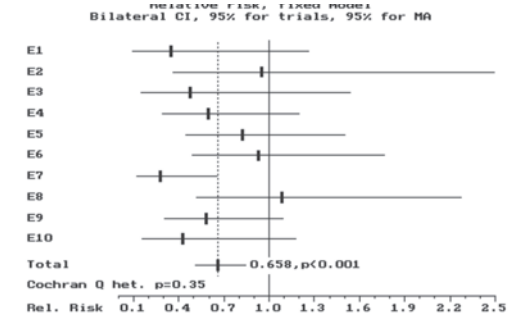


Figure 5. Meta-analysis of studies that used CHX in oral hygiene to reduce the incidence of VAP. Brazil, 2012



DISCUSSION

Systematic reviews and meta-analyses should be performed when there are doubts about the sufficiency of conclusions found by well-designed clinical trials or when new issues arise. Regarding the subject under investigation, although previous studies suggested that the use of oral hygiene with CHX prevents VAP, the best antiseptic concentration and the best way to do it remains an open question.

We chose to perform four different meta-analyses, having as the criterion for inclusion of studies the concentration of CHX. We believed that by assessing studies in similar categories we could evaluate the best concentration to perform oral hygiene.

Many studies showed large confidence intervals. Despite of a trend to use CHX to prevent VAP, only a single study (E7) had not crossed the line at 1.0, showing that the use of this antiseptic was effective in this study.

In the meta-analysis of G1 studies (CXH concentration of 0.12%) CHX was not identified as being protective, maybe due to the low antiseptic concentration. Meta-analysis of G2 studies (0.20% CHX concentration) was considered inconclusive. VAP protection was identified in the meta-analysis of G3 (2.00% concentration). However, is a matter of discussion whether the gender criterion used in the E10 study could introduced a bias in the randomization[28].

The hypothesis of performing different meta-analyses using the concentration of the antiseptic agent as inclusion criterion to help establish the best way to perform oral hygiene unfortunately did not yield with significant results.

On the other hand, although the meta-analysis with all studies included in the review showed that there is was a protective effect of CHX use in oral hygiene, it was impossible to determine which CHX concentration is the best one. However, it is important to highlight that the meta-analysis results can be affected by other important variables in addition to CHX concentration, such as the form of presentation (solution, gel, spray), frequency and methods used (swab, gauzes or gloves). The best way to determine a standard recommendation would be to compare researches that followed similar interventions, including the antiseptic form and the frequency of use.

Moreover, it is important to note that CHX is not innocuous. In case of oral ingestion, although the product is well tolerated in most cases, adverse effects may occur when ingested in large quantities[29]. Cases of pulmonary and tongue edema and oral ulcers in infants who received 0.05% CHX orally after the antiseptic agent was mistaken for sterile water have been reported[30]. After developing respiratory distress syndrome, an elderly patient died due to ingestion of 10 g of CHX in a 200 mL solution[31]. When performing oral hygiene with CHX, one should be careful not to allow contact with the eyes. Tests with 4% CHX caused stromal edema in animals, leading to corneal opacification within six weeks[32]. CHX is also toxic to the middle ear. Disinfection of the ear with CHX during preoperative procedures has been associated with deafness after myringoplasty[33].

Among fifty cases of adverse reactions related to CHX that occurred in Japan from 1967 to 1984, nine cases of anaphylaxis shock were reported, particularly when CHX was applied to the mucosa[34]. A similar case was described in Australia after CHX was applied to the vaginal mucosa at the end of a surgery[35].

Thus, even though we conclude that CHX is a product that can reduce the microbiota of the oral cavity or VAP, guidelines for its best use, which are less likely to cause harmful effects are essential in relation to cost-benefit to the patient. Nursing plan in critically-ill patients regarding oral care should be evidence-based and the use of chlorhexidine must be judicious, besides is important that nurses having sufficient time to provide care, prioritizing oral care[36].

CONCLUSION

When evaluating studies on the protective effect of CHX use in VAP prevention, it was not possible to establish a consensus regarding a standard recommendation about the antiseptic concentration to be used.

Well-designed primary studies, including careful control of confounding variables between the groups are still needed in order to identify the best concentration, frequency, technique and form of presentation of CHX. In addition, studies to verify the potential toxicity of CHX in contact with mucosal membranes should also be developed to ensure patient safety.

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