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The use of 2% chlorhexidine gel and toothbrushing for oral hygiene of patients receiving mechanical ventilation: effects on ventilator-associated pneumonia

Uso de clorexidina 2% gel e escovação mecânica na higiene bucal de pacientes sob ventilação mecânica: efeitos na pneumonia associada a ventilador

ABSTRACT

Objective: To evaluate the effects of oral chlorhexidine hygiene with toothbrushing on the rate of ventilator-associated pneumonia in a mixed population of critically ill patients under prolonged mechanical ventilation.

Methods: Prospective, randomized, and placebo-controlled pilot study. Patients who were receiving mechanical ventilation, had been admitted less than 24 hours prior, and were anticipated to require mechanical ventilation for more than 72 hours were included in the study. The patients were randomly divided into one of the following groups: chlorhexidine hygiene with toothbrushing or a placebo group (gel with the same color and consistency and toothbrushing).

Results: The planned interim analysis was conducted using 52 patients, and the study was terminated prematurely.

In total, 28 patients were included in the chlorhexidine / toothbrushing group, and 24 patients were included in the placebo group. Ventilator-associated pneumonia occurred in 45.8% of the placebo group and in 64.3% of the chlorhexidine hygiene with toothbrushing group (RR=1.4; 95% CI=0.83-2.34; p=0.29).

Conclusion: Because the study was terminated due to futility, it was not possible to evaluate the impact of oral hygiene using 2% chlorhexidine and toothbrushing on the incidence of ventilator-associated pneumonia in this heterogeneous population of critical patients receiving long-term mechanical ventilation, and no beneficial effect was observed for this intervention.

Keywords: Pneumonia, ventilator-associated; Oral hygiene; Chlorhexidine/ administration & dosage; Placebos; Manual brushing; Intensive care units

This study was conducted at the Medical-Surgical Intensive Care Unit, Hospital de Base de São José do Rio Preto - São José do Rio Preto (SP), Brazil.

Conflicts of Interest: None.

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INTRODUCTION

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common nosocomial infections among patients in intensive care units (ICUs). The risk of occurrence is 1% to 3% for each day a patient receives mechanical ventilation.⁽¹⁾ The incidence varies from 7% to 40%, depending on such factors as the study population, ICU type, and diagnostic criteria.⁽²⁾ Respiratory infections greatly affect hospitals financially, due to prolonged hospital stays and requirements for broad-spectrum antibiotics and additional exams.^(1,3)

The main mechanism for pathogens' entry into the lower respiratory tract of severely ill patients is aspiration of the contents of the oropharynx or secretions that accumulate above the endotracheal tube cuff, which are colonized by oral microorganisms from dental cavities, biofilms, and periodontal disease pockets.⁽⁴⁾ Although controversial, sinuses and the stomach may also be reservoirs for

bacteria that can colonize the oropharynx and trachea.⁽²⁾ For pneumonia to occur, pathogens must overcome respiratory-system defense mechanisms: mechanical (cough reflex, glottic reflex, and the mucociliary system); humoral (antibodies and the complement system); and cellular (polymorphonuclear leukocytes, macrophages, and lymphocytes).^(3,4)

Modifiable risk factors are possible targets for interventions in pneumonia prevention. Among the greatest risk factors for nosocomial pneumonia are endotracheal intubation and mechanical ventilation, which cause a 3- to 21-fold increase in the risk of developing nosocomial pneumonia.⁽⁵⁾ Several strategies have been recommended and applied in clinical practice, such sedation protocols with more interactive patients, daily interruption of sedation, maintenance of a semi-recumbent position (30 to 45 degrees), and oral hygiene.⁽¹⁾

Oral hygiene is considered crucial for preventing pneumonia; however, there are no clear guidelines for how oral hygiene should be performed, leading to different hygienic practices in different clinical settings. Chlorhexidine is used as an oral antiseptic for reducing dental plaque in critical-care and ICU patients.^(1,6-9) This measure may reduce the pathogenic load in the plaque and, potentially, reduce nosocomial pneumonia rates.^(1,9-12) The use of 0.12% chlorhexidine decreases the occurrence of HAP in patients undergoing cardiac surgery.⁽⁶⁾ A meta-analysis of 7 studies concluded that the occurrence of VAP decreased almost 30%, but this effect appears to have been more significant in populations of patients undergoing heart surgery.⁽¹³⁾ The aim of the present study was to evaluate the effects of an oral hygiene protocol (consisting of 2% chlorhexidine and manual brushing) in a heterogeneous population of ICU patients on the VAP incidence, duration of mechanical ventilation, and lengths of the patients' ICU and hospital stays.

METHODS

The present investigation was a prospective, randomized, and placebo-controlled pilot study approved by the Research Ethics Committee at the Faculdade de Medicina de São José do Rio Preto. Free and Informed Consent Forms (FICF) were obtained from the patients' next of kin. The study was conducted between July 2007 and December 2009 in the Clinical-Surgery ICU (23 beds) at the Hospital de Base de São José do Rio Preto.

Inclusion criteria for the study were as follows: over 18 years old, receiving mechanical ventilation for less than 24 hours after admission, and expected to require

ventilation for more than 72 hours. Exclusion criteria were aspiration pneumonia, tracheostomy, pregnancy, and immunosuppression.

The nursing team was trained on the importance of oral hygiene and on how to use the experimental protocol, which consisted of manual cleaning with a toothbrush (Bitufo, Itupeva, Sao Paulo, Brazil) and application of the gel to the entire oral cavity 4 times per day until the given patient was released from the ICU.

After obtaining the FICF, randomization was conducted using sealed envelopes in blocks of 10. The patients were randomly assigned to the chlorhexidine group (2% chlorhexidine gel) or to the placebo group (gel with the same color and consistency). Only the pharmacist responsible for preparing the solutions and for the randomization process knew the contents of the distributed gel tubes.

Dental exams were performed 3 or 4 times at 48-hour intervals, depending on the patient's length of stay in the ICU. The dental clinical examination involved evaluations for the presence of bacterial plaque. The oral condition was classified using the Löe and Silness index that was modified for recording plaque deposits (plaque index) on a scale of 0 to 3.⁽¹⁴⁾ The scale was as follows: 0, no plaque; 1, plaque observed after removal with a periodontal probe from the gingival margin of the tooth crown; 2, clinically visible plaque; 3, extensive plaque.

The primary outcome in this study was the occurrence of VAP, which was determined by the presence of a new radiological pulmonary infiltrate on chest X-rays after 48 hours in the ICU, plus 2 or more of the following clinical or laboratory signs: axillary temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$, leukocytes $>11,000/\text{mm}^3$ or leukopenia $<4,000/\text{mm}^3$, or the presence of purulent tracheal secretions.

Statistical analysis

The estimated incidence of VAP was 30% in the placebo group and 15% in the study group with a calculated sample size of 98 patients in each group, a statistical power of 80%, and a significance level of 0.05. The first formal interim analysis was planned to occur when 50% of the patients were included. The analysis was performed when 52 patients were included, and the study was suspended due to futility.

Student's t-test was conducted to compare 2 groups of continuous variables with normal distributions, and the Mann-Whitney test was used when the variables were not normally distributed. The incidence of the outcomes was evaluated using relative risk (RR) with a 95% confidence interval (95% CI). Statistical significance was set at $p < 0.05$.

RESULTS

In total, 2,774 patients were admitted to the ICU. Of these patients, 87 patients were evaluated in the study, 33 of which were excluded because they did not meet the inclusion and exclusion criteria, namely, receiving mechanical ventilation for <72 hours, missing the 24-hour window for inclusion, or release or death before 72 hours (Figure 1). Fifty-two patients (28 patients in the 2% chlorhexidine/toothbrushing group and 24 patients in the placebo group) were included in the study.

Table 1 lists the demographic data and characteristics of the patients. The study participants ranged from 18 to 81 years of age. The majority were surgical patients - 89% of the chlorhexidine group and 79% of the control group. The most common admission diagnosis was trauma, accounting for 48% of the patients.

Eleven patients (45.8%) in the placebo group and 18 patients (64.3%) in the 2% chlorhexidine/toothbrushing

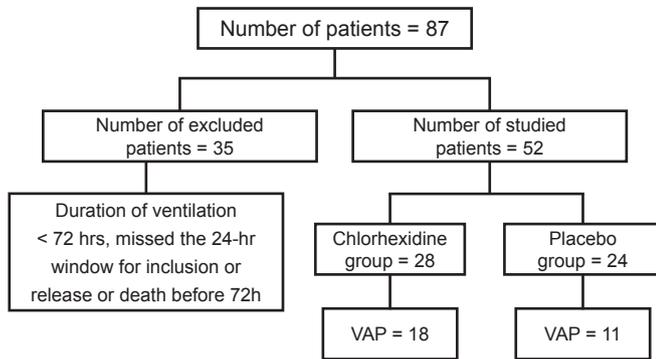


Figure 1 - Distribution of the study population. VAP - ventilator associated pneumonia.

Table 1 - Characteristics of patients in the placebo and 2% chlorhexidine/toothbrushing groups

Variables	Placebo	Chlorhexidine	p value
Number of patients	24	28	
Age (years)	41.0 ± 19.0	40.1 ± 14.6	0.84
APACHE II	16.7 ± 6.8	17.9 ± 4.5	0.45
Diagnosis			
Clinical	5(20.8)	3(10.7)	0.32
Surgical	19(79.2)	25(89.3)	0.53
Clinical condition			
Trauma	12(50.0)	13(46.4)	0.98
Stroke	3(12.5)	4(14.2)	0.81
Postoperative complications	3(12.5)	6(21.4)	0.62
Guillain-Barré syndrome	1(4.1)	0(0.0)	0.97
Rectal neoplasia	2(8.3)	1(3.5)	0.92
Septic shock	2(8.3)	2(7.1)	0.71
Acute pulmonary edema	1(4.1)	1(3.5)	0.54

APACHE II - Acute Physiology and Chronic Health Evaluation. Results are expressed as the mean ± standard deviation or the number (%).

group developed VAP (RR=1.4; 95% CI=0.83-2.34; p=0.29).

The average length of mechanical ventilation was 6 days in the placebo group and 8.5 days in the 2% chlorhexidine/toothbrushing group (p=0.17) (Table 2). More patients in the placebo group had shorter mechanical ventilation times compared with the chlorhexidine group (50% versus 17.8%; p=0.03). The average length of stay in the ICU for the studied patients was 12 days for the 2% chlorhexidine/manual brushing group and 11 days for the placebo group (p=0.36). The mortality rate was 46.5% in the 2% chlorhexidine/toothbrushing group and 37.5% in the placebo group (RR=1.24; 95%CI=0.64-2.37; p=0.07).

Table 2 - Outcomes of the placebo and 2% chlorhexidine/toothbrushing groups

Variables	Placebo N(%)	Chlorhexidine N(%)	p value
VAP rate	11(45.8)	18(64.3)	0.29
Microbiologically confirmed VAP rate	8(72.7)	12(66.6)	0.86
Duration of intubation (days)	6 [4-12.7]	8.5 [7.3-14.7]	0.17
Duration of intubation			
Between 3 and 5 days	12(50)	5(17.8)	0.03
Between 6 and 10 days	5(20.8)	14(50.0)	0.06
> 10 days	9(29.2)	7(32.2)	0.94
Duration of ICU stay (days)	11 [5-16]	12 [9-29]	0.36
Duration of hospital stay (days)	17 [11-23]	19 [9-34]	0.62
Mortality rate	9(37.5)	13(46.5)	0.07

VAP - ventilator-associated pneumonia; ICU - Intensive care unit. Results are expressed as the number (%) or median [25%-75%].

Tracheal aspirate cultures were collected from 38 patients (73%). The most commonly identified bacteria were *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* (Table 3). The patient's oral conditions, evaluated using the plaque score, are presented in table 4.

Table 3 - Microbiological agents in the tracheal aspirate cultures of the placebo and 2% chlorhexidine/toothbrushing groups

Agent	Placebo	Chlorhexidine
<i>Pseudomonas aeruginosa</i>	5	2
<i>Klebsiella pneumoniae</i>	2	4
<i>Staphylococcus aureus</i>	2	3
<i>Acinetobacter baumannii</i>	0	2
<i>Proteus mirabilis</i>	1	0

Table 4 - Data from oral-condition evaluations for the presence of bacterial plaque in all patients during the first 24 hours in the intensive care unit

Degree	Placebo N(%)	Chlorhexidine N(%)	p value
0	14(58.3)	15(53.5)	0.93
1	9(37.5)	11(39.2)	0.89
2 and 3	1(4.1)	2(7.1)	0.89

Results are expressed as the number (%).

DISCUSSION

During the interim analysis of the present investigation of patients subjected to prolonged intubation in a medical-surgical ICU, we were unable to evaluate the impact of oral hygiene involving toothbrushing and 2% chlorhexidine gel application compared with toothbrushing with placebo because the study was prematurely terminated due to futility.

The results of this investigation are not consistent with the first double-blind controlled study by DeRiso et al. regarding the use of 0.12% chlorhexidine in oral hygiene to prevent nosocomial pneumonia in a homogeneous population of 353 patients undergoing cardiovascular surgery. In that study, the researchers demonstrated a 69% decrease in the incidence of nosocomial pneumonia.⁽⁶⁾

Other studies performed in cardiac ICUs have yielded similar results. Houston et al.⁽¹⁵⁾ evaluated 561 patients who underwent myocardial revascularization surgeries and determined a 58% decrease in VAP rates using 0.12% chlorhexidine gluconate compared with oral hygiene using Listerine.⁽¹⁵⁾ Segers et al. analyzed 954 patients undergoing cardiac surgery and observed a significant reduction in respiratory tract infections after the preoperative application of 0.12% chlorhexidine for oral hygiene compared with the placebo.⁽¹⁶⁾

However, in heterogeneous, severely ill patient populations, the effect of chlorhexidine use on nosocomial-pneumonia infection rates is controversial. One study using 0.2% chlorhexidine for oral hygiene in critical patients demonstrated decreased pathogenic colonization of the oral cavity and positive results for VAP prevention.⁽¹⁷⁾ The same author published another randomized, double-blind study using 0.2% chlorhexidine and observed that the number of pathogens in the oral cavity decreased but not sufficiently to reduce the nosocomial pneumonia rates.⁽¹⁸⁾

Higher chlorhexidine concentrations, such as 2% chlorhexidine and 2% chlorhexidine with colistin, were tested in critical patients and resulted in a 65% reduction of nosocomial pneumonia cases in patients using 2% chlorhexidine and a 55% reduction in the group that included the antibiotic.⁽¹⁸⁾

Several meta-analyses have been published on this topic.^(9,10,13,19,20) One randomized study followed by meta-analysis was performed on a clinical-surgical ICU population using 2% chlorhexidine, and the researchers concluded that oral decontamination by 2% chlorhexidine is an effective and safe method for preventing VAP in this population.⁽⁹⁾ However, patients in the study received mechanical ventilation for less than 48 hours, the

randomization process was not adequate (as the study was not blind), and at least one-half of the included patients received mechanical ventilation for less than 48 hours, which was an exclusion criterion in our study.

Pineda et al. analyzed 4 studies using chlorhexidine. In these investigations, different concentrations of chlorhexidine and various patient populations were analyzed, and a beneficial effect of chlorhexidine use was not observed.⁽¹⁰⁾

A meta-analysis of 7 studies on antiseptic use for oral hygiene evaluated 2,144 patients receiving mechanical ventilation (including cardiac and surgical patients) and found a 44% reduction in nosocomial pneumonia prevalence.⁽¹⁹⁾ Another meta-analysis revealed benefits for a subgroup of patients who had undergone mechanical ventilation for less than 48 hours, most of whom had undergone cardiac surgery.⁽²⁰⁾ The last meta-analysis of chlorhexidine use for oral hygiene in adult patients receiving mechanical ventilation, which employed a fixed-effects model and moderate heterogeneity, demonstrated a significant reduction of 25% in the VAP rate. Analysis of the subgroup who underwent cardiac surgery revealed more favorable results for chlorhexidine, with a reduction of greater than 50%.⁽¹³⁾

Comparing data from these studies is difficult, as there was heterogeneity in these meta-analyses, and various chlorhexidine concentrations, mechanical cleaning methods, and populations were used. It is possible that the duration of intubation impeded adequate cleaning of the oral cavity, in contrast with the cardiac surgery patients, who are intubated for a short period, generally <48 hours.

In addition, more recent data has suggested that manual toothbrushing may not have any effect or may even be detrimental. Munro et al.⁽²¹⁾ demonstrated in a multicenter and factorial (2 x 2 design) study conducted in clinical, surgical, and neurological ICUs that chlorhexidine without brushing reduces the incidence of VAP and that brushing, whether alone or with chlorhexidine, does not yield any benefit. Recently, Lorente et al.⁽²²⁾ randomized 436 patients for receiving oral hygiene with or without manual brushing and concluded that brushing did not decrease the incidence of VAP.

For intubated patients, manual brushing performed by a caregiver, rather than the patient himself, might, contrary to expectations, increase the risk of adverse events and the VAP rate, which would explain the high rates observed in both groups in our study. It is also possible that toothbrushing causes bleeding gums and breaks the mucosal barrier, thereby allowing pathogen invasion into the blood stream, releasing additional

bacteria from dental plaque (increasing the pathogenic load during aspiration) or increasing the rate of accidental extubation—all of which are events linked to VAP.⁽²²⁾ Furthermore, toothbrushing without controlling the cuff pressure of the endotracheal tube before and after hygiene (i.e., not ensuring the cuff seal) might increase the chance of microaspiration. These data are consistent with the findings by Vieira et al.,⁽²³⁾ who demonstrated in a large number of patients that performing oral hygiene has a protective effect, decreasing VAP rates by more than 50% but only when performed along with monitoring of the pressure of the cuff. Failure to control the cuff pressure increased the risk by 60%.

It is clear that the oral cavity plays a fundamental role in colonization of the oropharynx with nosocomial pathogens and that lack of oral hygiene compromises oral immunity, facilitates biofilm formation, and/or causes loss of salivary function.^(7,21) However, it appears that oral hygiene involving 2% chlorhexidine and toothbrushing alone does not prevent VAP in heterogeneous populations of severely ill, intubated patients and thus should be performed in combination with other preventative measures.⁽¹⁰⁾ One such set of preventative measures reduced pneumonia in 89.7% of the studied patients. These measures were as follows: an oral hygiene protocol with suction toothbrushes and 0.12% chlorhexidine, increased hand antisepsis of the health professionals, daily interruption of sedation, daily evaluation of extubation, prophylaxis against peptic ulcers and venous thrombosis, and elevation of the head of the bed.⁽¹⁾

The most significant limitations of the present study were the small sample size and the large number of patients who were excluded because they did not follow procedures. The 15% reduction in VAP absolute risk that was assumed when the sample size was calculated might have been overly high, leading to underestimation of the number of patients required for the planned analysis. Patients without adequate records of oral hygiene procedures were excluded. These numbers suggest that evaluations of protocol adherence and continued training should have been conducted throughout the study rather than only at the beginning and the end.

Another significant limitation was the heterogeneity of the population. Other factors should be controlled to identify the direct effect of chlorhexidine on the occurrence of nosocomial pneumonia, including the characteristics of the primary pathology, patient age, duration of hospital stay, and the absence or presence of teeth. Rigorous measures for adherence to the oral hygiene protocol, type and frequency of application, and

quantity of gel used should also be performed. Moreover, in the present study, manual brushing was used in both groups, despite insufficient evidence supporting its use in intubated patients. Various techniques have been used in patients on ventilators, such as humidified gases,^(12,18,22) glove-protected hands,⁽¹¹⁾ cotton swabs,⁽²¹⁾ manual toothbrushes,^(21,22) electrical toothbrushes,⁽¹²⁾ and suction toothbrushes.⁽¹⁾ To the best of our knowledge, no data exist regarding the best oral-hygiene technique to employ, and our results confirm the fact that more studies on this topic are necessary.

Patients receiving mechanical ventilation are unable to perform self-care; their caregivers, in turn, may not have been adequately trained or instructed regarding the importance of oral hygiene under these conditions.^(24,25) In addition to informing, encouraging, and continually training the patients' caregivers, it is likely that hygienic measures that are overseen and performed by dental professionals would have a greater impact, which should be evaluated in future studies.

CONCLUSION

Because the present study was prematurely interrupted due to futility, it was not possible to evaluate the effect of employing 2% chlorhexidine and manual brushing for oral hygiene on the incidence of VAP in this heterogeneous population of critically ill patients receiving prolonged mechanical ventilation, and no benefits were observed for this intervention.

RESUMO

Objetivo: Avaliar os efeitos da higiene bucal com clorexidina 2% e escovação mecânica sobre a taxa de pneumonia associada a ventilador em uma população mista de pacientes sob ventilação mecânica prolongada.

Métodos: Estudo piloto prospectivo, aleatório e placebo-controlado. Foram incluídos pacientes sob ventilação mecânica, com menos de 24 horas de internação e cuja perspectiva de duração da ventilação mecânica era a de um período >72 horas. Os pacientes foram randomizados para o grupo clorexidina (gel com clorexidina a 2%) e escovação mecânica ou grupo placebo (gel da mesma coloração e consistência e escovação mecânica) na higiene bucal.

Resultados: A análise interina planejada foi realizada quando 52 pacientes foram incluídos, e o estudo foi interrompido precocemente. Um total de 28 pacientes foi incluído no grupo clorexidina/escovação mecânica e 24 no grupo placebo. As taxas de pneumonia associada a ventilador foram de 45,8% no grupo

placebo e de 64,3% no grupo clorexidine/escovação mecânica (RR=1,4; IC95%=0,83-2,34;p=0,29).

Conclusão: Devido a interrupção precoce por futilidade, não foi possível avaliar o impacto do uso de clorexidina a 2% e escovação mecânica na higiene bucal na incidência de pneumonia associada a ventilador nessa população heterogênea de

pacientes críticos sob ventilação mecânica prolongada, não tendo sido evidenciado nenhum efeito benéfico dessa intervenção.

Descritores: Pneumonia associada à ventilação mecânica; Higiene bucal; Clorexidina/administração & dosagem; Placebos; Escovação mecânica; Unidades de terapia intensiva

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