Pneumologia
REVISTA SOCIETĂȚII ROMÂNE DE PNEUMOLOGIE

The impact of 0.5% chlorhexidine oral decontamination on the prevalence of colonization and respiratory tract infection in mechanically ventilated patients

Preliminary study

Abstract

Aims: *To determine the effect of Chlorhexidine (CHX) 0.5% oral decontamination on the incidence of colonization/ infection of lower respiratory tract in critically ill mechanically ventilated patients.*
Methods: *The study was conducted in the multidisciplinary ICU. 30 patients, mechanically ventilated for at least 48 hours, were included. The oral care was performed every 6 hours (6 h CHX group) or 12 hours (12 h CHX group). Tracheal samples were collected every day and the mucosal plaque score (MPS) was also assessed.*
Results: *The MPS score averages were between 3.8 and 6 in the 6 hours CHX group and between 3.6 and 5 in the 12 hours CHX group. There was no positive association between MPS score and frequency of CHX decontamination (p= 0.898). For 60% of patients in 6 h CHX group and for 40% of patients in 12 h CHX group, colonization did not develop until leaving the study. No significant difference were found between groups with respect to frequency of colonization based on its time of onset (p= 0.523). There is a relationship between the isolation of MRSA and CHX oral decontamination at 12 hours (φc =0.392, p=0.032).*
Conclusions: *In our preliminary study, no signifficant differences were found between 6 or 12 hour CHX oral decontamination with respect to MPS score and colonization. However, MRSA is vulnerable to 6 hours CHX decontamination. Larger sample size studies are required to determine the efficacy of CHX in the prevention of colonization or respiratory tract infections in mechanically ventilated patients.*
Keywords: *colonization, oral decontamination, chlorhexidine, intensive care unit*

Rezumat

Impactul decontaminării orale cu clorhexidină în prevalența colonizării și infecției de tract respirator la pacienții ventilați mecanic. Studiu preliminar
Obiective: *Determinarea efectului decontaminării orale cu clorhexidină 0,5% asupra incidenței colonizării/infecției de tract respirator inferior la pacienții ventilați mecanic.*
Metodă: *Studiul s-a desfășurat în cadrul unei secții multidisciplinare ATI. Au fost incluși 30 de pacienți intubați și ventilați mecanic pentru cel puțin 48 de ore. Toaleta bucală s-a efectuat la fiecare 6 ore (grupul cu clorhexidină la 6 ore), respectiv 12 ore (grupul cu clorhexidină la 12 ore). Recoltarea secreției traheale și evaluarea scorului de mucoasă și placă (MPS) s-au efectuat zilnic.*
Rezultate: *Media scorului MPS a fost între 3,8 și 6 în grupul cu clorhexidină la 6 ore și între 3,6 și 5 în grupul cu clorhexidină la 12 ore. Nu a existat nici o corelație semnificativă între evoluția scorului MPS și frecvența decontaminării orale (p= 0.898). 60% din pacienții din grupul cu clorhexidină la 6 ore și 40% din cei cu clorhexidină la 12 ore nu au dezvoltat colonizare până în momentul ieșirii din studiu (p= 0,523). Deși nu a existat diferență semnificativă statistic între cele două grupuri în ceea ce privește frecvența colonizării, există o corelație între prezența MRSA și decontaminarea cu clorhexidină la 12 ore (φc =0.392, p=0,032).*
Concluzii: *Rezultatele studiului preliminar nu au arătat diferențe semnificative statistic între decontaminarea orală cu clorhexidină la 6 sau la 12 ore în ceea ce privește evoluția scorului MPS sau colonizarea. Sunt necesare studii pe eșantioane mai mari de pacienți pentru a determina eficiența decontaminării orale cu clorhexidină în reducerea incidenței colonizării și infecției de tract respirator la pacienții ventilați mecanic.*
Cuvinte-cheie: *colonizare, decontaminare orală, clorhexidină, terapie intensivă*

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Introduction

In the European Prevalence of Infections in Intensive Care study, ventilator-associated pneumonia (VAP) and lower respiratory tract infections accounted for 65% of all nosocomial infections in intensive care[1].

Mechanical ventilation is identified as one of the single most important risk factors for developing nosocomial pneumonia, increasing the risk 6 to 21-fold depending on the duration of ventilation[2-6]. Although epidemiological studies have been unable to demonstrate an association between acute respiratory disease and poor oral health in the general population, there is evidence that oral flora colonization is involved in the development of nosocomial pneumonia[7,8].

There are four possible mechanisms that can lead to nosocomial pneumonia: aspiration of oropharyngeal organisms[9], inhalation of aerosols containing bacteria, hemato-genous diffusion from distant body sites, and bacterial translocation from the gastrointestinal tract[10]. Aspiration of bacteria from the oropharynx is considered to be the most important of these mechanisms[11].

Dental plaque may serve as the main site of growth potentially pathogenic microorganisms in patients with poor oral hygiene[12,13], providing a specific reservoir of colonization, and subsequent nosocomial infection in ICU patients[14,15].

The purpose of our preliminary study was to determine the effect of Chlorhexidine 0.5% oral decontamination on the incidence of colonization/infection of lower respiratory tract in critically ill adult mechanically ventilated patients in ICU. Secondary endpoints included evolution of MPS score, time until endotracheal colonization and type of pathogens involved in colonization.

Materials and methods

The study protocol was approved by the Institutional Ethic Board of the Clinical Emergency County Hospital Cluj-Napoca. Written informed consent was obtained from all participants or a legal representative.

This preliminary study was carried out between December 2011 and January 2013 in the ICU unit of the Clinical Emergency County Hospital Cluj-Napoca. During that period, a number of 906 medical and surgical patients were admitted to the ICU. 585 patients needed intubation and mechanical ventilation. 364 patients were mechanically ventilated less than 48 hours. 221 were eligible for the study but only 30 patients fulfilled the entry criteria (for 49 patients oral hygiene was contraindicated and 142 patients had clinical diagnosis of lower respiratory tract infection). We provide a flow chart of the study according to the CONSORT requirements **(Annex 1)**.

Inclusion criteria: participants in the study had to be orotracheal intubated, without positive culture at admission, who required mechanical ventilation for at least 48 hours.

Exclusion criteria: a positive culture at admission; a clinical diagnosis of pneumonia at the start of the study; patients in whom oral hygiene was contraindicated (mandibular fixation after facial trauma, severe intraoral mucosal hemorrhages); patients with a known allergy and hypersensitivity to chlorhexidine (CHX); pregnancy.

Only subjects who met all eligibility requirements were randomized to the study. Oral decontamination was randomly assigned according to computer-generated identification numbers in blocks of two (one for the group treated with chlorhexidine 0.5% at 6 hours and one for the group treated with chlorhexidine 0.5% at 12 hours). Fifteen patients were allocated to each group.

Demographic and clinical data such as age, sex, clinical admission diagnosis, comorbidities, APACHE II score were recorded. Comorbidity was defined as a disease, disorder or condition that occurs at the same time as another disorder but is not related to it. The duration of mechanical ventilation was reported as ventilator days, beginning with the day of intubation and including the day of extubation. Intensive care length of stay was recorded including the day of admission and discharge respectively. The following data were assessed daily: bacteriological results from endotracheal aspirates, mucosal plaque score (MPS)[16].

Outcome variables: number of days on mechanical ventilation, time until endotracheal colonization, time until endotracheal infection, type of respiratory pathogens involved in colonization and MPS score.

Endotracheal aspirates samples were obtained daily using Trache-Sekretprobenset (BBraun, Germany). Endotracheal aspirate cultures were quantified using calibrated loops. Each microliter of aspirate and 100-fold diluted aspirate were streaked on sheep blood agar plates. All plates were incubated overnight in a 5% CO_2 atmosphere at 35°C. Colonies were then counted. Colonization was defined as more than 103 colony forming units per ml (CFU/ml), without signs of clinical infection[17]. When infection was clinically suspected (bronchorrhea, fever, leukocytosis) small volume bronchoalveolar lavage (mini-BAL) was performed. A cutoff of 104 CFU/ml was used to define pulmonary infection. The objective diagnostic criteria for VAP consisted of the presence of a new, persistent, infiltrate on chest X-ray in combination with at least three of four criteria: body temperature greater than 38°C, blood leukocytosis (>12.000/mm^3) or leukopenia (<4000/mm^3) and a positive quantitative culture from BAL (cutoff ≥ 104 cfu/ml) occurring after 48 hours of mechanical ventilation[8,18,19].

The patients were included in the study at admission in ICU for patients intubated in other medical units, operating room or at the time of intubation for nonintubated ICU patients. Surgical patients received prophylactic antibiotics. In the 6-hour CHX group one surgical patient with diagnosis of mesenteric ischemia with bacterial translocation that received Ertapenem was included. In the 12-hour CHX group we included three surgical patients: a patient with acute billiary pancreatitis who received Ampicillin-Sulbactam, a patient with mesenteric ischemia that received Ertapenem and a patient with gynecologic source of sepsis who received Clindamycin. These antibiotics cover neither MRSA, nor Acinetobacter.

All patients were intubated with KIMVENT* MICROCUFF* Kimberly-Clark (Roswell, USA) endotracheal tube. Tracheal samples were collected immediately after intubation, and every day thereafter until discharge from the study (extubation or death) using a sterile suction catheter placed into the endotracheal tube.

Endotracheal aspiration was performed using only the closed endotracheal aspiration system (KIMVENT* Turbo-Cleaning Closed Suction System for adults, Kimberly-Clark, Roswell, USA).

The oral care was performed every 6 or 12 hours using Kimberly-Clark Ready Care kit (Roswell, USA) and included brushing teeth and the surface of the tongue and applying suction at completion and as needed during the brushing. CHX (Clorhexin B- Hexi Pharma Co.) was applied using a sterile swab. All teeth, the oral soft tissues including buccal mucosa, vestibule, gingiva, and the floor of the mouth and tongue dorsum were swabbed. Excess rinse was suctioned out of the subject's mouth. Also, before every oral care was performed, the pressure in the cuff was measured and maintained at more than 20 cm H_2O.

The amount of dental plaque was assessed daily using mucosal-plaque score. MPS is a modified oral hygiene index (OHI) sugested by Ahlbom and consists of the sum of a four-point mucosal score (MS) and a four-point plaque score (PS). The sum of MS and PS was labeled MPS (score 2-8). An MPS status was judged as good or acceptable when MPS = 2-4, as unacceptable when MPS = 5-6, and as poor when MPS = 7-8 (Annex 2)[16].

Table I Subject characteristics and outcomes between groups

Variables	Total (n= 30)	6 h CHX (n= 15)	12 h CHX (n= 15)	P
Age (years)*	55.8 ± 18.1	57.8 ± 18.8	53.9 ± 17.8	NS
Gender: male/female	18/12	9/6	9/6	NS
Admission indication, n (%) Surgical Medical Trauma Renal Neurologic Other	 4 (9%) 9 (20%) 10 (22%) 3 (7%) 3 (7%) 1 (2%)	 1 (7%) 7 (47%) 5 (33%) 0 (0%) 2 (13%) 0 (0%)	 3 (20%) 2 (13%) 5 (33%) 3 (7%) 1 (7%) 1 (2%)	
Co-morbidities, n (%) Cardiac Gastrointestinal Pulmonary Renal Central nervous Diabetes Obesity Alcoholism	 19 (36%) 4 (8%) 5 (10%) 6 (11%) 3 (6%) 4 (8%) 5 (10%) 5 (10%)	 11 (46%) 2 (9%) 2 (9%) 2 (8%) 2 (8%) 1 (4%) 2 (8%) 2 (8%)	 8 (29%) 2 (7%) 4 (14%) 4 (14%) 1 (3%) 3 (11%) 3 (11%) 3 (11%)	
APACHE II*	20.43±7.8	19.8±7.3	21.04±7.06	NS
Days in ICU*	14.5±11.7	12.47±11.79	16.6±11.79	NS
Days ventilated*	6.9±4.6	7.07±4.88	6.69±4.48	NS
Deaths, n (%)	7 (19%)	4 (27%)	3 (20%)	NS

**data are expressed as mean±standard deviation; CHX= Chlorhexidine gluconate; NS= not significant; APACHE II= Acute Physiology and Cronic Health Evaluation II; ICU= Intensive Care Unit*

Except the contraindications, the patients were maintained in a semi-recumbent position with the head of the bed elevated 30° to 45°.

Statistical analysis

This study was a prospective, randomized study. Once subjects were enrolled to the study site, study personnel completed protocol specific case report forms according to the study evaluation schedule. The case report forms were entered into the study database and statistically analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) and SPSS 15.0 (SPSS Inc.-IBM, Chicago, USA). The G power 3.1.6 (free software - Kiel University, Germany) was used to evaluate the statistical power of study. In order to have a 0.9 power of detecting a difference between colonization in 6-hour CHX group and 12-hour CHX group, it was determined that a minimum group size would require 40 patients (β 0.90, α 0.05).

Data are expressed as absolute numbers with or without percentages, as means with standard deviation or as medians with ranges. Chi-square or Fisher exact test were used to compare proportions, t test or Mann-Whitney-Wilcoxon test to compare continuous variables. To quantify the relationship between categorical variable *Phi* and Cramer`s V coefficiens were used. A *p* value <0.05 was considered statistical significant.

Results

Demographic and clinical characteristics of the subjects enrolled in this study are presented in **Table 1**. The mean age of the 30 study subjects was 55.8 years (range: 17 to 82), with the majority being males.

No significant differences were found between groups with respect to APACHE II, ventilator days, days in ICU or mortality.

At the beginning of the study the MPS mean was approximately equal between the two groups. Regarding the development of mucosal-plaque score for the group of patients undergoing oral decontamination with chlorhexidine at 6 hours, MPS remained constant at an average of 3 until day 6 of study, after which the score begins to increase reaching an average value of 6 on day 9 of the study. In the group treated with chlorhexidine at 12 hours MPS remains constant at an average of 3 and begin to increase on day 8 of endotracheal intubation, reaching an average of 5 on day 10 of the study **(Figure 1)**.

None of the above differences were statistically significant (p= 0.898).

Analyzing the frequency of colonization based on its time of onset, the results show that for 60% of patients in 6 hours CHX group colonization did not develop until leaving the study (extubation or death). In 12 hours CHX group 40% of

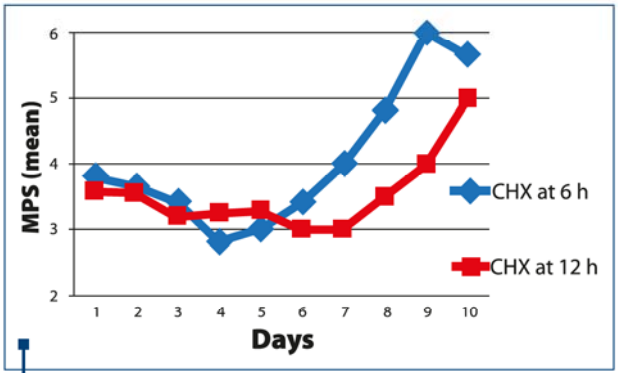

Figure 1. *Sequential changes in mucosal-plaque score (MPS) for the two groups of patients*
Vertical: *MPS (mean)= mean of mucosal-plaque score (1-8)*
Horizontal: *Days = days of study (1-10)*
CHX at 6 h = 6-hour chlorhexidine decontamination group
CHX at 12 h = 12-hour chlorhexidine decontamination group

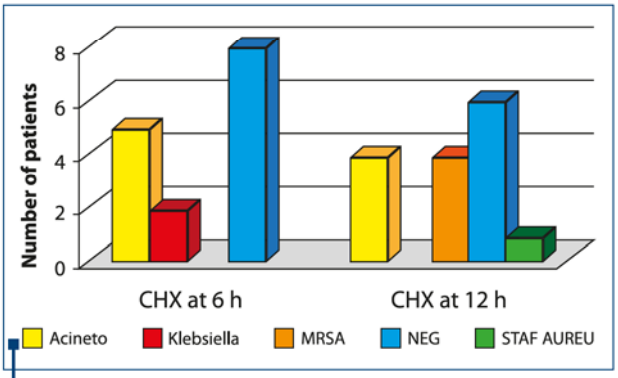

Figure 2. *Bacteriologic etiology of colonization/infection*
Vertical: *Number of patients (1- 8)*
Horizontal: *CHX at 6 h= 6-hour chlorhexidine decontamination group; CHX at 12 h= 12-hour chlorhexidine decontamination group; Acineto= Acinetobacter spp; MRSA= Methicilin resistant Staphylococcus Aureus; NEG= negativ*

patients showed no colonization until leaving the study.

Table 2 shows the frequency of colonization based on its time of onset for the two groups of patients.

No significant difference were found between groups with respect to frequency of colonization based on its time of onset (Mann-Whithey-Wilcoxon test, p=0.523). The statistical power for this comparison was 0.75.

Among the 30 patients admitted, tracheal aspirate samples were colonized by Acinetobacter in 5 patients in the 6 hours chlorhexidine group and in 4 patients in the 12-hour chlorhexidine group. There is no significant association between 6 hours CHX decontamination and prevalence of Acineobacter (coefficient Phi and Cramer's V- ϕ_c =0.073, p=0.690).

In 12-hour chlorhexidine group four tracheal samples were colonized by MRSA (Figure 2). In the 6-hour chlorhexidine group MRSA was absent.

The association between 12-hour chlorhexidine group and the presence of MRSA was not significant (Fisher exact - p=0.1), however, there is a relationship between the isolation of MRSA and CHX oral decontamination at 12 hours (correlation coefficient Phi and Cramer's V ϕ_c =0.392, p=0.032).

The results of bacterial sampling and strains isolated from tracheal aspirate in both groups are described in **Figure 2**.

Discussion

Ventilator-associated pneumonia (VAP) has been associated with significant morbidity and mortality. Crude mortality rates of 20–50% and attributable mortality rates of 30% have been documented[20]; in one study, the number of deaths linked to nosocomial pneumonia reflected 60% of all deaths resulting from nosocomial infections[21]. Other studies have indicated that the development of VAP prolongs hospital stay and significantly increases resource utilization and cost[20]. As VAP continues to be a common complication of critical care, development of preventive approaches are essential to reduce the incidence of this costly infection[22].

It is generally accepted and supported by several studies that periodontal disease and poor oral hygiene in ICU patients present a potential reservoir for nosocomial pathogens[14,23]. Oropharingeal colonization and micro-inhalation or aspiration of these pathogens in ICU patients can lead to the development of nosocomial infections, especially pneumonia[23]. DeRiso et al. showed in a prospective study that application of topical oropharyngeal chlorhexidine gluconate 0.12% decreased nosocomial respiratory infections overall in patients undergoing cardiac surgery[24]. Chlorhexidine is widely used in the hospital setting as a general disinfectant because of broad-spectrum microbicidal activity.

Chlorhexidine is of particular interest as an oral disinfectant in mechanically ventilated, intensive care unit patients because of its substantivity (the ability to bind to oral tissues with subsequent slow release and thus a relatively long period of action - up to 6 hours)[24].

The goal of the present preliminary study was to determine the frequency (two or four times a day) of oral decontamination with 0.5% chlorhexidine required to improve oral hygiene and to reduce tracheal colonization by potential pathogens.

The MPS score averages were between 3.8 and 6 in the 6-hour CHX group and between 3.6 and 5 in the group treated with chlorhexidine in 12 hours. Oral decontamination with 0.5% CHX had no significant effect on the development of dental plaque. In both groups MPS score worsened during the ICU stay. There was no positive relationship between MPS score and frequency of CHX decontamination. In contrast, MPS score worsened earlier (day 6 of IOT) in group treated with CHX at 6 hours. A possible explanation for these results is that a four time chlorhexidine 0.5% oral decontamination can cause mucosal irritation. Colonization of the tracheobronchial tree was recorded in 40% of patients in the 6-hour CHX group, compared with 60% of patients in the 12-hour CHX group.

Even if no statistical significance was found between the frequency of colonization in the two groups, the results show that the use of oral topical chlorhexidine four times a day resulted in a reduction in the frequency of MRSA

colonization of tracheal secretion of mechanically ventilated ICU patients. This finding supports previously published studies that suggest that MRSA is vulnerable to CHX disinfection[15]. However, chlorhexidine did not appear to reduce the frequency of Acinetobacter colonization in tracheal aspirate. The possible explanation why CHX did not reduce the numbers of Gram-negative pathogens in endotracheal secretions is the fact that Gram-positive pathogens such as MRSA are more sensitive to CHX than are Gram-negative pathogens[25,26].

A number of published studies suggest that topical CHX twice a day prevents VAP[15,25,27-29]. Furthermore, several studies have demonstrated the genetic similarity of bacteria isolated from the lung to bacteria isolated from dental plaque, demonstrating that dental biofilms are an important reservoir for these pathogens[30, 31]. The subsequent reduction in the number of viable potential respiratory pathogens (PRPs) in the secretions thus reduces the number of viable organisms aspirated into the lower airway and therefore will prevent subsequent infection. Alternatively, the virulence potential of the bacteria may be reduced by CHX. Previous studies have suggested that CHX is able to bind to bacterial components such as lipopolysaccharide and proteases[32]. Such interactions may diminish the biologic activity of such components to reduce the virulence potential of bacteria. It is also possible that concomitant use of other oral care products such as toothpaste might reduce CHX efficacy[33].

Previous meta-analyses of trials conclude that this CHX is effective in prevention of VAP[34,35]. These analyses revealed, however, that there was variation in the populations studied as well as in the concentration, preparation, and dosing schedule of CHX. Clinical trials of CHX have tested concentrations of 0.12%, 0.2%, and 2%, applied two to four times a day, and delivered as a rinse, gel or in Vaseline. Thus, although topical application of CHX to the oral cavity of ventilated ICU patients in some cases appears to prevent VAP, the optimal concentration and frequency of application of this agent has not been validated. The novelty of the present study consist of using a 0.5% chlorhexidine concentration, two or four times a day, for oral decontamination in mechanically ventilated patients.

In summary, in our preliminary study, no significant difference between two versus four times a day 0.5% CHX decontamination in terms of reducing tracheal colonization/infection by PRPs was found, with the exception of MRSA, whose number of colonizations was reduced in individuals treated with CHX delivered at 6 hours. Despite this potential benefit, MPS score worsened earlier in 6-hour CHX group.

The potential limitation of the study need to be discussed. Given the fact that this is a preliminary study, the sample size was not sufficiently large to show a statistically significant difference between the two groups. Larger samples of ICU patients are needed to determine the optimal concentration and frequency of oral chlorhexidine aplication for achieving reduction in tracheal colonizations, nosocomial infections, length of hospitalization, duration of mechanical ventilation in the ICU.

Acknowledgment: The study was accomplished inside POSDRU /86/1.2/S/61577 project, without financial support. ■

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