

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

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

To the Editor

An article titled “The use of 2% chlorhexidine gel and tooth brushing for oral hygiene of patients receiving mechanical ventilation: effects on ventilator-associated pneumonia” was published in *Rev Bras Ter Intensiva* (2012; 24(4):369-74).⁽¹⁾ While the researchers terminated the study due to the futility of the applied method, the unrealistic results of the study inspired us to write this letter. The mentioned paper had the following fundamental scientific and technical problems:

- Chlorhexidine belongs to the family of N1, N5-substituted biguanides. At physiological pH, it can serve as an antiseptic for the maintenance of oral hygiene. Moreover, the application of 0.12% chlorhexidine solution is necessary for the healing and regeneration of oral tissues.⁽²⁾ In addition, the antibacterial effects of oral rinses containing 0.1% chlorhexidine solution have been well documented by several clinical studies.⁽³⁾ The bactericidal effects of chlorhexidine salts are attributed to the dissociation and release of the positively charged chlorhexidine cation. The released cation will then bind to negatively charged bacterial cell walls. Therefore, while chlorhexidine has antiseptic properties at low concentrations ($\leq 0.12\%$), at high concentrations ($> 0.15\%$), it is a disinfectant capable of causing cellular disruption and cell death.⁽⁴⁾ Unfortunately, the esteemed authors did not clarify the type and potency of the applied chlorhexidine compound.
- Based on the available data, due to the cationic nature of chlorhexidine, its efficacy as a potent disinfectant is reduced in the presence of serum, blood, pus, soaps, and other anionic compounds. However, the authors did not consider such effects in gel preparation.⁽⁵⁾
- The sample size and statistical methods applied were inadequate. Additionally, the methodology was not comprehensively discussed. The authors did not appear to have benefitted from the numerous valuable and relevant reports published in this regard.
- In the study in question, the patients were divided into two groups: placebo and intervention. Ideally, there should have been an extra control group that received neither placebo nor the intervention.
- The authors determined that the incidences of ventilator-associated pneumonia (VAP) were 45.8% in the placebo group and 64.3% in the intervention group. However, the incidence of VAP in the absence of placebo/intervention was not determined. Although increased bacterial growth in the oral cavity due to the presence of organic substances in the gel might have been responsible for the mentioned incidences, the exact

Conflicts of interest: None.

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reasons could not be clarified. If the researchers had designed the study correctly by examining three groups (intervention, placebo, and control), they would have been able to compare the results among all groups and would understand the reasons underlying the failure of their approach.

- Although 1% chlorhexidine has been shown to exert antiseptic effects, the authors used a 2% chlorhexidine gel for no particular reason. It is possible that the basic materials present during gel preparation might have contained anionic components that could affect the intrinsic cationic activity of chlorhexidine. In fact, changing the gel formulation could have led to different results. Previous research has indicated that natural extracts of *Morinda citrifolia* and *Aloe vera* as well as papain extracts exhibited different activities.⁽⁶⁾

The destructive effects of chlorhexidine on the oral mucosa might have been responsible for the higher

infection rates in the intervention group compared to the placebo group. In other words, the gel might have facilitated bacterial growth by destroying one of the most important defensive barriers. Furthermore, reactions between chlorhexidine and the gel components might have accelerated bacterial growth by providing nutrition.

Nevertheless, from an oral hygiene standpoint, chlorhexidine is considered crucial for preventing pneumonia and mouth infections. Therefore, studies in this field must focus on both the advantages and disadvantages of this oral antiseptic. Such evaluations will not only enhance medical team members' and researchers' understanding of the existing facts but also lay the ground for future research.

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AUTHOR'S RESPONSE

We appreciate Dr. Ali Ataee's comments and the opportunity to contribute to the discussion on this important topic. Chlorhexidine solution has been used as an anti-infective oral agent in dental medicine either as a rinse or in gel form. The reasons that led us to choose 2% chlorhexidine gel in the study "The use of 2% chlorhexidine gel and toothbrushing for oral hygiene of patients receiving mechanical ventilation: effects on ventilator-associated pneumonia"⁽¹⁾ are specifically related to this subset of mechanically ventilated, critically ill patients in whom homogeneously effective care of the oral mucosa cannot be guaranteed via the use of rinse solutions over a long term. Additionally, there is a higher risk of extubation as well as a

fear of bronchial aspiration when aqueous solution is used for the oral hygiene of these patients.

Two previous studies used 2% chlorhexidine and showed a reduction in the incidence of ventilator-associated pneumonia (VAP) in the treated group.^(2,3) Although oral decontamination with low concentrations of chlorhexidine (0.12%-0.2%) has been found to be effective in preventing pneumonia in patients undergoing cardiothoracic surgery, 2% chlorhexidine was tested in a in vitro study and showed better activity against multidrug-resistant bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*.⁽³⁾ In this study, the rate of oropharyngeal colonization with gram-negative

bacilli was reduced or the onset of colonization was delayed in patients who received 2% chlorhexidine as an oral rinse.⁽³⁾ These multidrug-resistant pathogens are currently the most prevalent agents causing VAP in non-cardiac surgery and trauma patients. In fact, other authors have claimed that the use of 2% chlorhexidine might be more effective in reducing the incidence of VAP.⁽⁴⁾ We speculated that a more highly concentrated antimicrobial in gel form would be retained longer in the mucosa while being more effective and less detrimental.

In our opinion, it is possible but not likely that the local lesive effects of chlorhexidine on the oral mucosa were responsible for the increase in infections. A total of 9.8% of the patients who received 2% chlorhexidine oral solution developed irritation of the oral mucosa in a study by Tantipong et al.⁽³⁾ In their study, the irritation was caused by vigorous rubbing of the oropharyngeal mucosa with gauze soaked with 2% chlorhexidine solution and was resolved after the personnel were instructed to clean the oropharyngeal mucosa more gently. In our study, the healthcare workers were aware of this side effect and were alerted to discontinue the use of 2% chlorhexidine oral solution if there were any adverse events related to the use of the gel. In addition, one of the authors (MCAM), a dental surgeon, evaluated the patients on a daily basis to evaluate irritation and accumulation of gel.

We would like to remark again that this is a pilot study that was interrupted in the first interim analysis, and the small sample size is a very important limitation.⁽¹⁾ We completely agree that a factorial design would be the ideal choice. With such an elegant design, Munro et al. reported that toothbrushing alone did not reduce ventilator-associated pneumonia, and combining toothbrushing with 0.12% chlorhexidine oral swab twice daily did not provide an

additional benefit over chlorhexidine alone.⁽⁵⁾ Nevertheless, we believe that despite its limitations, our study may help other investigators to design their own studies.

Despite our contradictory results, we do not doubt that using chlorhexidine rinse or gel can reduce the rate of VAP in at-risk patients, as even an early single application of chlorhexidine to the oral cavity significantly reduced the Clinical Pulmonary Infection Score, and thus VAP, in trauma patients.⁽⁶⁾ A recent meta-analysis of 5375 patients concluded that oral hygiene care that includes either chlorhexidine mouthwash or gel is associated with a 40% reduction in the odds of developing ventilator-associated pneumonia in critically ill adults.⁽⁷⁾ However, we believe that in this particular group of intubated patients on mechanical ventilation, the best care practices have not yet been defined. As we discussed in the paper, manual brushing performed by a caregiver could increase the risk of adverse events and the VAP rate by breaking the mucosal barrier and spreading pathogens in the blood stream or the oral cavity. Furthermore, we strongly believe that toothbrushing without controlling the cuff pressure of the endotracheal tube before and after hygiene might increase the chance of microaspiration, as shown by Vieira et al.⁽⁸⁾ Interestingly, a recent systematic review and meta-analysis of randomized trials evaluating ventilator-associated pneumonia concluded that in intubated, mechanically ventilated, critically ill patients, toothbrushing did not significantly reduce the risk of ventilator-associated pneumonia overall and had no effect on mortality or length of stay.⁽⁹⁾

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