Enfermería Intensiva 34 (2023) 227–229

SEEIUC
Sociedad Española de Enfermería Intensiva y Unidades Coronarias

Enfermería *Intensiva*

www.elsevier.es/ei

LETTER TO THE EDITOR

Oral care with chlorhexidine: One size does not fit all

Higiene oral con clorhexidina: una recomendación única no sirve para todos

Dear Editor,

We read with interest the article by Arias-Rivera et al. in a supplementary issue of *Enfermería Intensiva* (September 2022)[1] reporting on an update on the Zero Pneumonia recommendations in view of the overall increase in ventilator-associated pneumonia (VAP) cases in Spain during the SARS-Cov-2 pandemic. However, we question the continued endorsement of chlorhexidine mouthwashes to prevent VAP in all critically ill patients. Firstly, the evidence underpinning the widespread application of oral chlorhexidine mouthwashes for the prevention of VAP is of low certainty. Secondly, and even so important, chlorhexidine interferes with important physiological processes in the oral cavity and triggers antimicrobial resistance. Furthermore, large studies suggest an association with mortality.

The complex flora in the human oral cavity has critical physiological functions, including an active role in food digestion, metabolic regulation, detoxification, and immunological barrier functions which prevent the growth of disease-promoting microorganisms.[2] This suggests there is a physiological equilibrium between pro-inflammatory and anti-inflammatory processes, which can be substantially deranged by oral antiseptics.

A recent review hypothesises that the elimination of oral bacteria by antiseptic mouthwashes may have a detrimental influence on the nitrate-nitrite-nitric oxide pathway (N-N-NO pathway).[3] The latter is an important mechanism for nitric oxide (NO) generation in which oral bacteria play a vital role by reducing nitrate to nitrite. Nitrite-rich saliva is subsequently swallowed and absorbed into the system where it is further reduced to NO. NO has multiple beneficial effects including vascular tone regulation, wound healing, and antiseptic properties. Interruption of this pathway by killing essential oral bacteria results in a condition of deficient NO bioavailability. This impairs metabolic functions and affect patient outcomes, particularly in septic and cardiovascular patients. Likewise, in intubated patients, the swallowing of nitrite-rich saliva is already compromised, and oral antiseptics will add to this disrupted pathway.

While it is unclear whether oral antiseptics are harmful in patients with extreme disease severity, the evidence suggests that patients with a more favourable prognosis have an increased risk of mortality when exposed to antiseptic mouthwashes.[4]

Moreover, xerostomia, a recognised side effect of the use of antiseptics, may increase the development of oral lesions with increased infection risk, an important consideration in immuno-compromised patients. Furthermore, recent advances in antimicrobial stewardship initiatives that focused on acquired bacterial resistance have warned of emerging resistance against chlorhexidine, especially in Gram-negative bacteria.[5] Additionally, low-level exposure to chlorhexidine triggers cross-resistances to antibiotics thereby constituting a clinical threat beyond chlorhexidine-resistance.[5] Therefore, antiseptic stewardship initiatives have been suggested restricting the use of chlorhexidine and carefully assess the application of the agent where benefits to patient care are questionable.

Consequently, the argument in favour of de-adoption of chlorhexidine mouthwashes has gained momentum. A review that included the paper from Dale and colleagues observed an overall improvement in oral health with a de-adoption strategy and detected no difference in mortality regardless of whether chlorhexidine was administered or not. As such, oral bacteria and their role in metabolic homeostasis are likely to be more important than previously thought.[6]

The need for oral care should not be questioned, however, we must be aware that antiseptics are not harmless and their application needs to be individualised. Future research needs to point out how to perform oral care with respect to the commensal flora. For now, some evidence points out that we should toothbrush 2–3 times/day without applying oral antiseptics[6] and future research should measure the benefits of additional interventions to provide the best standard of care.

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https://doi.org/10.1016/j.enfie.2023.08.001

In response to «Oral care with chlorhexidine: One size does not fit all»

Respuesta a «Higiene oral con clorhexidina: una recomendación única no sirve para todos»

Dear Editor,

We appreciate the comments by Llaurado-Serra et al. in relation to the article ''Update on the recommendations of the Zero Pneumonia project'' published in 2022 in **Enfermería Intensiva**.[1] In response to your comments, we would like to make some clarifications. On the one hand, we feel we need to clarify that the updating of the Zero Pneumonia (NZ) recommendations, together with those of the rest of the Zero Projects (PZ), is due to the negative impact of the SARS-Cov-2 pandemic on the application of PZ recommendations and the infection rates monitored in ICUs,[2] as well as the need to review and adapt the recommendations made in 2011. In these recommendations, and as part of the NZ Bundle, the measure of oral hygiene with chlorhexidine in intubated patients had already been included, after having demonstrated its efficacy nationwide in reducing rates of pneumonia associated with mechanical ventilation (NAVM) in Intensive Care Units (ICUs).[3]

On the other hand, we continue to support oral hygiene with 0.12%–0.2% chlorhexidine to prevent VAP in critically ill patients. This is essentially because, as evidenced in a recent systematic review and meta-analysis that includes 10 randomised clinical trials (RCTs),[4] chlorhexidine prevents VAP in critically ill patients, even at low doses, as recommended, showing no adverse effect on mortality rates. Specifically, the oral application of chlorhexidine reduced the incidence of VAP, (RR, 0.73 [95% CI, 0.55, 0.97]) and did not show an increase in all-cause mortality (RR, 1.13 [95% CI, 0.96, 1.32]).[4]

Indeed, as we recognise in the NZ Project document,[5] the use of chlorhexidine is not without adverse effects. However, these are not limited to intubated patients with MV, observing irritation of the buccal mucosa in only 10% of those treated with 2% chlorhexidine, a higher dose than recommended.

With regard to what has been argued regarding the increased risk of mortality associated with oral hygiene with antiseptics, as previously mentioned, no RCT has been found that has shown an association between oral hygiene with chlorhexidine and higher mortality rates. It should also be mentioned that the cohort study cited by the authors to argue for this association[6] includes patients from the entire hospital. This association was not seen in ICU patients with mechanical ventilation (MV), the population to which we address this recommendation, but rather in hospitalised neurological patients. In addition, the high risk of bias in this type of study cannot be ignored when interpreting the results.

Therefore, and taking into account the evidenced beneficial effect of chlorhexidine on the prevention of VAP in critically ill patients, we believe that removing it from the NZ bundle would place hospitals in a dilemma as to what to use instead of chlorhexidine for oral hygiene.

We appreciate the interest shown in our article, by your letter, although we do not share the title, since we recommend its use only in critically ill patients who require MV, where its effectiveness has been demonstrated. Furthermore, the arguments provided against chlorhexidine in oral hygiene are already known and discussed in the scientific literature. Like the rest of the drugs that are administered to patients with the intention of preventing infections, the pros and cons of administering them must always be weighed up. For that reason, after conducting an exhaustive review of the literature and assessing the advantages of 0.12%–0.2% chlorhexidine in oral hygiene in patients who require MV, we decided to maintain this recommendation within the bundle of measures in the NZ project.

DOI of refers to article: https://doi.org/10.1016/j.enfi.2023.05.002