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LETTER TO THE EDITOR

Antiseptic mouthwashes and mortality: look beyond chlorhexidine

Enjuagues bucales antisépticos y mortalidad: más allá de la clorhexidina

Dear Editor:

Ventilator-associated pneumonia (VAP) remains a concern calling for optimal prevention strategies.[1] In this regard, we read with interest the article by Vieira et al. concerning chlorhexidine oral care in ICU patients.[2] The authors wonder whether there is still room for this practice in VAP prevention care bundles. Indeed, the scientific evidence supporting chlorhexidine mouthwashes is limited to cardiac-surgery patients. Additionally, Vieira's question originates from the accumulating body of literature illustrating excess mortality in patients exposed to chlorhexidine mouthwashes.[3] These observations have incited controversy because of the lack of a pathogenic mechanism explaining the mouthwash-mortality relationship. Initially, micro-aspiration of mouthwash solution has been proposed as a potential explanation because of chlorhexidine's lung toxicity. However, the theoretical basis is small as it is based on, on one hand, an accidental case of massive aspiration of abundant amounts of the mouthwash solution, and, on the other hand, an experimental model exposing lungs of mice to chlorhexidine dosages way beyond what is used in daily practice. Moreover, in the hospital-wide cohort study by Deschepper and colleagues, the harmful impact of chlorhexidine mouthwashes appeared to be higher in non-critically ill and non-ventilated patients, thereby annihilating the micro-aspiration hypothesis.[4]

We recently suggested that a disturbance of the enterosalivary nitrate-nitrite-nitric oxide (NO) pathway may explain the increased mortality risk observed in patients exposed to chlorhexidine mouthwashes.[5] NO is a key molecule in human physiology with an essential role in neurotransmission, mitochondrial respiration, the maintenance of vascular permeability and tonicity, the inhibition of leucocyte adhesion and platelet aggregation, and protection against anti-oxidants. An essential step in the nitrate-nitrite-NO pathway is the reduction of nitrate to nitrite. This process takes place in the oral cavity and is provided by facultative anaerobic bacteria located at the posterior surface of the tongue. Evidently, antiseptic mouthwashes eradicate these bacteria thereby interrupting the pathway. This may lead to a reduced bio-availability of NO, a condition that puts patients at risk for ischaemic heart events and sepsis as has been reported in literature (data summarized in Ref.[5]).

The combination of (i) the limited evidence that chlorhexidine mouthwashes reduce VAP risk, (ii) multiple studies indicating deleterious effects associated with chlorhexidine mouthwashes, and (iii) the presence of a plausible pathogenic mechanism, strengthens the call to abandon the use of chlorhexidine from our oral care routine.[3] Albeit that so far no deleterious outcomes have been reported with other oral solutions, we believe it would be a mistake to replace chlorhexidine-based solutions by another type of antiseptic mouthwash. If an interruption of the nitrate-nitrite-NO pathway is indeed responsible for the increased mortality risk, the harmful effect is not chlorhexidine-specific. Therefore, all antiseptic mouthwashes are to be avoided, and not only chlorhexidine-based solutions. We propose a 'back-to-basics approach' with emphasis on mechanical cleaning (i.e., toothbrushing) rather than a chemical disinfection threatening that all-important oral microbiome.

We are eager to hear the thoughts of Vieira and colleagues about the nitrate-nitrite-NO theorem and, more importantly, about our recommendation to avoid all oral antiseptics rather than only chlorhexidine-based oral care solutions.

Conflict of interest statement

Both authors have no conflicts of interest to declare regarding the letter to the editor.

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Reply to ''Antiseptic Mouthwashes and Mortality: Look Beyond Chlorhexidine''

Respuesta a ''Enjuagues bucales antisépticos y mortalidad: más allá de la clorhexidina''

Dear Editor:

We have read with great interest the yet unpublished letter from Blot and Deschepper analyzing our article,[1] about oral care with chlorhexidine in critically ill patients, and we have some comments to make regarding the authors' considerations.

Due to the evidence of the association between oral care with chlorhexidine and increased risk of mortality, the International SHEA/IDSA/APIC 2022 Guidelines, in their ventilator-associated pneumonia (VAP) prevention bundles, recommend providing oral hygiene, but without chlorhexidine.[2] However, the pathophysiological mechanisms that explain this association are not well understood.

Indeed, micro-aspirations of chlorhexidine, an acidic substance, which could lead to lung injury, alone do not justify the mechanism of increased mortality. So much so that, in our article,[2] we have presented this as just one, among several, of the possible justifications. Therefore, other theories should be evaluated, including the suggestion by Blot and Deschepper that a disturbance in the enterosalivary nitrate-nitrite-nitric oxide (NO) pathway could help explain the increased mortality risk observed in patients exposed to chlorhexidine mouthwashes. According to the authors, oral antiseptics eradicate the anaerobic bacteria located on the posterior surface of the tongue, interrupting the process of reducing nitrate to nitrite, which occurs in the oral cavity, thus reducing the bioavailability of NO, a condition that could lead to increased mortality due to ischemic events and sepsis.

This theory is attractive, however, it does not fully explain the phenomenon, because: (1) studies evaluating selective oral decontamination with topical antibiotics, in critically ill patients on mechanical ventilation, reported lower hospital mortality[2,3]; (2) reduced bioavailability of the NO could actually be associated with an increased risk for ischemic cardiac events, however, there is evidence of increased mortality with the use of oral chlorhexidine also in young people without heart disease[4] and, in patients undergoing cardiac surgery, the use of oral chlorhexidine is associated with better outcomes[1]; and (3) if, on the one hand, the vasoconstrictor effect of low NO levels can be harmful for septic patients, on the other hand, high levels of this inflammatory mediator are associated with worse outcomes and increased mortality.[5] NO exerts an important role in the pathophysiology of sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), by causing increased endothelial permeability, vascular leakage, mitochondrial dysfunction, impaired migration of neutrophils to the focus of infection and worsened cardiovascular responsiveness in severe cases of sepsis.[5]

Besides the various possible justifications described in our article,[1] and the NO theorem proposed by Blot and Deschepper, other pathophysiological mechanisms that could explain the increased mortality risk observed in patients undergoing oral care with chlorhexidine should be sought and evaluated.

To our knowledge, there are no studies reporting increased mortality with the use of other oral antiseptics. Therefore, we believe that the issue of not using any antiseptic mouthwash, in the care of critically ill patients, should be explored in research comparing oral hygiene with chlorhexidine, with an alternative antiseptic, and with no antiseptic at all.

Conflict of interest

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