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Review

Evaluation of the Effect of Chlorhexidine Mouthwash on Blood Pressure: A Narrative Literature Review

Mayara Yonezaki [1,‡], Pollyanna Almeida [1,‡], Eduarda de Oliveira [1,‡], Giovanna Ramos [1,‡], Giovanna Bezerra [1,‡], Marcos Vinícius da Silva [1,‡], Raphael Moutinho [1,‡], Cláudia Lucia Moreira [1,‡] and Adriana Cruz [1,‡,*]

[1] Centro Universitário Uniceplac, School of Dentistry, SIGA Área Especial para Indústria nº 02 Setor Leste, Gama, DF, 72445-020, Brazil; mmyonezaki@gmail.com (MY); pollyanna.suelyn@gmail.com (PA); edudabessa@gmail.com (EO); giovannamoraesramos@gmail.com (GR); giovannavictoriaramos02@gmail.com (GB); marcossvs01@gmail.com (MVS); raphael.damaceno15@gmail.com (RM); claudia.moreira@uniceplac.edu.br (CLM)
[‡] these authors contributed equally to this work

* Correspondence: adriana.cruz@uniceplac.edu.br

Abstract: This article presents a narrative review investigating the use of chlorhexidine mouthwash and its impact on blood pressure and cardiovascular health. Chlorhexidine, a widely used antimicrobial in Dentistry, has been associated with risks, such as increased blood pressure. The bibliographic research included articles published between 2014 and 2024, using the PubMed, SciELO, and the Virtual Library of the Ministry of Health databases, with keywords including "chlorhexidine", "mouthrinse", "mouthwash", "nitrate" and "blood pressure". The results indicate that chlorhexidine may disrupt nitric oxide homeostasis, essential for blood pressure regulation, by inhibiting oral microbiota bacteria that reduce nitrate to nitrite. Although effective in reducing pathogenic microorganisms, chlorhexidine should be prescribed with caution, considering its potential hypertensive effects. The study concludes that further research is needed regarding the contexts of chlorhexidine use and prescription, as well as the development of oral hygiene protocols that balance the elimination of pathogenic microorganisms with the preservation of beneficial microbiota.

Keywords: chlorhexidine; mouthrinse; mouthwash; nitrate; blood pressure

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Introduction

Chlorhexidine is a broad-spectrum antimicrobial first described in 1954 [1]. Its mechanism of action is related to microbial cell membranes, where it causes damage and leakage of cytoplasmic material [2]. The substance is active against Gram-positive bacteria, with a less pronounced effect on Gram-negative bacteria, fungi, and enveloped viruses [2]. It is widely used as an antiseptic for skin and mucous membranes.

In Dentistry, chlorhexidine has been widely used for various purposes. A quantitative reduction in oral microbiota and microbial biofilm formation was demonstrated following mouth rinsing with 0.12% chlorhexidine [3]. It is recommended as an antiseptic during both pre- and post-operative periods of surgeries for dental biofilm control in patients with difficulty brushing, in the treatment of gingivitis and periodontal disease, and for irrigation and cleaning of root canals, among other applications. Currently, it is the most commonly used antiseptic for oral decontamination in hospitalized patients under mechanical ventilation [4].

However, some studies have raised concerns about potential risks and adverse effects associated with the use of chlorhexidine. Among the reported risks, there is preliminary, yet inconclusive, evidence suggesting increased blood pressure levels in patients using chlorhexidine as a mouthwash antiseptic [5]. Considering the clinical relevance of this possible adverse effect, it is important to explore the relationship

between chlorhexidine use and hypertension. Therefore, this narrative review aims to provide an overview of the relationship between the use of chlorhexidine mouthwash and its potential impact on blood pressure and other cardiovascular health parameters.

Materials and Methods

The present paper is a narrative literature review conducted through bibliographic research, aiming to determine whether the use of chlorhexidine mouthwash is associated with an increase in blood pressure. The bibliographic research sought to address the following question: Do individuals who use chlorhexidine as a mouthwash antiseptic experience an increase in blood pressure?

Studies in Portuguese and English, published between 2014 and 2024, were selected. The databases used for the article search included the Virtual Library of the Ministry of Health (BVS-Brazil), Scientific Electronic Library Online (SciELO), and PubMed. The keywords used were: "chlorhexidine", "mouthrinse", "mouthwash", "nitrate", and "blood pressure". The selected studies were analyzed and interpreted to support the writing of this article.

Results

Chlorhexidine, when used as a mouthwash antiseptic, is recognized for its effectiveness in reducing oral pathogens and lowering the incidence of ventilator-associated pneumonia in hospitalized patients in intensive care units [6]. It has been demonstrated that chlorhexidine causes a significant reduction in the diversity of bacterial species in the oral cavity during the mouthwash use period, with substantial alterations in the composition of the oral microbiota [7]. Therefore, although chlorhexidine has proven effective in reducing known oral pathogens, it also negatively impacts some beneficial bacterial species, raising concerns about the product's potential effects on oral health [7].

Significant evidence currently links microorganisms in the oral cavity to cardiovascular diseases, such as hypertension [8]. This correlation has been associated with the reduction of nitrate to nitrite by commensal bacteria in the mouth, enabling the formation of nitric oxide—a gas that enhances blood vessel elasticity, promotes vasodilation, facilitates blood flow, and helps maintain blood pressure balance while preventing vascular lesions [9]. Approximately 25% of plasma nitrate is secreted into the oral cavity, where facultative anaerobic bacteria on the tongue's dorsum reduce nitrate to nitrite via reductase enzymes. Most of the nitrite produced enters the stomach upon ingestion, where it is converted into nitric oxide under acidic conditions [10].

The composition of the oral microbiota may be influenced by the frequency of tongue cleaning. Daily tongue cleaning appears to increase the abundance and metabolic activity of species that metabolize nitrate/nitrite, suggesting an association between tongue cleaning frequency and nitrate circulation in saliva [11]. Individuals who included tongue cleaning as part of their hygiene routine experienced changes in the composition of their lingual microbiota and increased blood pressure after seven days of using chlorhexidine as a mouthwash antiseptic [11]. A rapid recovery followed after three days of discontinuing its use, along with a reduction in blood pressure. Conversely, the group of individuals who did not clean their tongues exhibited the opposite response, with a significant decrease in systolic blood pressure after seven days of chlorhexidine use, and an increase after three days of recovery. These findings suggest that the composition of the lingual microbiome may hold diagnostic and therapeutic value for individuals with hypertension [11].

A clinical trial conducted by Bondonno and colleagues in 2015 showed that the use of a chlorhexidine mouthwash for three days by hypertensive patients undergoing treatment decreased oral nitrate reduction and caused a concomitant increase in systolic blood pressure [5]. In another clinical trial conducted in 2016, the effects of different concentrations of commercially available mouthwashes on nitrate and nitrite concentrations in saliva and plasma were examined after the ingestion of 8.4 mmol of inorganic nitrate contained in beetroot juice [12]. The results demonstrated that the conversion of nitrate to nitrite depends on bacteria located in the mouth, and that chlorhexidine almost eliminated any conversion reactions performed by these bacteria. Plasma nitrate and salivary nitrite concentrations were lower when chlorhexidine mouthwash was used compared with other products, and an increase in systolic blood pressure was also observed [12].

The impact of mouthwashes with different chemical compositions on salivary nitrate and nitrite levels, as well as on the levels of *Veillonella dispar*, a representative species of nitrate-reducing bacteria in the oral cavity, was examined [13]. Mouthwashes containing chlorhexidine were used at a low concentration of 0.0025%; nevertheless, there was inhibition of *V. dispar*, although no reduction in salivary nitrite production was observed [13]. A study conducted in 2020 demonstrated that the use of chlorhexidine mouthwash for seven days was associated with changes in the salivary microbiome, increased salivary acidity, and reductions in nitrites in saliva and blood, along with a trend toward increased systolic blood pressure [7]. This study employed a single-blind, crossover, non-randomized design in which 36 healthy individuals used a placebo mouthwash followed by a chlorhexidine mouthwash for seven days, swishing for 1 minute, twice daily. The study highlighted the importance of nitrite production in the oral cavity for cardiovascular health regulation [7].

However, a clinical trial conducted in 2016 showed that, in healthy young women, a 0.2% chlorhexidine mouthwash interrupted the oral conversion of bacterial nitrate to nitrite, but this was not associated with changes in plasma nitrite, basal metabolism, or blood pressure [14]. In another study, the use of mouthwash also did not significantly impact the risk of death from cardiovascular diseases [15]. Data from 354 adult individuals who participated in a cohort study were analyzed to evaluate the association between brushing habits, flossing, mouthwash use, and the risk of death from cardiovascular diseases [15]. The individuals in this study had a median follow-up of 18.8 years, and the results showed that better oral hygiene was associated with a significant reduction in the risk of mortality from heart disease, but no additional impact from the use of mouthwash was found [15].

In a systematic review with meta-analysis that included 16 randomized clinical trials, the authors concluded that oral hygiene with chlorhexidine may be beneficial in preventing pneumonia in a group of patients, specifically those in the postoperative period of cardiovascular surgeries [16]. The results indicated that the use of chlorhexidine did not show benefits in patients hospitalized for causes other than heart surgery. Additionally, the analysis found no evidence that the use of the antiseptic in oral hygiene reduced mortality or other important clinical outcomes, such as the length of hospital stay, and adverse effects associated with its use were reported [16]. A systematic review published by Cochrane in 2020 concluded that oral antisepsis with chlorhexidine can prevent ventilator-associated pneumonia, but no benefits were found for other outcomes, such as hospitalization time, intensive care unit (ICU) stay, or mortality [6].

Two retrospective cohort studies found an increased risk of mortality in hospitalized patients who underwent oral hygiene with chlorhexidine [17,18]. Deschepper and colleagues analyzed data from 82,274 patients, of whom 11,133 received oral antisepsis with chlorhexidine. The authors concluded that the use of chlorhexidine for oral hygiene in hospitalized patients was associated with increased mortality, and the risk of death was higher for patients with a more favorable prognosis [17]. In the cohort study conducted by Parreco *et al.*, data from 64,904 patients across 186 hospitals in the United States were analyzed. This study concluded that oral hygiene with chlorhexidine was an independent risk factor for death and sepsis, and there was no reduction in the incidence of pneumonia in patients in the ICU [18].

In a narrative review by Blot *et al.*, the hypothesis was argued that the increased risk of mortality among hospitalized patients who used chlorhexidine mouthwashes may be attributed to changes in the oral microbiome caused by the substance [19]. Although it is not possible to exclude the possibility that other confounding factors were involved, the hypothesis was raised that the reduced bioavailability of nitric oxide may be related to the increased mortality associated with the use of antiseptic mouthwash [19].

A 2024 narrative review discussed the role of the oral microbiota in maintaining blood pressure, particularly the connection between nitrate-reducing bacteria in the mouth and the bioavailability of nitric oxide in the bloodstream, as well as blood pressure regulation [20]. The same study also explored the possibility of using nitrate-reducing bacteria as oral probiotics in the prevention and treatment of hypertension [20].

Discussion

This paper addressed the use of chlorhexidine as an oral antiseptic and the potential risks associated with it, focusing on the risk of increased blood pressure. Published articles demonstrate that blood pressure rises when nitric oxide homeostasis is disrupted by the use of antiseptic mouthwashes, particularly those containing chlorhexidine [5,10,12].

The nitrate-nitrite-nitric oxide biotransformation pathway has been described, depending on the reduction of nitrate to nitrite by bacteria present in the mouth (Fig. 1). Nitrate can be found in foods, such as leafy greens and beets, and can also be secreted by the salivary glands [21]. The main nitrate-reducing bacterial species belong to the *Veillonella*, *Prevotella*, *Neisseria*, *Haemophilus*, and *Actinomyces* genera, but it is believed that the reduction of nitrate to nitrite depends on a consortium of microorganisms in the mouth, where some play a role that is still poorly understood, as they are genetically incapable of performing nitrate reduction [21].

The need for this microbial consortium for nitrate reduction may explain the results of the study by Mitsui and Harasawa (2017), which showed the inhibition of the bacterium *Veillonella dispar* by chlorhexidine, but without a reduction in salivary nitrite concentration [13]. In other words, the inhibition of this bacterium, one of the main representatives of the group with nitrate-reducing capability, may have occurred, but not that of other species with the same role. Additionally, an explanation for this result may lie in the low concentration of chlorhexidine used in the study, well below the concentrations typically used in the clinics [13].

While some studies have reported an increase in blood pressure following the use of chlorhexidine mouthwash [5,10,12], others have not observed this effect [7,14]. These contradictory findings may be attributed to the lack of standardization of variables such as duration of use, antiseptic concentration, and patient profile. Some clinical trials included hypertensive participants [5], whereas others involved healthy individuals but with different follow-up periods [7,12,14]. Increases in blood pressure have been reported with chlorhexidine concentrations of 0.2% [10], 0.12% [11,12], and even lower concentrations [5]. However, two other clinical trials found no significant increase in blood pressure with the use of chlorhexidine at a concentration of 0.2% [7,14]. A possible explanation for these conflicting results is the sample profile

of these studies, as the trials that did not confirm changes in blood pressure included younger and overall healthy participants [7,14].

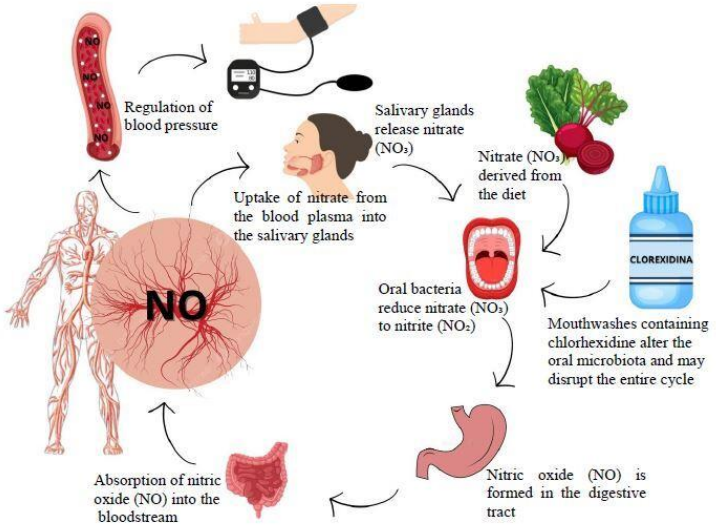

Figure 1. Nitrate/nitrite/nitric oxide cycle (Authors' elaboration).

A study by Tribble *et al.* found interesting results in which patients who had the habit of cleaning their tongue experienced an increase in blood pressure values after seven days of using 0.12% chlorhexidine mouthwash. In contrast, patients who did not clean their tongue showed the opposite result, with a decrease in blood pressure after the same period [11]. It is believed that this may be explained by the presence of nitrate-reducing bacteria in the deeper layers of the tongue surface, which become more sensitive to the effects of chlorhexidine in patients whose tongues are cleaner. Meanwhile, in patients with a buildup of tongue coating, though the activity of nitrate-reducing bacteria was initially impaired, it was aided by the effect of chlorhexidine in removing the biofilm layer covering the surface.

For hospitalized patients, a benefit was found in oral cleaning with chlorhexidine in specific contexts, such as in patients in the postoperative period of cardiovascular surgeries [16]. However, the study by Janket *et al.* stated that there was no relationship between the use of mouthwash and cardiovascular events. Nevertheless, this study, despite having a follow-up of 18.8 years, has an important limitation: the sample did not consist of hospitalized patients, and the information about the composition of the mouthwash used was imprecise, as it was obtained through a questionnaire answered by the research participant, without specifying the brand or composition of the product used [15].

A systematic review published by Cochrane in 2020 concluded that oral cleaning with chlorhexidine was able to reduce the incidence of pneumonia in intubated patients hospitalized in ICUs [6]. However, some cohort studies have shown an increased risk of mortality in patients whose oral cleaning is performed with chlorhexidine [17,18]. A possible explanation can be suggested by noting that the systematic review conducted in 2020 did not assess the risks associated with the use of chlorhexidine, nor did it detect a reduction in mortality or hospitalization time [6]. Therefore, it can be concluded that the reduction of pneumonia rates in isolation may not justify the indiscriminate use of chlorhexidine in all hospitalized patient profiles.

The cohort study by Deschepper *et al.* indicated that the use of chlorhexidine is potentially riskier in hospitalized patients with a higher initial chance of survival [17]. Therefore, the risk of mortality becomes higher in patients hospitalized for less lethal conditions, suggesting that chlorhexidine should not be used in less critical patients, nor in those who can perform their oral hygiene while hospitalized [17]. The conclusions found in the study emphasize the need for a cautious approach when prescribing chlorhexidine, especially in vulnerable populations, such as hospitalized and hypertensive patients.

Recent literature discusses the relationship between oral microbiota and blood pressure regulation, suggesting that the increased risk of mortality in hospitalized patients may be attributed to this chain of events triggered by chlorhexidine [19]. There are perspectives that nitrate-reducing bacteria could be used as probiotics to aid cardiovascular disease treatment and prevention [20,21].

Although chlorhexidine is recognized as an effective antimicrobial in reducing pathogenic microorganisms, its prescription as a mouthwash should be done with caution, especially in hypertensive and hospitalized patients. It is clear that this substance can disrupt the balance of the oral microbiota, and the conflicting results of clinical trials regarding its effects on blood pressure underscore the urgent need for further research to conclusively determine whether the use of chlorhexidine mouthwash may elevate blood pressure.

Future research should explore the appropriate contexts for the indication and use of chlorhexidine, considering the patient profile that would benefit most, the concentration deemed safe, and the optimal duration and mode of use. Additionally, studies are needed to identify alternative oral hygiene strategies for hospitalized patients and approaches to modulating the oral microbiota to maintain homeostasis. It is essential to develop oral hygiene protocols that consider both the need to reduce pathogenic microbiota and the preservation of beneficial microbiota.

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Author Contributions

MY and PA acquired, analyzed, interpreted the data, and drafted the present manuscript. EO, GR, GB, MVS, and RM acquired, analyzed, interpreted the data, and made substantial contributions to the work's design. CLM made substantial contributions to the design of the work and revised it critically. AC planned and conceived the work's overall design, acquired, analyzed, interpreted the data, and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no competing interests.

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