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Antimicrobial Efficacy of the Use of Mouthwash with Cetylpyridinium Chloride for Aerosol Producing Procedures. A Systematic Review

Eficacia antimicrobiana del uso del enjuague bucal con cloruro de cetilpiridinio en procedimientos que generan aerosoles. Revisión sistemática

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ABSTRACT: The present research aims to determine the antimicrobial efficacy of the mouthwashes based on cetylpyridinium chloride (CPC), before aerosol producing dental procedures. A data search was performed during August 2021 in five databases MEDLINE (PubMed), SCOPUS, SCIELO, Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar. Randomized clinical trials (RCTs) were included based on the PICO question, comparing the efficacy of the mouthwashes based on cetylpyridinium chloride (CPC), versus other mouthwashes and water, before aerosol producing dental procedures, papers in English, Spanish and Portuguese were included without time limits. The risk of the included studies was evaluated with the tool RoB 2.0. Number of registration PROSPERO N° CRD42021275982. 120 papers were obtained in the preliminary search, discarding those that didn't comply with the selection criteria, leaving only 3 studies. These papers reported the use of cetylpyridinium chloride (CPC) was effective for the reduction of bacteria during the ultrasonic prophylactic procedure. The use of CPC mouthwashes previous to the dental treatment with ultrasonic prophylaxis showed only antibacterial capacity.

KEYWORDS: Mouthwash; Rinse; Cetylpyridinium; Aerosol; Antiseptics; Contaminated air.

RESUMEN: El presente trabajo de investigación tiene como objetivo determinar la eficacia antimicrobiana de los colutorios a base de cloruro de Cetilpiridinio (CPC), previo a tratamientos dentales que generen aerosol. Se realizó una búsqueda bibliográfica hasta agosto del 2021 en cinco bases de datos: MEDLINE (vía PubMed), SCOPUS, SCIELO, Cochrane Central Register of Controlled Trials (CENTRAL) y Google Scholar. Se incluyeron ensayos clínicos aleatorizados (ECAs), basándose en la pregunta PICOS, que compare la eficacia del colutorio a base de cloruro de Cetilpiridinio (CPC) con otro colutorio, placebo o agua, previo a un tratamiento dental que genere aerosol, en los idiomas español, inglés o portugués y sin límite de tiempo. El riesgo de los estudios incluidos se evaluó con la herramienta RoB 2.0. Número de registro PROSPERO N° CRD42021275982. Se obtuvo un total de 120 artículos en la búsqueda preliminar, descartando aquellos que no cumplían con los criterios de selección, quedando sólo 3 artículos. Estos artículos informaron que el uso de CPC es efectivo para la reducción de bacterias durante el procedimiento de profilaxis con ultrasonido. El uso de los enjuagues bucales a base de CPC previo al tratamiento dental de profilaxis con ultrasonido sólo tiene eficacia antibacteriana.

PALABRAS CLAVE: Colutorio; Enjuagar; Cetilpiridinio; Aerosol; Antisépticos; Aire contaminado.

INTRODUCTION

Mouthwashes are chemical solutions that prevent diseases and reduce microorganisms in the oral cavity (1-5). They are classified into cosmetic and therapeutic mouthwashes (6-7). Cosmetics mouthwashes offer temporary relief for halitosis. The therapeutic mouthwashes contain active ingredients, such as Cetylpyridinium Chloride (CPC), fluorides, Chlorhexidine Gluconate (CHX) or essential oils such as eucalyptol, menthol, methyl salicylate and/or thymol, that reduce or control dental plaque, gingivitis, halitosis and dental cavities (8,9).

Cetylpyridinium chloride (CPC) is a monocationic quaternary ammonium compound, ampho-teric surfactant (10-11), positively charged, which binds to negatively charged microorganisms, it exerts its antimicrobial activity by degradation of the lipid bilayer of the cell and the disruption of bacterial metabolism (12-14). Currently, CPC has received a label from the FDA of Generally

Regarded as Safe (GRAS) (15-16), demonstrating high antibacterial potential at concentrations of 0.05% and 0.07% or 0.5 and 0.7 mg/ml (17-22). Its antiviral activity against respiratory infections, herpes virus and hepatitis B virus has also been described (23-27).

In dental procedures that use aerosol-generating equipment, such as ultrasonic scalers, high-speed handpieces or triple syringes, this equipment could cause cross-contamination in the dental office through aerosols containing microorganisms (28-32), since aerosols are particles of less than 50 micrometers in diameter that remain floating in the air for prolonged periods (33), risking the health of patients and dentists (34-37).

The condition caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has seriously affected people in a short period in recent years (38-40); Therefore, to prevent the transmission of these microorganisms with contaminated saliva, information showing mouthwashes

can reduce the risk of infection of this disease was found (12,18,29,38).

For this reason, dentists and the general population both need research data that provides adequate information on the benefits of this mouthwash with CPC against these microorganisms, (41-44). The objective of this systematic review is to determine the Antimicrobial efficacy of CPC-based mouthwashes prior to aerosol-generating dental treatments.

METHODOLOGY

PROTOCOL AND REGISTRATION

This systematic review was prepared following the TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSIS (PRISMA). It was registered in PROSPERO: A registry for systematic review protocols (N° CRD42021275982).

TYPE OF STUDY AND PARTICIPANTS

Randomized clinical trials published until August 2021 on the antimicrobial efficacy of the use of CPC-based mouthwashes in patients who have undergone aerosol-producing dental procedures.

To prepare and structure this review, the question was formulated using the PICO format (population, intervention, comparison and results) as detailed below: a) population: patients who have received any dental treatment that generates aerosol.

b) intervention: application of CPC mouthwash prior to the dental treatment. c) comparison: placebo, water, other mouthwashes or no mouthwash before dental treatment. d) results: reduction of microorganisms that are produced during dental treatments that generate aerosols.

PICO'S QUESTION

Do CPC-based mouthrinses prior to aerosol-generating dental treatment have antimicrobial efficacy?

SOURCE OF INFORMATION AND SEARCH STRATEGY

A bibliographic search was carried out in 5 electronic databases: Pubme/Medline, Cochrane library, Scopus, Scielo and Google Scholar until August 2021; combining the keywords and titles according to the thesaurus of each database: "anti-infective agents, local", "antiseptics", "cetylpyridinium", "cetylpyridinium chloride", "mouthwash", "mouthrinse", "prevention mouthrinse", "mouthrinse", "rinse", "contamination", "air contamination", "aerosol". The literature search strategy is available in Supplemental material (Table 1).

SELECTION CRITERIA

Studies comparing CPC mouthwash with another mouthwash, placebo or water, prior to aerosol-generating dental treatment, based on the PICOS question strategy (Table 2).

Table 1. Search strategy according to database.

Database	Search Strategy
Pubmed/Medline	((("anti-infective agents, local") OR "antiseptics") OR "cetylpyridinium") OR "cetylpyridinium chloride") AND (((("mouthwash") OR "mouthrinse") OR "prevention mouthrinse") OR "mouth rinse") OR "rinse") AND (((("contamination") OR "air contamination") OR "aerosol").
Scopus	(TITLE-ABS-KEY ("anti-infective agents, local") OR TITLE-ABS-KEY ("antiseptics") OR TITLE-ABS-KEY ("cetylpyridinium") OR TITLE-ABS-KEY ("cetylpyridinium chloride")) AND (TITLE-ABS-KEY ("mouthwash") OR TITLE-ABS-KEY ("mouthrinse") OR TITLE-ABS-KEY ("prevention mouthrinse") OR TITLE-ABS-KEY ("mouth rinse") OR TITLE-ABS-KEY ("rinse")) AND (TITLE-ABS-KEY ("contamination") OR TITLE-ABS-KEY ("air contamination") OR TITLE-ABS-KEY ("aerosol") OR TITLE-ABS-KEY ("aerosols")) AND (TITLE-ABS-KEY ("clinical trial")) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "DENT")) AND (LIMIT-TO (EXACTKEYWORD , "Human")) .
Scielo	((("anti-infective agents, local") OR "antiseptics") OR "cetylpyridinium") OR "cetylpyridinium chloride") AND (((("mouthwash") OR "mouthrinse") OR "prevention mouthrinse") OR "mouth rinse") OR "rinse") AND (((("contamination") OR "air contamination") OR aerosol) OR aerosols)).
Google Scholar	cetylpyridinium + "mouthwash" + "aerosol" + "clinical trial" -"systematic review".
Cochrane Library	#1 MeSH descriptor: [Anti-Infective Agents, Local] explode all trees. #2 MeSH descriptor: [Cetylpyridinium] explode all trees. #3 ("antiseptics") OR ("cetylpyridinium") OR ("cetylpyridinium chloride") AND ("anti-infective agents, local") (Word variations have been searched). #4 #1 OR #2 OR #3. #5 MeSH descriptor: [Mouthwashes] explode all trees. #6 ("mouthwash") OR ("mouthrinse") OR ("prevention mouthrinse") OR ("mouth rinse") OR ("rinse") (Word variations have been searched). #7 #5 OR #6. #8 ("contamination") OR ("air contamination") OR ("aerosol") OR ("aerosols"). #9 MeSH descriptor: [Aerosols] explode all trees. #10 #8 OR #9. #11 #4 AND #7 AND #10.

Table 2. PICO’s question table.

Component	Description
P: Problem	People who have received any dental treatment that generates aerosol.
I: Intervention	Application of the Cetylpyridinium Chloride (CPC)-based mouthwash prior to dental treatment.
C: Comparison	Placebo, water, other mouthwash prior to dental treatment.
O: Outcome	Reduction of number of microorganisms that are produced during dental treatments that generate aerosols.
S: Study	Randomized clinical trials.

INCLUSION CRITERIA

The inclusion criteria of the articles were: a) randomized clinical trials; b) languages: Spanish, English or Portuguese; c) without time limit, until August 2021.

EXCLUSION CRITERIA

The exclusion criteria of the articles were: a) case reports; b) case series; c) preclinical studies; d) systematic reviews; e) pilot studies; f) gray literature; g) letters to the editor; h) literature reviews; i) ongoing and/or unpublished studies; j) publications in languages other than Spanish, English or Portuguese.

ARTICLE SEARCHERS

Article searches of electronic databases were performed independently by two investigators (JPAT) and (AILF), who were initially blinded to report their results separately. Disagreements were resolved by discussion with a third reviewer (HIAV). After comparing them, the titles and abstracts were read, discarding articles that are not relevant and/or those that did not meet the eligibility criteria. Second, an analysis of the entire scientific article was carried out, independently extracting the necessary information. These

data were compared for accuracy and to avoid any differences in the present review.

DATA COLLECTION

During the data collection process, a predefined table was used to collect data from each chosen study (Tablet 3) including author-year, country, total number of patients, age (range), study groups, patients by group, follow-up time, type of procedure, collection method, microbial analysis, type of microorganisms, conclusions. Data from each study was entered and analyzed into an Excel sheet for qualitative analysis. Finally, these data were recorded in a pre-established diagram, according to the PRISMA DECLARATION (Figure 1).

RISK OF BIAS

The data search was carried out following the Cochrane Library guidelines, managing to identify the type of risk in the studies. The RoB 2.0 was used to determine the risk of bias in randomized clinical trials (Figure 2). Clinical trials were assessed across five domains, then classified as: low, some concern, or high risk of bias. Included studies were independently assessed by two calibrated authors (JPAT and AILF) using RoB 2.0. Ultimately, all disagreements were resolved by discussion with a third reviewer (HIAV).

Table 3. Characteristics of the Parallel RCTs included.

Author/ year	Country	Total number of patients (H/M)	Age (range)	Study Groups	Patients by groups	Follow- up time	Type of procedure	Collection method	Microbial analysis	Type of microorganism	Conclusions
Retamal- Valdes <i>et al.</i> 2017	Brasil	60 (24/36)	42.32 (18-70)	No mouthwash water 0.075% CPC + 0.28% Zn + 0.05% F 0.12% CHX	15 15 15 15	72 horas	Profilaxis con ultrasonido	5 honokiol agar plates: 3 on the support board, 1 on the participant's chest, and 1 on the clinician's forehead	1. Anaerobic culture: counting of CFU with Labline Colony Counter 2. Checker- board DNA-DNA hybridization (40 species)	Anaerobic gram positive and gram negative bacteria	The results of this study showed that a mouthwash containing 0.075% CPC, 0.28% zinc lactate, and 0.05% sodium fluoride as a pre-procedure mouthwash was effective in reducing bacterial species present in oral aerosols. viable during prophylaxis with ultrasonic instruments
Joshi <i>et al.</i> 2017	India	40 (28/12)	32.5	0.05% CPC 47° 0.2% CHX 47° 0.05% CPC 18° 0.2% CHX 18°	10 10 10 10	1 hora	Profilaxis con ultrasonido	3 blood agar plates: 1 on the participant's chest, 1 on the dentist's chest, 1 on the assistant's chest	Counting of CFU with Labline Colony Counter	Bacteria	The results clearly indicate that a pre-procedure mouthwash containing 0.05% CPC can be considered as a promising alternative to reduce aerosol contamination during ultrasonic scaling procedures compared to the gold standard of 0.2% chlorhexidine. Furthermore, the amount of viable bacteria in the aerosol is highest in the chest area of the patient followed by the operator and assistant in descending order.
Feres <i>et al.</i> 2010	Brasil	60	(30-70)	0.05% CPC 0.12% CHX Agua No mouthwash	15 15 15 15	1 hora	Profilaxis con ultrasonido	5 honokiol agar plates: 3 on the support board, 1 on the participant's chest, and 1 on the clinician's forehead	1. Anaerobic culture: counting of CFU with Labline Colony Counter 2. Checker- board DNA-DNA hybridization (40 species)	Gram positive y gram negative bacteria	Mouth rinses containing 0.05% CPC and 0.12% CHX are equally effective in reducing the levels of bacterial splash generated during ultrasonic scaling and their use could help decrease the level of microbial contamination in the dental office.

RCT: Randomized clinical trial, CPC: Cetylpyridinium Chloride, CHX: Chlorhexidin, FCU: Forming Colony units.

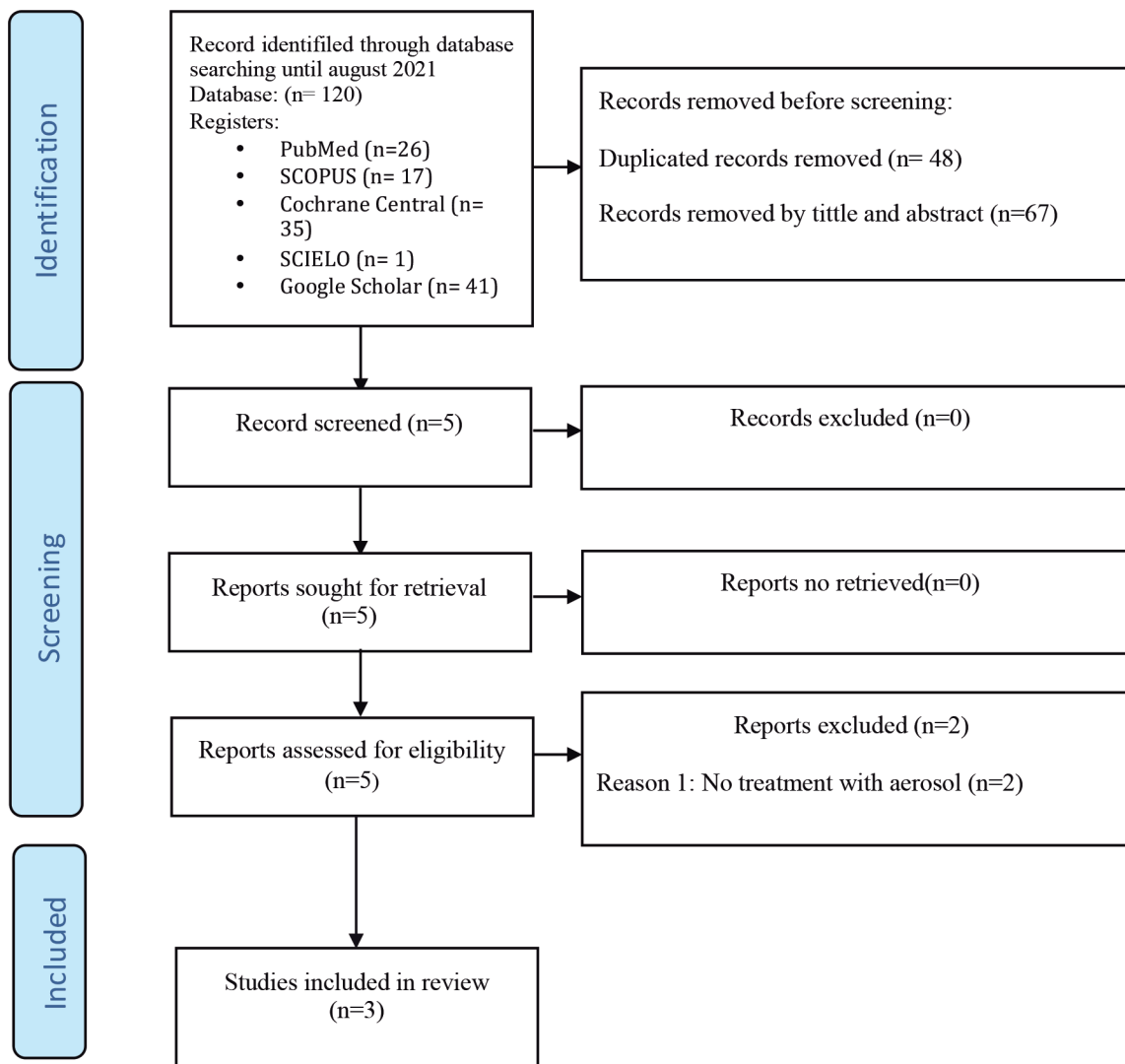


Figure 1. PRISMA diagram showing the inclusion and exclusion process of scientific articles found in the scientific search, for this Systematic Review.

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall	
1	Retamal-Valdes e	CPC	Placebo	NA	1	+	+	+	+	+	+	Low risk
2	Joshi et al.	CPC	Placebo	NA	1	+	+	+	+	+	+	Some concerns
3	Feres et al.	CPC	Placebo	NA	1	+	+	+	+	+	+	High risk

D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Figure 2. Risk of Bias of the studies included in this research according to the Cochrane Rob 2.0 tool.

RESULTS

The results of the electronic and manual search strategy included 120 articles in total, excluding 48 duplicate articles and 67 articles eliminated by title and abstract, leaving 5 articles selected. Subsequently, 2 articles that did not meet the eligibility criteria were excluded, resulting in 3 randomized clinical trial articles that were included for qualitative synthesis (Figure 1). The reason for exclusion of the articles is shown in Table 4.

Table 4. Reason for exclusion of scientific articles.

Author	Reason
De Macedo Máximoa <i>et al.</i> Anderson <i>et al.</i>	No treatment with aerosols

CHARACTERISTICS OF INCLUDED STUDIES

Overall, 3 articles were included, all were parallel RCTs, and the years of publication ranged from 2010 to 2017. The countries for these articles were: Brazil and India. The total number of participants was between 40 and 60 people, with a range of years from 18 to 70 years (Table 3).

In all the articles, the experimental group was the use of CPC (in different concentrations and/or with other components) and the control group was chlorhexidine, water and the non-use of mouthwash prior to spray treatment. Follow-up time ranged from 1 to 72 hours. All articles described ultrasound prophylaxis as an aerosol-generating procedure and the microorganisms found were gram-positive and negative bacteria. All studies concluded that the use of CPC is effective in reducing bacteria during the ultrasound prophylaxis procedure; however, one of the studies mentions that CPC is better than CHX and other mentions that both are equally effective (Table 3).

In all studies, microbiological samples were collected using Blood Agar or Honokiol plates, which were placed at different locations and distances such as on the patient's chest, dentist's chest, assistant's chest, dentist's front, or on the dashboard medium.

Regarding the microbiological analysis, the results were expressed in relation to the reduction in the number of colony-forming units (CFU) in the aerosol collection places where the agar plates were located. In all the studies, the method used was counting the total number of CFUs using Labline (32, 36, 37); only in two studies, a second method was used for microbiological analysis, which was through the use of the DNA-RNA checkerboard hybridization technique (36, 37).

ANALYSIS OF RISK OF BIAS

Three articles were considered, all at low risk of bias (Figure 2).

ANALYSIS OF THE RESULTS

Data from each study was entered and analyzed in an Excel spreadsheet for qualitative analysis (Table 3).

DISCUSSION

During patient care, there are various dental treatments that use aerosol-generating equipment, such as the handpiece, the triple syringe or ultrasound. These aerosols could carry microorganisms that exist in the patient's mouth, such as viruses or bacteria (38, 39), which would lead to a contaminated atmosphere or possible cross-contamination in the dental office (45). It is known that these aerosol particles can remain floating in the environment for up to 4 hours after a dental procedure (46), producing a risk for the dentist

and the patient due to the possible contamination of the respiratory tract by these microorganisms, even after the end of the appointment (47).

To minimize cross-infections in the dental office, different methods have been described in the literature, such as the use of mouthwashes prior to dental treatment (10, 27, 36), whose purpose is to reduce the number of microorganisms in the oral cavity. These mouthwashes can present different components, as is the case of Cetylpyridinium Chloride (1, 2, 8, 31), which has been widely mentioned in recent years in different publications (4, 10), indicating that it has a great capacity antimicrobial against viruses (25-28,46) and bacteria (11, 12, 17, 34), as reviewed in the literature.

According to the results obtained in the present investigation, all concluded that the use of CPC is effective in reducing bacteria during the dental procedure, ultrasound prophylaxis, which generate aerosol; when compared to water or no mouthwash; however, no significant difference in colony-forming unit (CFU) reduction was found when compared to CHX, indicating that CPC-based mouthrinses are equally effective as CHX-containing mouthrinses (32,36-37). This could be due to the fact that both mouthwashes are broad-spectrum antibacterial and present the same mechanism of action, degrading the bacterial membrane and producing cell lysis of the microorganism (7, 11).

Joshi *et al.* (32). They reported that the antimicrobial activity of CPC was higher when it was used at 47°C, maintaining the maximum reduction in bacterial count in all areas analyzed, compared to the use of CPC at 18°C. This may be because there would be a greater bactericidal activity of CPC at high temperatures; since as the temperature increases, the speed at which chemical reactions take place increases, known as Thermodynamic Treatment (48).

Likewise, it is observed that the antimicrobial efficacy achieved by CPC rinses is only limited to one type of bacterial microorganisms (36,37), but no information was found on viral microorganisms. This may be due to the fact that bacteria (6,17) are able to cultivate and grow on blood agar plates, the same culture media used in the three investigations, while viruses require a specialized medium for their growth (26); that is why it is suggested to carry out future research including these types of microorganisms.

Based on bacterial composition analysis (36,37), it showed statistically lower ratios for orange complex pathogens when CPC was compared to subjects who received no mouthwash or those who only rinsed with water. This is a beneficial effect, since certain species of the orange complex, such as fusobacteriums, can cause respiratory or ophthalmic etiologies (49,50), which would lead to a possible reduction in cross-diseases in the dental office, as long as the CPC mouthwash is used prior to any dental procedure that generates aerosols.

Retamal-Valdes *et al.* (37). He indicated that the use of CPC was effective in reducing bacteria found in dental aerosols, but it should be noted that, in said study, CPC was used with other additional components, such as zinc lactate and sodium fluoride, so it could not be concluded if its antibacterial action is thanks to CPC or its other previously mentioned components.

The main limitation of the present study was that it only found results for a single dental procedure, ultrasound prophylaxis, which has been shown to have great potential for aerosol generation in the dental office (38). Therefore, it could be assumed that the CPC mouthwash, prior to dental treatments that generate aerosols, would also produce similar benefits for the dentist and the patient, if it is used with other equipment that

also generates aerosols, as is the case with the piece hand or triple syringe.

Finally, it is worth mentioning that this is the first study that systematically reviewed the antimicrobial efficacy of Cetylpyridinium Chloride-based mouthwash in the reduction of microorganisms prior to any treatment that generates aerosol, not finding enough information regarding this product in relation to mouthwashes and sprays; Therefore, the results of our present investigation must be evaluated with caution. Despite demonstrating that there is a decrease in the number of microorganisms, the influence of this decrease in the infection rate towards health professionals is unknown, so there is no direct evidence indicating that cetylpyridinium chloride mouthwash can reduce the rate of clinical infection in the dental area.

CONCLUSION

The use of CPC-based mouthwashes prior to ultrasonic prophylaxis only has antibacterial efficacy.

CONFLICT OF INTEREST

The authors declare that we have no conflict of interest.

ETHICAL CONSIDERATIONS

The present study was approved by the Comité Institucional de Ética en Investigación de la Universidad Científica del Sur.

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AUTHOR CONTRIBUTION STATEMENT

Conceptualization and design: J.P.A.T.

Literature review: J.P.A.T. and A.I.L.F.

Methodology and validation: A.I.L.F. and H.I.A.V.

Formal analysis: J.P.A.T.

Investigation and data collection: A.I.L.F. and H.I.A.V.

Resources: J.P.A.T. and A.I.L.F.

Data analysis and interpretation: H.I.A.V.

Writing-original draft preparation: J.P.A.T.

Writing-review & editing: A.I.L.F.

Supervision: H.I.A.V.

Project administration: J.P.A.T.

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