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A critical appraisal of evidence in the use of preprocedural mouthwash to avoid SARS-CoV-2 transmission during oral interventions

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Abstract. – OBJECTIVE: The study aimed to review and report the current evidence supporting the use of mouthwashes as a preprocedural protocol on dental offices.

MATERIALS AND METHODS: This study is a secondary one that performed a comprehensive literature search of scientific studies published up to 10th August 2020 in PubMed, Scopus, Web of Science, and Scientific Electronic Library Online (Scielo) databases. The electronic search strategy was performed using free text and DeCS/MeSH terms.

RESULTS: Only five studies were included in this work, despite 140 studies that were identified with the research strategy. *In vivo* studies were carried out in two works, *in vitro* studies were described in two papers, and a in silico approach was used in one work. No cetylpyridinium chloride studies were identified, while chlorhexidine and povidone studies were more studied.

CONCLUSIONS: There is reduced evidence about how preprocedural mouthwashes decrease SARS-CoV-2 salivary load.

Key Words:
COVID-19, New coronavirus, Mouth rinse, Dental practice.

Introduction

Salivary glands are a vital reservoir to the new Coronavirus and play an essential role in viral dissemination[1]. As we know, mouth rinses are commonly used before oral interventions as a protocol to avoid bacteremia and decrease cross-infection risks[2]. Besides, the SARS-CoV-2 has high human-human transmissibility due to its capacity to spread on aerosols. Then, should we use mouth rinses as a pre-clinical protocol against SARS-CoV-2 spread during oral interventions? Is there any evidence?

Until now, no treatment has scientific confirmation facing COVID-19, the SARS-CoV-2's disease. In this context, some protocols have been suggested by different organizations worldwide, aimed at decreasing aerosols' transmission of SARS-CoV-2 during dental care[3], which could be used to other oral interventions. However, we believe these suggestions have inadequate scientific support.

Consequently, to summarize the current scientific evidence is of noteworthy importance to guide protocols and improve safety to dentists, students, and patients. Then, the present paper aims to review and report the current evidence about the use of mouthwashes as a preprocedural protocol on dental offices.

Materials and Methods

This study is a secondary one that performed a comprehensive literature search of scientific studies published up to 10th August 2020 in PubMed, Scopus, Web of Science, and Scientific Electronic Library Online (Scielo) databases. The electronic search strategy was performed using free-text and DeCS/MeSH terms as follows: (((mouthwash* or mouth rinse* or "mouth wash*" or

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"mouth rinse*") and (sars-cov-2 or "COVID19" or "COVID-19")) or ((sars-cov-2 or COVID)) or ((sars-cov-2 or COVID) and povidone) or ((sars-cov-2 or COVID) and "hydrogen peroxide") or (sars-cov-2 or COVID) and "cetylpyridinium chloride")). The eligibility criteria set were published or *in press* studies in English, Portuguese, Spanish or French. Preprints with no peer reviews process, review studies, protocols, letter to the editor, and studies that did not assess the antiviral activity of the mouthwash against SARS-CoV-2 were excluded.

The database construction process was carried out by two researchers, who collected the same data independently, thus building two separate databases, verified through consistency, followed by a comparative evaluation carried out by a third researcher. In cases of divergence, the article was analyzed by a third and categorized by a consensus among them.

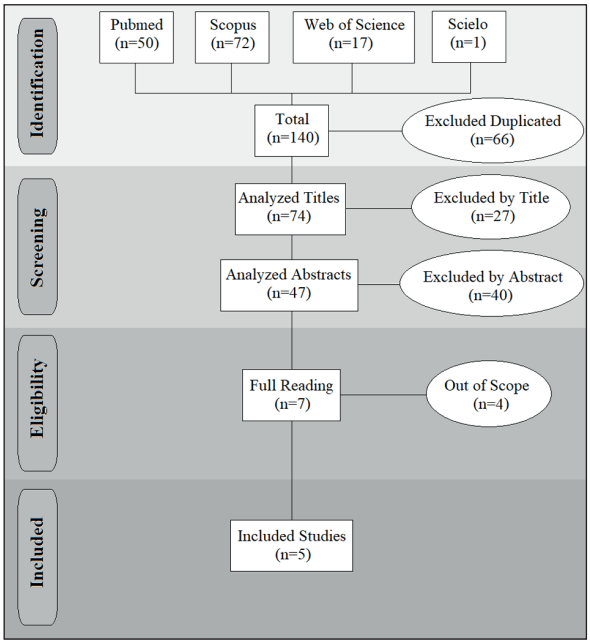

Figure 1. Steps of bibliographic survey process carried out on the selected databases.

Results

Only five investigations were included in this analysis, despite 140 works that have been identified with the research strategy. *In vivo* studies were carried out in two works; however, they are exclusively observational case reports, with a small 'n', and no appropriate controls. No cetylpyridinium chloride (CCP) studies were identified, and one was performed through *in silico* approach.

Discussion

The efficacy of chlorhexidine digluconate solution (0.12 %) was clinically evaluated in two hospitalized patients[5]. A remarkable decrease in the salivary load of SARS-CoV-2 was observed to up two hours after using the mouthwash. However, patients were receiving lopinavir/ritonavir (400 mg/ 100 mg) twice a day, and the possible interference of antiviral agents was not evaluated. Besides this, the use of chlorhexidine digluconate was able to reduce the salivary SARS-CoV-2 load just once. Despite chlorhexidine digluconate 0.12% is considered the standard gold antimicrobial in dental practice, we cannot assume that it would be safe to use it as a mouth rinse to avoid SARS-CoV-2 contamination[9].

Also, the efficacy of the povidone-iodine (PVPI) solution (1.0%) was clinically evaluated in four hospitalized patients[8]. The first PVPI's clinical test was carried out while some patients were receiving antimicrobial drugs, similar to chlorhexidine *in vivo* study. The salivary load of SARS-CoV-2 was decreased in two patients, with no statistical test or adequate control to support this. On the other hand, two *in vitro* studies reported the antiviral effect of PVPI against SARS-

Table I. Included studies on this work, according to design.

Compound	Concentration (%)	*In silico*	*In vitro*	*In vivo*
CCP	–	-	–	–
CHX	0.12	Choudhury et al[4]	–	Yoon et al[5]
HP	1.5 to 3.0	–	Bidra et al[6]	–
PVPI	0.5 to 1.5	–	Bidra et al[6]; Bidra et al[7]	Martínez Lamas et al[8]

CHX: chlorhexidine digluconate; CCP: cetylpyridinium chloride; PVPI: povidone-iodine; HP: hydrogen peroxide.

CoV-2[6,7]. Although an inhibitory effect of povidone-iodine had been shown *in vitro*, we would not adopt a safety protocol based just on this.

Another studied compound was hydrogen peroxide. No *in vivo* study was available in the literature using hydrogen peroxide facing SARS-CoV-2. The viricidal activity of hydrogen peroxide solutions (1.5 and 3.0%) was evaluated *in vitro*, and a reduction was observed after 30 seconds of surface contact[6]. However, *in silico* studies with SARS-CoV-2 proteins and hydrogen peroxide must be carried out to evaluate its binding energy with Glycoprotein Spike, an essential protein involved in the mechanism of cell invasion. This possible linkage could be helpful once SARS-CoV-2 would not enter on host cells.

Many countries recommend using some mouthwash as a pre-operative protocol facing SARS-CoV-2, even with no scientific evidence[3]. We understand that in a pandemic context is urgent to establish protocols which goal to control the spread of the infection. However, some clinicians may be lulled into the use of mouthwashes without scientific validation, due to the haste to decrease transmission risks. Thus, to base these protocols on appropriate evidence is essential to enhance general safety.

Conclusions

Based on our findings, there is reduced evidence about how preprocedural mouthwashes decrease SARS-CoV-2 salivary load. Currently, chlorhexidine 0.12% seems to be a remarkable alternative to be used as a preprocedural protocol.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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References

1) Xu R, Cui B, Duan X, Zhang P, Zhou X, Yuan Q. Saliva: potential diagnostic value and transmission of 2019-nCoV. Int J Oral Sci 2020; 12: 11.
2) Souza FB, Marques AELR, Oliveira KMS, Bezerra GM, Marques IRC, Weber Sobrinho CR. Influence of chlorhexidine mouthwashes on air contamination of dental offices. J Dent Health Oral Disord Ther 2019; 10: 23-26.
3) Clarkson J, Ramsay C, Richards D, Robertson C, Aceves-Martins M. Aerosol generating procedures and their mitigation in international dental guidance documents - a rapid review. Available at: https://oralhealth.cochrane.org/news/aerosol-generating-procedures-and-their-mitigation-internationalguidance-documents [accessed 30 July 2020].
4) Choudhury S, Moulick D, Saikia P, Mazumder MK. Evaluating the potential of different inhibitors on RNA-dependent RNA polymerase of severe acute respiratory syndrome coronavirus 2: a molecular modeling approach. Med J Armed Forces India 2020. doi: 10.1016/j.mjafi.2020.05.005 [Epub ahead of print].
5) Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, Noh JY, Cheong HJ, Kim WJ. Clinical significance of a high SARS-CoV-2 viral load in the saliva. J Korean Med Sci 2020; 35: e195.
6) Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Comparison of in vitro inactivation of SARS CoV-2 with hydrogen peroxide and povidone-iodine oral antiseptic rinses. J Prosthodont 2020 Jun 30:10.1111/jopr.13220. doi: 10.1111/jopr.13220. Epub ahead of print.
7) Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Rapid in-vitro inactivation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) using povidone-iodine oral antiseptic rinse. J Prosthodont 2020; 8: 1-5.
8) Martínez Lamas L, Diz Dios P, Pérez Rodríguez MT, Del Campo Pérez V, Cabrera Alvargonzalez JJ, López Domínguez AM, Fernandez Feijoo J, Diniz Freitas M, Limeres Posse J. Is povidone iodine mouthwash effective against SARS-CoV-2? First in vivo tests. Oral Dis 2020 Jul 2:10.1111/odi.13526. doi: 10.1111/odi.13526. Epub ahead of print.
9) Al-Kamel A, Al-Hajj WA, Halboub E, Abdulrab S, Al-Tahami K, Al-Hebshi NN. N-acetyl cysteine versus chlorhexidine mouthwashes in prevention and treatment of experimental gingivitis: a randomized, triple-blind, placebo-controlled clinical trial. Clin Oral Investig 2019; 23: 3833-3842.