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Authors' response

The viewpoint of Barenghi et al on chlorhexidine (CHX) based mouthwash during the coronavirus disease 2019 (COVID-19) pandemic raises an interesting hypothetical question. The recent articles by Becker et al[1] and Hong[2] do not consider the available scientific evidence supporting the virucidal effects of either CHX or povidone iodine (PVP-1) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and thus were somewhat inconclusive. We respectfully maintain that when we wrote our Letter to the Editor, emerging robust scientific data concerning the virucidal effects of CHX and PVP-1 were taken into consideration. In reference to the other queries put forth by Berenghi et al, we wish to supplement evidence-based literature regarding the use and composition of preprocedural mouthrinses as has been recently updated in scientific literature.

We acknowledge that in the early stages of a pandemic, health authorities such as the Centers for Disease Control and Prevention[3] recommended preprocedural mouthrinses for dental treatment even without robust clinical evidence. However, we would like to highlight the fact that despite relatively fewer in vitro studies being published during the first wave of the pandemic, the Guidance for Dental Settings by the Centers for Disease Control (last updated on December 9, 2020) did not reflect the emerging evidence supporting virucidal effectiveness of PVP-1 against SARS-CoV-2.

Regarding the European Centre for Disease Prevention and Control[4] guidance, there is no mention regarding the use of prophylactic preprocedural mouth rinse (PPMR). In addition, the Cochrane review by Burton et al[5] could identify only ongoing studies, including 14 randomized controlled trials (RCTs) but found no completed studies worth including. Given the unprecedented dynamic nature of COVID-19 infection and being a translational research field, it is not surprising that Cochrane reviews are likely to conclude as low certainty or unclear evidence because of a lack of RCTs. However, we firmly believe that the absence of evidence may not necessarily reflect evidence of absence.[6] On further exploration, we found that at the time of publishing of the review commentary by Kelly et al,[7] only insufficient direct in vitro evidence of the efficacy of specific compounds in PPMR against SARS-CoV-2 was available. The majority of the evidence was extrapolated from other viruses, including influenza, HIV, and herpes simplex.

A critical analysis of the studies by Jain et al[8] and Yoon et al[9] revealed that cell toxicity effects were not considered while assessing virucidal effects of CHX against SARS-CoV-2. In contrast, after the use of a suspension assay on the basis of EN14476 methodology, no cytotoxic effects have been reported with the use of 1% PVP-1 mouthwash at a concentration of 0.63 mg/mL or a 1:16 or lower dilution of the product.[10] Moreover, in early periods of the outbreak, a first report on the in vitro efficacy of PVP-1 (1.0%, 1.5%, and 3% concentration) also demonstrated complete inactivation of SARS-CoV-2 without any cytotoxic effects.[11] In accordance with EN 14476 standards, a recent in vitro study[12]

indicated limited efficacy of the 2 tested CHX formulations against SARS-CoV-2. Octenidine dihydrochloride-based formulation exhibited good virucidal efficacy in the presence of low organic soiling, which further needs to be substantiated with clinical trials data, as has also been pointed by the authors of the study.[12]

Although the study Yoon et al[9] (May 2020) was among the earliest attempts to support the role of CHX as PPMR in the prevention of COVID-19, our team found that relatively stronger and low bias studies in the latter half of the pandemic favored the role of PVP-1; and that the clinical study by Martínez Lamas et al[13] demonstrated the same increased real-time sample size. Moreover, similar to the limitations of the study by Martínez Lamas et al,[13] absence of placebo controls (gargling with saline) for comparison were limitations acknowledged by Yoon et al[9] in their study demonstrating the analogous benefit of CHX. In addition, the absence of a viral culture test made it impossible to determine the survival of the virus over time. However, although using Vero E6 cells, Meister et al[14] observed that formulation containing 1% PVP-1 drastically reduced viral infectivity to background levels by up to 3 orders of magnitude. CHX based mouth rinse was found to exhibit weak virucidal efficacy.[14]

As for the findings of the cited preprint, the significant reductions in viral burden were found to be at 20 minutes for PVP-I and 90 minutes with CHX.[15] A recent editorial[16] in the *Journal of the American Medical Association* stresses the need for exercising caution and scrutiny, specifically when the results of the studies pertain to the treatment of patients as the posted findings are not peer-reviewed. Accordingly, we respectfully disagree with the suggestion offered by the authors regarding the suitability of CHX in orthodontic care as it is not substantiated with strong underpinning evidence.

It has been rightly pointed out that the RCT by Elzein et al[17] found no significant difference between the Delta Ct of patients using 0.2% CHX and 1% PVP-1 solutions ($P = 0.24$). However, the antiviral effects of CHX mouthwash were found to be transitory. This is in accordance with the findings of Yoon et al,[9] who also observed transient salivary viral suppression for up to 2 hours, but beyond the 2 hours, an increase in viral load was observed. In contrast, Seneviratne et al[18] reported 6-hourly sustained virucidal effects after rinsing with 0.5% PVP-1 for 30 seconds.

Although the recent computational drug modeling study[19] showed promising results regarding the increased binding affinity of CHX with SARS-CoV-2 proteins, in silico-based compound-protein physical interactions might not yield the same results in real-time clinical settings.

We agree with the point regarding the influence of mouthwashes with different pH on dental demineralization, frequently observed in orthodontic patients. Brownish teeth, darkening of the dorsum of the tongue, and taste disturbances are some of the side effects of CHX.[20] In contrast, PVP-1, exhibiting favorable gradual iodine release and oxidative virucidal effect, has been shown to be tolerable at doses up to 2.5% for up to 5 months, with no tooth or tongue discoloration or taste abnormalities.[21] Regarding the probable risk of tooth demineralization because of its low pH (2-7), PVP-1 should be used with caution and under supervision.

To conclude, considering the conflicting findings related to the effectiveness of CHX among studies,[22] further population-based interventions and clinical trials with robust and standardized methodologies are warranted for validating its therapeutic use against SARS-CoV-2. In contrast, considering the widely- and time-tested antiseptic and remarkable virucidal (99.99%) properties of PVP-1 along with robust prevailing evidence from 6 in vitro studies,[10,11,14,23-25] 2 RCTs,[17,18] 1 comprehensive literature review[26] and 2 recent systematic reviews[22,27] demonstrating effectiveness of PVP-I against SARS-CoV-2, extrapolation to real-time orthodontic settings may be considered therapeutically feasible.

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