Potential mouth rinses and nasal sprays that reduce SARS-CoV-2 viral load: What we know so far?

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Dear editor:

In parallel with the efforts of the global scientific community toward investigating the pathophysiology, prevention, and treatment of coronavirus disease (COVID-19), all medical specialties that deal with frontline care have readapted their care protocols to better treat patients and protect their teams when fighting against the pandemic.

Concerning COVID-19 transmission, publications have focused on the premise that saliva plays a central role in the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and that procedures performed in oral and nasopharyngeal areas can generate a large number of droplets and aerosols. However, in the absence of vaccines or effective therapies, it is crucial to explore existing treatments to reduce the SARS-CoV-2 viral load. Infection control measures are still the only option for reducing the number of new infections (1). These studies reinforce the importance of biosafety and cross-infection prevention protocols in limiting viral spread during these procedures (2-4).

On the basis of the few previously published studies that focused on understanding the potential effectiveness of antimicrobial solutions against COVID-19, in this study, we aimed to review publications on local control measures that contribute toward the reduction of SARS-CoV-2 viral load in patients with COVID-19, with the intent of making the host oral cavity and nasopharyngeal mucosa less contagious, controlling droplet transmission mainly to healthcare providers, and flattening the COVID-19 curve.

To assess the literature on the virucidal effect of antimicrobial solutions, a systematic review was carried out with an electronic search of the following databases: PubMed/Medline and Cochrane. To establish the search strategy, all studies had to address the following question: “What are the local measures to decrease the coronavirus viral load in the nasopharyngeal and oropharyngeal tracts?” A described search strategy was structured with Boolean operators (AND/OR/NOT) and the following keywords: (SARS-cov-2) OR (COVID-19) OR (coronavirus) AND (povidone-iodine) OR (chlorhexidine digluconate) OR (hydrogen peroxide) OR (oral rinse) OR (mouthwashes) OR (anti-infective agents) OR (PVP-I) OR (β-cyclodextrin) OR (Citrox) AND (saliva) OR (nasal cavity) OR (mouth) OR (oral cavity) OR (throat) OR (nasopharyngeal) OR (oropharyngeal). The search included published articles until August 10, 2020. In addition, the gray literature was also reviewed, including papers that eventually met the eligibility criteria upon discussion. This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (5). All studies met the criteria established by the Patient, Intervention, Comparison, and Outcome strategy, as follows: participants (P), patients with COVID-19; intervention (I), solutions with virucidal activity; control (C), patients not using antimicrobial solutions; and outcome (O), the reduction of salivary SARS-CoV-2 viral load.

The inclusion criteria were as follows: 1) in vitro, in vivo, and randomized clinical trials that addressed the use of mouthwashes or nasal sprays to reduce the viral load of SARS-CoV-2, 2) unlimited study period, and 3) having no language restriction. The exclusion criteria were as follows: 1) case reports and 2) systematic reviews.

Overall, 75 articles were identified in the selected databases: 65 studies in PubMed/Medline, eight in Cochrane, and two in the gray literature. The final sample included 11 papers that fulfilled all of the above-mentioned inclusion and exclusion criteria (Figure 1).

The data and outcomes obtained from these selected articles are listed in Table 1.

In healthcare settings, including hospital intensive care units (ICU) and dental offices, COVID-19 transmission because of the overabundance of SARS-CoV-2 in droplets of saliva released as aerosols is not traceable to an index patient because the particles remain airborne for some time and then settle over horizontal surfaces in rooms/offices (13-15). As there are no drugs or vaccines for COVID-19
available yet, local infection control measures are the only
available alternatives to slow viral transmission/infection.

The Guideline for the Diagnosis and Treatment of Novel
Coronavirus Pneumonia (the 5th edition) (16), released by
the National Health Commission of the People’s Republic of
China, concluded that chlorhexidine may not be effective in
eliminating SARS-CoV-2. In addition, an in vitro study also
revealed the inefficacy of chlorhexidine digluconate in killing
human coronaviruses, such as those causing SARS and
Middle East Respiratory Syndrome and the endemic human
coronavirus (17).

However, a recently published study that evaluated SARS-
CoV-2 dynamics in various body fluid specimens, such as
saliva, oropharyngeal swabs, and nasopharyngeal swabs,
concluded that viral load in the saliva can transiently be
decreased for 2 h after using chlorhexidine mouthwash in
COVID-19 patients (18). However, to better understand the
effectiveness of chlorhexidine in decreasing the viral load,
randomized controlled trials with a greater number of
patients are still necessary.

On the basis of the outcomes of this review, we strongly
recommend the use of povidone-iodine (PVP-I) as a pre-
procedure mouth rinse and nasal spray to reduce the SARS-
CoV-2 viral load in oral aerosols (19). In our opinion, PVP-I
could be considered an adjunct to personal protective equip-
ment during this pandemic. PVP-I is a simple, affordable,
and practically innocuous intervention that has shown
promising virucidal results in a few in vitro studies and in
the first in vivo study. Its use at the lowest concentration
(0.5%) and for the lowest contact time (15 s) led to the
complete inactivation of SARS-CoV-2. Hence, it is indicated
for patients and healthcare workers.

Although PVP-I showed better virucidal activity than that
of hydrogen peroxide, we elucidated the fact that most of
the studies were performed in an in vitro scenario, which
does not take into account the impact of host immunity when
using the solution (where the response to the agent would be
different).

Although aerosols are not the major source of SARS-CoV-2
transmission, they are considered a potential risk of con-
tamination among frontline workers. We are aware that it is
not possible to eliminate all risks in a healthcare setting.
However, as the viral load of the mucosa in the oral cavity,
throat, and nose is high and anatomically integrated, recon-
tamination will occur soon after rinsing. Thus, the literature
recommends applying PVP-I every 2–3 hours, up to four
times per day, in those who have suspected or confirmed
SARS-CoV-2 infection and are undergoing high-risk proce-
dures that involve aerosol production, such as orotracheal
intubation, beyond the oral care administered in an ICU to
patients under mechanical ventilation (20).

To date, the substances that have been suggested to poten-
tially reduce the viral load in COVID-19 patients in the studies
that we reviewed are primarily PVP-I, followed by hydrogen
peroxide and chlorhexidine. We do not recommend the use of
cyclodextrin combined with Citrox, as there is no evidence in
the literature regarding its real impact on the SARS-CoV-2
viral load. Four randomized clinical trials are underway,
which may help better formulate guidelines and strategies to
minimize COVID-19 transmission.
Table 1 - Mouth rinses or nasal sprays to reduce SARS-CoV-2 viral load.

<table>
<thead>
<tr>
<th>Authors, Year (Country)</th>
<th>Type of Publication Study</th>
<th>Sample (N)</th>
<th>Antimicrobial Solutions (Mouth rinse/Nasal spray)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoon et al., 2020 [7] (South Korea)</td>
<td>Clinical trial</td>
<td>2 patients</td>
<td>Chlorhexidine</td>
<td>Chlorhexidine mouthwash was effective in reducing the SARS-CoV-2 viral load in the saliva transiently (2 h).</td>
</tr>
<tr>
<td>Anderson et al., 2020 [8] (Singapore)</td>
<td>In vitro study</td>
<td>NA</td>
<td>PVP-I</td>
<td>Antiseptic solution (PVP-I 10%), skin cleanser (PVP-I 7.5%), gargle and mouth wash (PVP-I 1%), and throat spray (PVP-I 0.45%) achieved 99.99% virucidal activity against SARS-CoV-2 within 30 s. PVP-I oral antiseptic rinse at all three concentrations completely inactivated SARS-CoV-2. H₂O₂ solutions at concentrations of 1.5% and 3.0% showed minimal virucidal activity after 15 s and 30 s of contact time. PVP-I oral antiseptics, at all tested concentrations, completely inactivated SARS-CoV-2 within 15 s of contact. Ethanol 70% was only able to inactivate the virus at 30 s of contact.</td>
</tr>
<tr>
<td>Bidra et al., 2020 [9] (USA)</td>
<td>In vitro study</td>
<td>NA</td>
<td>PVP-I oral rinse (0.5%, 1.25%, and 1.5%) H₂O₂ aqueous solutions (3% and 1.5%)</td>
<td>In two of the four patients, PVP-I resulted in a significant drop in viral load, which remained for at least 3 h. Dose- and time-dependent inactivation of SARS-CoV-2 was observed in both the cases.</td>
</tr>
<tr>
<td>Bidra et al., 2020 [10] (USA)</td>
<td>In vitro study</td>
<td>NA</td>
<td>PVP-I oral rinse (0.5%, 1.25%, and 1.5%)</td>
<td>Positive control - Ethanol (70%) Negative control - Water</td>
</tr>
<tr>
<td>Lamas et al., 2020 [11] (Spain)</td>
<td>In vivo study</td>
<td>4 patients</td>
<td>PVP-I (1%)</td>
<td></td>
</tr>
<tr>
<td>Liang et al., 2020 [12] (China, USA)</td>
<td>In vitro study</td>
<td>NA</td>
<td>PVP-I eye drop (gel forming) PVP-I nasal spray (gel forming)</td>
<td></td>
</tr>
<tr>
<td>NCT04410159</td>
<td>Clinical Trial</td>
<td>NR</td>
<td>Povidone-iodine versus essential oil versus tap-water gargling for COVID-19 patients</td>
<td>NR</td>
</tr>
<tr>
<td>NCT04409873</td>
<td>Clinical Trial</td>
<td>NR</td>
<td>Antiseptic mouthwash pre-procedural rinse on SARS-CoV-2 load (COVID-19)</td>
<td>NR</td>
</tr>
<tr>
<td>NCT04449965</td>
<td>Clinical Trial</td>
<td>60</td>
<td>Betadine sinonasal rinses, Betadine mouth gargle, and 6% PVP-I gel forming nasal spray</td>
<td></td>
</tr>
<tr>
<td>NCT04347954</td>
<td>Clinical Trial</td>
<td>NR</td>
<td>PVP-I nasal sprays and SARS-CoV-2 nasopharyngeal titers (for COVID-19)</td>
<td>NR</td>
</tr>
</tbody>
</table>

LEGEND: NA=not applicable; Citrox=combination of natural bioflavonoids extracted from citrus fruits; δCD=δ-cyclodextrins; NR=not reported; PVP-I=povidone-iodine; H₂O₂=hydrogen peroxide.
REFERENCES


