Antiseptic Mouthwash/ Gargle

RECOMMENDATION

There is insufficient evidence to recommend the use of antiseptic mouthwash or gargle to prevent COVID-19 in healthy individuals. *(Very low quality of evidence)*

Consensus Issues

The panel did not provide a recommendation on the use of antiseptic mouthwashes/ gargles because the indirect evidence found included COVID-19 positive patients instead of healthy individuals. Furthermore, the surrogate outcomes reported were more on the decrease in forward transmission (clearance of SARS CoV2 virus) rather than prevention of a healthy individual from contracting the infection. Noted was one completed study in Canada which involved COVID-19 negative individuals, the result of which is not yet available.

EVIDENCE SUMMARY

Are antiseptic mouthwashes/gargles effective in preventing COVID-19?

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Key Findings

There is no direct evidence on the use of antiseptic gargle or mouthwash in preventing COVID-19 among healthy individuals. There is indirect evidence that shows conflicting results as to whether antiseptic gargle or mouthwash decreases viral load. There is also indirect evidence on the adverse effects of mouthwashes used in the home setting.

Introduction

The use of a mouth-rinse for COVID-19 patients was mainly based on the general vulnerability of SARS-CoV-2 toward oxidation, and on the finding that products containing oxidizing agents such as hydrogen peroxide and povidone iodine (PI) were able to inactivate coronaviruses on inanimate surfaces [1] within a thirty-second [2] or one-minute exposure period. Safety concerns arise from possible irritations to the oral mucosa, or allergic reactions to components of the product. [3] Moreover, local application of antimicrobials will disrupt the normal oral microbiota,

[1,3] which is increasingly recognized for its vital role in preventing the colonization of pathogens and supporting a person's immune system.

Review Methods

We did a search on March 1, 2021 for published studies on PubMed, Cochrane CENTRAL, in pre-print databases, primary trial registries, guideline sites such as NICE, Australian, WHO, the USPSTF and Canadian Task Force on Preventive Health. We used "ANTISEPTIC ORAL RINSE," "ANTISEPTIC MOUTHWASH," "ANTISEPTIC GARGLE" besides the search words for COVID-19. We searched both clinical trials and non-clinical experiments that measured outcomes on efficiency of antiseptic gargle or mouthwash.

Results

Efficacy

There is no direct evidence on the use of antiseptic gargle or mouthwash in the prevention of COVID-19. There is limited indirect evidence, and this was from studies that included patients with either symptoms of COVID-19 or positive viral load.

A laboratory study (4) tested the efficacy of povidone-iodine (PI) nasal rinse and oral rinse antiseptic formulations in inactivating SARS-CoV-2. The test compounds for oral rinse antiseptic were mixed with virus solution, resulting in PI concentrations of 1.5%, 0.75% and 1.5%. These were incubated at room temperature for 60 seconds, and thereafter processed for quantification of surviving virus. Results show that oral antiseptics were effective at inactivating SARS-CoV-2 at the three different concentrations after 60-second exposure times. Cytotoxicity or cell death was not observed in the test wells.

A prospective clinical pilot study in Germany [1] studied the effects of a mouth-rinse of 1% hydrogen peroxide on the intraoral viral load of SARS-CoV-2 -positive patients from April to May 2020. Baseline oropharyngeal specimens were taken for RT-PCR tests, and patients were asked to perform a mouth-rinse with 20 ml 1% hydrogen peroxide by gargling their mouth and throat for 30 seconds. Post-gargle specimen collection and testing was then done after 30 minutes. Twelve patients were initially included, but two were excluded because there was no SARS CoV2 RNA detected in their baseline specimens. Of the remaining ten, nine had underlying diseases, and one had replicating viral load (>106) at baseline. There was no significant difference between viral load at baseline and viral load 30 minutes after the hydrogen peroxide mouth-rinse (p=0.96).

The efficacy of three commercial mouth-rinses, specifically povidone-iodine (PI), chlorhexidine gluconate (CHX) and cetylpyridinium chloride (CPC), in reducing the salivary SARS-CoV-2 viral load in COVID-19 positive patients were compared with water in a small randomized clinical trial. (5) A total of 36 COVID-19 positive patients were recruited, but 19 did not have SARS-CoV-2 at baseline assay while one did not comply with study protocol and hence were excluded. The remaining 16 subjects were randomly assigned to four groups: PI group=4, CHX group=6, CPC group=4, water = 2). Saliva samples were collected from all patients at baseline and at 5 min, 3

h and 6 h post-application of mouth-rinses/water, and these were subjected to SARS-CoV-2 RT-PCR analysis. Outcome measures were in terms of cycle threshold (Ct, or the number of cycles needed to detect SARS-CoV-2 in a sample) values and fold changes in Ct values (Ct at timepoint/ Ct at baseline) of each substance compared to water. Results showed that Ct values detected in all 16 patients were within the range of 15.64 to 34.58, with a mean value of 27.73 ± 4.77. No statistical differences were obtained in the Ct values with regards to any time point in all the groups. A statistically significant increase in fold change of Ct value at 5 minutes and 6 h was observed post-rinsing with CPC mouth rinse compared to the water group ($p<0.05$). Although the fold changes in Ct values were higher at 3 h in CPC group, no statistical significance was achieved ($p=0.20$). In povidone iodine mouth-rinse, statistically significant increase in fold change was obtained only at 6 h post rinsing with PI in comparison with water ($p<0.01$). The effect of decreasing salivary load with CPC and PI mouth-rinsing was observed to be sustained at 3 h and 6 h time points compared to the control group.

An open-label randomized clinical trial [6] compared the effect of gargling for 30 seconds, thrice daily using 1% povidone iodine (1% PI), essential oils (EO, Listerine), and tap water on SARS-CoV-2 viral clearance among asymptomatic (Stage 1) COVID-19 patients. A total of 20 participants were randomly assigned, 5 participants each, to the 3 arms and a control group (no gargling). The gargling activity was run for 7 days, and nasopharyngeal and oropharyngeal swabs were collected on days 4, 6 and 12 of the intervention. The study reported that all patients in the PI group (5/5) had negative RT-PCR on all days of testing, and the difference compared to control was statistically significant at days 4 ($p=0.048$), 6 ($p=0.008$) and 12 ($p=0.048$). Similar analyses for 1% PI versus tap water group, EO versus the control group and EO versus tap water group were stated as not significant, but the results were not shown. Side effects were not reported from the use of 1% PI, EO or tap water.

Safety

Safety outcomes were not mentioned in any of the included clinical trials. The included laboratory study mentioned in its narrative that cytotoxicity or cell death was not observed in the test wells. There is indirect evidence from a systematic review by Tartaglia et al. which included studies that enrolled systemically healthy patients with home use of mouthwashes, measured for the outcome of adverse events. They reported several adverse effects, according to the active ingredient and the duration of use: CPC - no or moderate teeth staining on short-term use, staining on long term use, burning, taste alteration, mouth ulcers; essential oils (EO) – taste problems, mouth ulcer, burning; CHX – tooth staining (most commonly tested and reported) and taste alteration; triclosan – aphthous ulcers, leukoplakia and poorly-defined tongue lesions, and hydrogen peroxide – tongue alterations. Due to wide variations across studies, meta-analysis was not performed. [7]

Recommendations from Other Groups

On the use of pre-procedural mouth rinses (PPMR), the Centers for Disease Control state that PPMRs with an antimicrobial product (chlorhexidine gluconate, essential oils, povidone-iodine or

cetylpyridinium chloride) may reduce the level of oral microorganisms in aerosols and spatter generated during dental procedures. [8]

The Philippine Dental Association has recommended the use of 1% hydrogen peroxide or 0.2% povidone-iodine as pre-procedural mouth-rinse to reduce the salivary load of oral microbes, including potential SARS-CoV-2 carriage. [9]

Ongoing Studies

There are nine ongoing clinical trials [10–18] and two recently completed studies [19,20]. Results of the completed trials are still pending.

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Appendix 1. Characteristics of Included Studies (Indirect Evidence)

Study ID	Patients (n)	Interventions	Outcomes	Method
Gottsauner	patients with a positive test for SARS-CoV-2 within the last 72 h hospitalized at the isolation ward of the hospital	EXPERIMENTAL Hydrogen peroxide CONTROL none	Copies/ml of SARS-CoV-2 RNA, +/- viral culture	Single arm pilot study
Seneviratne	COVID-19 positive patients laboratory confirmed N=16 (from 36 recruited)	EXPERIMENTAL 1 (n=6): chlorhexidine gluconate EXPERIMENTAL 2 (n=4): povidone-iodine EXPERIMENTAL 3 (n=4): cetylpyridinium chloride CONTROL (n=2): water	Cycle threshold (Ct), Ct fold change	Block randomization

Mohamed et al.	adults aged 18 years and above asymptomatic COVID-19 patients (Stage 1) less than 5 days from diagnosis (first positive swab sample) N=20	EXPERIMENTAL 1 (n=5): povidone-iodine EXPERIMENTAL 2: Essential oils EXPERIMENTAL 3: water CONTROL: no mouthrinses	No. of cases with viral clearance at days 4, 6, 12	Randomized parallel Open label

Appendix 2. Ongoing Studies

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	Evaluation of the Effectiveness of an Oral Antiseptic in Improving the Clinical Status, Decreasing Viral Load and Substantivity in Patients with SARS-CoV-2 UTN code: U1111-1255-3454 Registration Code: RBR-58ftdj	Recruiting	Start: 10/28/2020	Interventional, randomized-controlled, parallel, triple blind, with two arms	Brazil	Patients 18-80 yo, with mild to moderate SARS-COV2	N=20 Mouthwash/gargle (30 sec/30 sec) plus active toothpaste, 5x/day,	N=20 Mouthwash/gargle (30 sec/30 sec) plus control toothpaste	Viral load; coronavirus infections in saliva (collected in posterior oropharynx) on D0, D2 and D5
2	Effectiveness of a mouthwash and toothpaste containing PHTALOX in controlling symptoms of COVID-19 and flu UTN code: U1111-1260-4839 Registration Code: RBR-8x8g36	Not yet recruiting	Start: 01/11/2020	Clinical safety / efficacy trial, randomized, parallel, with triple concealment, with two arms, phase 3	Londrina, Brazil	Patients 18-70 yo, with symptoms of SARS-COV2	N=250 Oral care kit PLUS mouthwash and dental gel containing PHTALOX Rinse/gargle for 1 min, 5x/day	N=250 Oral care kit PLUS mouthwash and dental gel WITHOUT PHTALOX Rinse/gargle for 1 min, 5x/day	Improvement of clinical symptoms in 14 days, measured via self-administered questionnaire At least 30% reduction of respiratory symptoms
3	Evaluation of the effectiveness of an oral antiseptic and nasal spray in improving the clinical picture, decreasing viral load and its	Recruiting	Start: 01/16/2020	Clinical trial of treatment, randomized-controlled, parallel, triple-blind, with	Brazil	Patients 18-70 yo, volunteers; infected with SARS-CoV-2; both sexes; age between 18	N=15 Active oral antiseptic (0.010% active ingredient) with active	N=15 Placebo mouthwash (30 sec/30 sec), 5x/day) and placebo	It is expected to find a reduction in the SARS-CoV-2 viral load in the naso-oropharyngeal

	substantivity in patients with Sars-cov-2 UTN code: U1111-1260-7525 Registration Code:RBR-8tygcz7			three arms, phase 1		to 70 years; be able to gargle.	nasal spray (fluocyanine) N=15 Oral antiseptic with 0.010% active ingredient and placebo nasal spray Gargle (30 sec/30 sec), 5x/day	nasal spray	samples through the RT-PCR method
4	Povidone-Iodine Intranasal Prophylaxis in Front-line Healthcare Personnel and Inpatients (PIIPPI) NCT04364802	Recruiting	Start: 04/28/2020 Est. completion May 2021	Non-randomized, parallel, open label, phase II clinical trial	USA	Total target N= 300 Healthcare workers Inpatients with >7 days hospitalization or will undergo significant surgical procedure Community participants who are (-) COVID-19	Community: pre- and post-study nasal swab COVID19 test PLUS povidone-iodine spray and gargle (10% diluted 1:30) Inpatients: Community PLUS standard care HCW:Community PLUS PPE; (PI) nasal spray and gargle at beginning, middle and end of shift	HCW: standard PPE, pre- and post-study test for COVID-19 Inpatient: standard care, pre- and post-study test for COVID-19 Community: pre- and post-study test for COVID-19	% HCW (+) COVID-19 in 3 weeks % inpatients (+) COVID-19 in 2 weeks % community participants (+) COVID-19 in 3 weeks
5	Mouth Rinses for Inactivation of COVID-19 (MOR) NCT04584684	Recruiting	Start: Dec 18, 2020 Estimated Study Completion Date: Sept 2023GOtt	Randomized, double-blind, triple mask, prospective, Phase II trial	USA	Total target N= 480 18 to 65 years Diagnosed COVID+ status by physician In good oral health. No known allergies to commercial dental products or cosmetics Non-pregnant	Drug: 1.5-2% w/v Hydrogen Peroxide Drug: 0.12% Chlorhexidine Gluconate Drug: 21% Ethanol plus essential oils Drug: 1% w/v Povidone-iodide Drug: 0.075% Cetylpyridinium Chloride	Saline solution	Change in quantitative polymerase chain reaction (qPCR) from baseline to 15, 30, 45, 60 minutes
6	Nitric Oxide Releasing Solutions to Prevent and Treat Mild/Moderate COVID-19 Infection (NOCOVID) NCT04337918	Completed Study, posting of results pending	Start: May 8, 2020 End: Jan 31, 2021	Multi-center, prospective, randomized, controlled, phase II, parallel group	Canada	COVID-19 (-) at baseline	Standard screening and protection for COVID-19 PLUS Nitric Oxide Releasing Solution (NORS) treatment for 14 days	Standard screening and protection for COVID-19	proportion of subjects with either swab positive COVID-19 or presentation of clinical symptoms as measured by fatigue with either fever >37.2

									(oral)and/or a persistent cough.
7	Efficacy of Mouthwash in Reducing Salivary Carriage of COVID-19 NCT04603794	Recruiting	Published: Oct 27, 2020	andomized, cross-sectional, double blinded, negative controlled, four armed, prospective, interventional study	US	Total target N=60	Povidone iodine Hydrogen peroxide CLorhexidine	Normal saline	real time reverse transcriptase quantitative PCR
8	Antiseptic Mouth Rinses to Reduce Salivary Viral Load in COVID-19 Patients (BUCOSARS) NCT04707742	Completed	Start: June 15, 2020	multicentre, randomized, triple-blind, five-parallel-group, placebo-controlled trial	Spain	N=84 18 years and above <7 days from the positive SARS-COV-2 PCR test of a nasopharyngeal sample	PVI, Hydrogen peroxide, chlorhexidine, Cetylpyridinium chloride	Distilled water	SARS-Cov2 viral load. [Time Frame: Minute 0 (before mouthwash) - Minute 30 (after mouthwash) - Minute 60 (after mouthwash) - Minute 120 (after mouthwash)]
9	A Clinical Trial of Gargling Agents in Reducing Intraoral Viral Load Among COVID-19 Patients (GARGLES) NCT04341688	Not yet recruiting	Estimated start: Feb 1, 2021	quadruple blind randomized controlled trial followed by laboratory based analysis	Pakistan	N=50 laboratory confirmed Covid-19, 18-65 years, within seven days of the onset of mild to moderate symptoms of viral infection, already admitted in the hospital.	Gargles and nasal lavages: PVI, hydrogen peroxide, Neem extract, hypertonic saline	Positive control: distilled water Negative control: no gargles or nasal lavages	Primary: Intraoral viral load as deciphered by RT-PCR Secondary: Salivary cytokine profiles of IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ and IL-17
10	The Efficacy of Pre-procedural Mouth Rinses on SARS-CoV-2 Saliva Viral Load: A Randomized Control Clinical Trial NCT04721457	Recruiting	Start: Jan 3, 2021 Est. study completion: June 30, 2021	randomized, cross-sectional, triple-blinded, five-armed, interventional study	Jeddah, Saudi Arabia	Target N=120 18 years and above COVID-19 (+) with RT-PCR within 2 days of oral or nasopharyngeal swab Asymptomatic or within 7 days of symptoms Able to rinse and expectorate	Gargles and nasal lavages: 1% PVI, 1.5% hydrogen peroxide, 0.075% cetylpyridinium chloride (CPC), 0.1% sodium hypochlorite	Distilled water	Saliva load was expressed in copies x 10 8 of COVID-19 RNA Cycle thresholds
11	Reduction of Sars-CoV-2 Oral Viral Load With Prophylactic Mouth Rinse NCT04719208	Recruiting	Start: Oct 6, 2020 Est. study completion: June 2021	Randomized, parallel assignment, double blind, interventional study	US	Target N = 60	Povidone iodine 1.5% Hydrogen peroxide 0.2% Clorhexedine gluconate Alcohol mouthwash	Water	Change in oral SARS-CoV-2 load in oral cavity of COVID-19 patient using prophylactic mouth rinse