Original Article

Effect of 0.5% povidone-iodine on the nasopharyngeal and oropharyngeal viral loads in patients with COVID-19: A double-blind placebo-controlled randomized clinical trial

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Abstract

Background and Objective: The povidone-iodine (PvP-I) nasal antiseptic has been shown to completely inactivate the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *in vitro* at variable concentrations. This study was performed to investigate the effect of 0.5% PvP-I nasal drops and oral gargles on the nasopharyngeal and oropharyngeal viral loads in SARS-CoV-2-positive patients. **Methods:** This was a double-blind, placebo-controlled, randomized clinical trial among patients aged ≥18 years with reverse-transcriptase polymerase chain reaction confirmed in the mild to moderate category of SARS-CoV-2 infection. A total of 32 patients were randomly assigned to receive either freshly prepared 0.5% PvP-I solution or distilled water in the form of supervised self-administered 4–5 nasal drops, followed by 20 ml for gargling for at least 30 seconds. The main outcome measure was the mean change in viral titer and Ct values in the nasopharyngeal and oropharyngeal samples at baseline, 5 minutes, and 3 hours post intervention. **Results:** The mean change in viral titers across the time duration for the test group when compared with the control group was not statistically significant ($P = 0.109$). However, the mean change in Ct value was found to be borderline statistically significant ($P = 0.042$). Noticeable differences were noted among the mean viral titers and Ct values in the intervention group when plotted against the time of testing as compared to the control group. PvP-I solution at 0.5% dilution was well tolerated, and no evident side effects were reported. **Conclusions:** This study shows that 0.5% PvP-I has an effect on reducing nasopharyngeal and oropharyngeal viral loads in COVID-19 patients. This can be of substantial aid for the primary care physicians, especially for the practitioners in remote and resource poor areas.

Keywords: Coronavirus, COVID-19, Ct value, povidone-iodine, SARS-CoV-2, viral load

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is highly contagious and has been an ongoing global pandemic since its first occurrence in December 2019. Despite various strategies for its control, including developing extensive treatment protocols and vaccines, efforts to curtail the pandemic have not been entirely successful. Hence, it is imperative to devise, at the earliest, methods to mitigate the virus transmission among the health care workers and the general population. It has been demonstrated that SARS-CoV-2 primarily infects the nose, following which the lower respiratory tract is secondarily infected by aspiration and seeding of the virus.[1,2] This mandates research

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for possible prophylactic agents for intra-nasal and intra-oral administration, which can be validated to break the chain of transmission. The povidone-iodine (PvP-I) nasal antiseptic has been shown to completely inactivate SARS-CoV-2 *in vitro* at variable concentrations of 0.5%, 1.25%, and 2.5% without any cytotoxic effect.[3] It has also been shown to be effective against other respiratory pathogens, including, but not limited to, severe acute respiratory syndrome and Middle East respiratory syndrome coronaviruses (SARS-CoV and MERS-CoV) in the past.[4-6] However, evidence for clinical use of PvP-I against SARS-CoV-2 is only scanty. Therefore, we conducted a double-blind, randomized, placebo-controlled clinical trial to investigate the effect of 0.5% Povidone-iodine nasal drops and oral gargles on the nasopharyngeal and oropharyngeal viral loads in SARS-CoV-2-positive patients were used for establishing its role as a prophylactic measure to mitigate the viral transmission and to determine its safety, tolerability, and the possible side effects, if any.

Methods

Trial design and oversight

We designed and conducted this double-blind, randomized, placebo-controlled trial to assess the efficacy of 0.5% povidone-iodine (PvP-I) solution against SARS-CoV-2 when used as nasal drops and oral gargles in patients admitted with mild and moderate categories of COVID-19, as compared with placebo (distilled water). Patients found to be eligible after screening were randomly assigned in a 1:1 ratio to receive either 0.5% PvP-I nasal drops and oral gargle or a placebo in the form of distilled water.

The authors take full accountability for the design and the conduct of this trial and adherence to the trial protocol (available in full text as the supplementary material) and affirm the accuracy and completeness of the data and their analyses. The Institutional Review Board and the Clinical Trials Registry-India (CTRI) approved the trial protocol (CTRI/2020/11/029063). Amendments to the protocol before trial commencement have been updated and duly notified to the trial registry and Institute's Review Board. Before enrollment of the study participants, informed written consent was obtained, and the trial was conducted in accordance with the principles defined by the Declaration of Helsinki and the Good Clinical Practice guidelines.[7]

Study setting and participants

The study was conducted at a dedicated COVID-19 multi-specialty hospital in the central zone of Uttar Pradesh, India, from November 2020 to May 2021. Patients aged 18 years and above, hospitalized with mild or moderate categories of COVID-19, were screened for enrollment in this trial. The case definitions were as per the latest guideline published by the Ministry of Health and Family Welfare, Govt. of India.[8] For inclusion in the study, participants had to fulfill all the inclusion criteria, that is, age ≥18 years, presenting with reverse-transcriptase polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection, presenting with the mild or moderate category of COVID-19 illness, presenting to the hospital within 10 days of symptom onset, and being able to provide informed legal consent. Participants infected with SARS-CoV-2, those who were admitted to the hospital for more than 1 day, those who have severe illness debilitating the patient to give consent or to adopt the study procedure, those aged less than 18 years at the time of enrollment, those who were already using some oral/intra-nasal antiseptic, those with a known case of thyroid disorders, pregnant and lactating women, and those who disagree to give consent for participating in the study were excluded from enrollment in the study. Baseline data, including the socio-demographic profile, present and past medical history, and smoking history, of all the included study participants were recorded. Data collection was terminated at the completion of 16 study participants in each of the study arms.

Intervention

After collection of the baseline demographic data and baseline nasopharyngeal and oropharyngeal swabs, the study participants assigned randomly to the intervention arm received freshly diluted 0.5% PvP-I solution in the form of 4–5 supervised self-administered nasal drops in each nostril, followed by 20 ml of 0.5% PvP-I solution for gargling for a minimum of 30 seconds. A trained pharmacist prepared the dilution from a stock solution of 5% PvP-I. This ensured accuracy and uniformity of the diluted test agent. A designated interventionist who was unaware of allocation ensured that the study participants were adopting a proper method of gargling and administration of nasal drops. Trained laboratory technicians collected the subsequent nasopharyngeal and oropharyngeal swabs at a time interval of 5 minutes and 3 hours post intervention. The control group in this trial underwent the same procedure with the control agent, distilled water. The investigators implemented all the Indian Council of Medical Research (ICMR)-recommended biosafety and biosecurity precautions for sample collection. Samples were transported in carefully labeled viral transport medias (VTMs) to the designated Cartridge Based Nucleic Acid Amplification Test (CBNAAT) laboratory in the Department of Microbiology, situated at the same designated COVID-19 multi-specialty hospital, under adequate cold-chain conditions and with triple-layered packaging. The analysis for cycle threshold (Ct) values and the corresponding viral load of the samples was undertaken at the earliest time possible since sample collection. We employed serially diluted positive controls of the Exact Diagnostics (EDX) SARS-CoV-2 Standard kits (Bio-Rad Laboratories, USA) to estimate the corresponding viral load quantities from the Ct values.[9]

Outcome measures

Primary outcome

The mean change in viral titer in the nasopharyngeal and oropharyngeal samples of the patients at 5 minutes and 3 hours

post intervention from the baseline (pre-intervention) in both the test and the control arms.

Secondary outcomes

1. The mean change in Ct value in the nasopharyngeal and oropharyngeal samples of the patients at 5 minutes and 3 hours post intervention from the baseline (pre-intervention) in both the test and control arms.
2. Trends of change in the viral titers and the Ct values over 5 minutes and 3 hours post intervention from the baseline (pre-intervention) in both the test and the control arms.

Sample size

Based on the primary outcome, we estimated a sample size of 32 (16 in each arm) at 80% power and 95% confidence interval (CI), with the assumption that 50% samples in the intervention group and 10% of the samples from the control group will have decreased viral titers after introduction to the interventional agent and placebo, respectively. This has been employed keeping in view that until the formulation of this study, the first and the only *in vivo* research conducted on PvP-I mouthwash rinse effectiveness in reducing salivary viral load in COVID-19 had reported a reduction of viral load in 50% of the study participants.[10]

Randomization

We randomly assigned each participant to either the test or the control group in a 1:1 ratio. A computerized random number list was used to generate the random allocation sequence. It was concealed from the researcher in charge of enrolling and assessing study participants, who duly noted the participants' identification on a total of 32 sequentially numbered, tightly sealed and opaque when held to light, envelopes that contained the details of the allocated group. Following the enrollment process, the interventionist determined the intervention assignment by opening sealed envelopes with appropriate patient information written on them and then provided the patients' bottles containing either the test or the control agent with a sequence number that matched the opened envelopes. The test and control agents were stored in amber-colored vials to ensure blinding and masking of both the interventionist and research participants and to protect PvP-I from light. All the other investigators, staff, and lab technicians involved in outcome measurements were kept blinded. During the conduct of the trial, no untoward health-related incident occurred that necessitated unblinding of any participant at any point. Assessment and reporting for any adverse events and side effects were in place throughout the trial.

Statistical analyses

We analyzed the data as per the intention-to-treat protocol because there was a complete adherence to the intervention procedure in both arms. We used repeated-measures analysis of variance (ANOVA) for the primary and secondary endpoints (mean change in the viral titers and the Ct values). We employed descriptive statistics for the baseline socio-demographic and clinical characteristics and plotted curves to convey the trend of change in Ct values and viral titers over time. A two-tailed *P* value of less than 0.05 at a 95% CI was considered statistically significant. All the statistical analyses were performed using the SPSS software (IBM, USA), version 24.

Results

Study participants

We assessed a total of 59 patients for eligibility between November 2020 and May 2021, of which 27 patients were excluded. Upon fulfillment of the inclusion criteria, subjects were continually enrolled and then subsequently randomized into either of the groups until a total of 16 participants were reached in each group [Figure 1].

The mean age of the study participants was 61.3 years (SD: 10.8), with persons aged 60 and above accounting for 53.1% of the total population. The mean days since symptom onset was 5.9 days (SD, 2.5), and the most common presenting symptom was found to be fever, reported by 25 patients (78.1%), followed by shortness of breath, dry cough, fatigue, and altered smell, which were reported by 21 (65.6%), 12 (37.5%), 12 (37.5%), and eight (25.0%) participants, respectively [Table 1]. PvP-I solution at 0.5% dilution was well tolerated, and no evident side effects were reported by the study participants. No statistically significant differences were found between the two groups in terms of length since symptom onset, log viral titers, and Ct values (baseline parameters were comparable).

Primary outcome

The mean change in the log viral titer from baseline to 5 minutes post intervention and from baseline to 3 hours post intervention in the test group was 0.51 and 0.42, respectively. Consequently, the mean change in the log viral titer from baseline to 5 minutes post intervention and from baseline to 3 hours post intervention in the placebo group was 0.05 and -0.1, respectively. However, compared to the placebo group, the mean change in the log viral titer from baseline to 5 minutes and to 3 hours post intervention was not statistically different for the test group, as determined by repeated measures ANOVA ($F(2,60) = 2.305$, $P = 0.109$) [Table 2 and Figure 2].

Secondary outcomes

The mean change in the polymerase chain reaction Ct value from baseline to 5 minutes post intervention and from baseline to 3 hours post intervention in the test group was -1.65 and -1.33, respectively. Consequently, the mean change in the Ct value from baseline to 5 minutes post intervention and from baseline to 3 hours post intervention in the placebo group was -0.17 and -0.63, respectively [Figure 2]. When compared to the placebo group, the mean change in the Ct value from baseline to 5 minutes and to 3 hours post intervention was found to be statistically

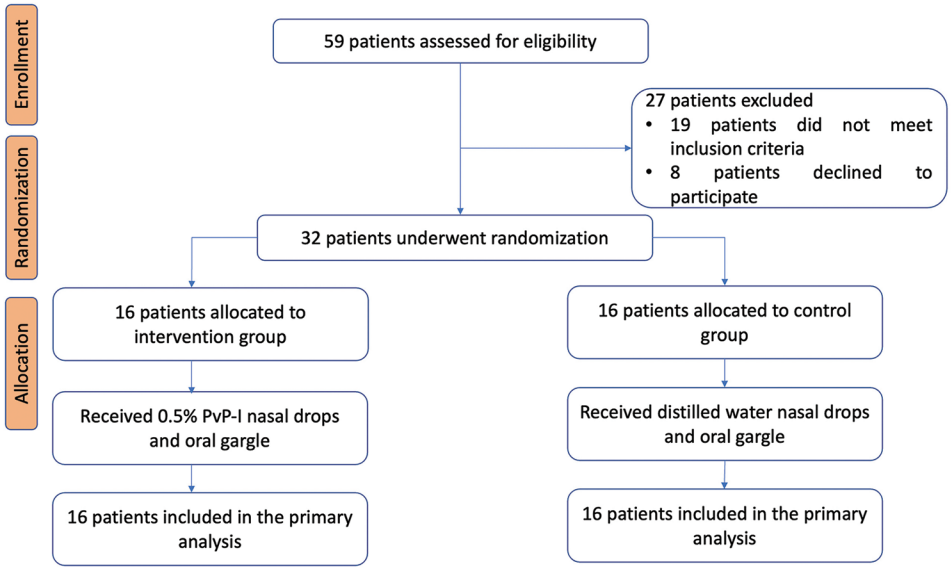

Figure 1: Enrollment and randomization schematic

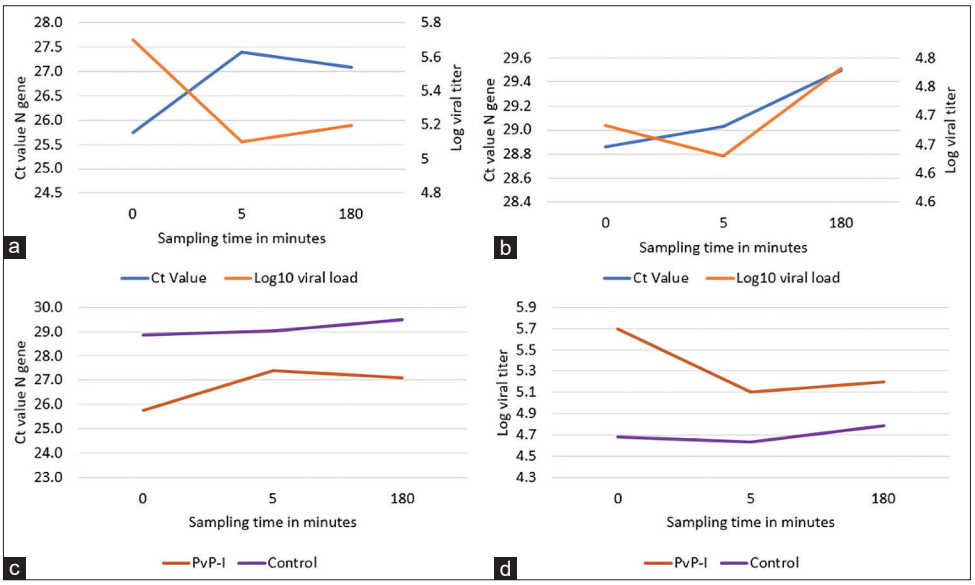

Figure 2: Comparisons of the trend of change in viral titers and Ct values. (a) Viral titers and Ct values in the PvP-I intervention arm over the sampling time intervals, (b) Viral titers and Ct values in the control arm over the sampling time intervals, (c) Ct values between the intervention and control arms, (d) Viral titers between the intervention and control arms

different for the test group as determined by repeated measures ANOVA (F (2,60) = 3.332, $P = 0.042$) [Table 2].

The mean changes in viral titers and Ct values between the intervention and placebo groups throughout the 3-hour trial interval are displayed as line graphs to highlight the distinct patterns [Figure 2].

Discussion

Despite extensive measures to devise preventive and therapeutic modalities, the COVID-19 pandemic continues to advance globally. Although the proportion of vaccinations against SARS-CoV-2 is increasing, primary health care workers and people, in general, are still largely dependent on physical barriers [masks and personal protective equipment (PPE)] for preventing infection. Hence, it is crucial to establish evidence for the efficacy and feasibility of supplementary strategies to control viral transmission. The method in question here is the use of the antiseptic agent povidone-iodine as a virucidal and de-colonizing agent to mitigate the high transmissibility of the disease. This could prove to play a pivotal role in limiting the spread of the disease as it has already been demonstrated that the disease transmission occurs early after infection, during the incubation period, by asymptomatic carriers, and even during convalescence.[11,12]

Table 1: Demographic and clinical characteristics of the study participants

Characteristic	PvP-I test arm (*n*=16)	Placebo-Controlled arm (*n*=16)	Total (*n*=32)
Gender - no. (%)			
Male	8 (50.0)	7 (43.8)	15 (46.9)
Female	8 (50.0)	9 (56.3)	17 (53.1)
Age Group (in years) - no. (%)			
≥18-60	8 (50.0)	7 (43.8)	15 (46.9)
>60	8 (50.0)	9 (56.3)	17 (53.1)
Days since symptom onset - Mean±SD	6.4±2.2	5.4±2.7	5.9±2.5
Presenting symptom - no. (%) *			
Fever	14 (87.5)	11 (68.8)	25 (78.1)
Dry cough	8 (50.0)	4 (25.0)	12 (37.5)
Chest pain	1 (6.3)	0 (0.0)	1 (3.1)
Breathlessness	9 (56.3)	12 (75.0)	21 (65.6)
Altered Smell	8 (50.0)	0 (0.0)	8 (25.0)
Altered Taste	2 (12.5)	0 (0.0)	2 (6.3)
Fatigue	11 (68.8)	1 (6.3)	12 (37.5)
Myalgia	1 (6.3)	0 (0.0)	1 (3.1)
Diarrhea	1 (6.3)	0 (0.0)	1 (3.1)
Other - Swelling over the face	0 (0.0)	1 (6.3)	1 (3.1)
None	0 (0.0)	1 (6.3)	1 (3.1)
First symptom - no. (%)			
Fever	10 (62.5)	8 (50.0)	18 (56.3)
Dry cough	1 (6.3)	2 (12.5)	3 (9.4)
Breathlessness	3 (18.8)	4 (25.0)	7 (21.9)
Diarrhea	1 (6.3)	0 (0.0)	1 (3.1)
Altered Smell	1 (6.3)	0 (0.0)	1 (3.1)
Other - Swelling over the face	0 (0.0)	1 (6.3)	1 (3.1)
None	0 (0.0)	1 (6.3)	1 (3.1)
Oxygen saturation at the time of admission - no. (%)†			
90%-93%	11 (68.8)	13 (81.3)	24 (75.0)
>93%	5 (31.3)	3 (18.8)	8 (25.0)
Respiratory rate per minute at the time of admission - no. (%)			
≥24	11 (68.8)	13 (81.3)	24 (75.0)
<24	5 (31.3)	3 (18.8)	8 (25.0)
COVID-19 criteria at the time of enrollment - no. (%)			
Mild	5 (31.3)	3 (18.8)	8 (25.0)
Moderate	11 (68.8)	13 (81.3)	24 (75.0)
Medical history - no. (%)			
Type 2 Diabetes Mellitus	1 (6.3)	2 (12.5)	3 (9.4)
Hypertension	2 (12.5)	0 (0.0)	2 (6.3)
Type 2 Diabetes Mellitus and Hypertension	3 (18.8)	2 (12.5)	5 (15.6)
COPD	1 (6.3)	0 (0.0)	1 (3.1)
Bronchial Asthma	1 (6.3)	0 (0.0)	1 (3.1)
Chronic Renal Disease	0 (0.0)	1 (6.3)	1 (3.1)
None	8 (50.0)	11 (68.8)	19 (59.4)
History of smoking - no. (%)	4 (25.0)	1 (6.3)	5 (15.6)

* Calculated as multiple response variables. †Measured using a pulse oximeter

Table 2: Mean, SD, and repeated measures ANOVA statistics for log viral titers and Ct values

Variable	Time interval	Mean±SD		ANOVA			
		PVI-P Group	Control Group	*F* ratio	Df	η^2	*P*
Log Viral Titer	Baseline	5.65±1.78	4.68±1.32	2.305	(2,60)	0.071	0.109
	5 mins	5.14±1.59	4.63±1.45				
	3 hours	5.23±1.73	4.78±1.11				
Ct Value	Baseline	25.75±5.75	28.86±4.25	3.332	(2,60)	0.100	0.042‡
	5 mins	27.40±5.12	29.03±4.68				
	3 hours	27.08±5.58	29.49±3.70				

Abbreviations: SD – Standard Deviation, Df – degrees of freedom, η^2 – partial Eta (effect size). ‡ Indicates a statistically significant value, $P<0.05$ at 95% CI

Upon analyzing the outcomes of this study, we observed that the PvP-I administration produced a statistically significant mean change in the Ct values of serial samples in the test group as compared to the control group. However, the study could not demonstrate a statistically significant change in the mean viral load over time being caused by PvP-I as compared to the administration of the control agent (distilled water). On the contrary, a graphical representation of the outcomes, in turn, depicts PvP-I to be relatively superior to the control agent, judging by the trends of decreasing viral load and increasing Ct values in the test arm over the control arm. These results were found to be consistent irrespective of the sex, age, duration of symptoms, and the severity of the disease.

The effects of PvP-I in other respiratory viral diseases and COVID-19, in particular, have been assessed previously.[3-6] Eggers M *et al.*[4,5] first established the ground for the clinical use of the bactericidal and, especially, the virucidal activities of PvP-I through its *in vivo* and *in vitro* use as an antiseptic and demonstrated their rapid inactivation even at dilute concentrations of 0.23% for an extremely short exposure of just 15 seconds. Frank S *et al.*[3] exhibited complete inactivation of SARS-CoV-2 *in vitro* by the PvP-I nasal antiseptics at varying concentrations, the least being 0.5%, with a contact time of 15 seconds without any cytotoxic effect. Berkelman RL *et al.*[13] had also illustrated before that dilute preparations (up to 0.1%) of PvP-I have superior bactericidal activity than its full-strength solutions. Naqvi S.H.S. *et al.*[14] have also recently suggested a topical povidone-iodine-based prophylactic protocol for SARS-CoV-2 transmission during upper aerodigestive tract procedures which also utilizes the virucidal properties of PvP-I causing reduced infectious aerosol generation.

It is worth mentioning that none of the samples in our study reported complete conversion to negative RT-PCR after administration of PvP-I, which is in contrast to the findings highlighted by Lamas LM *et al.*,[10] who observed a significant decrease in the viral load and 50% inactivation of the samples to negative by RT-PCR and that such an effect lasted for a duration of at least 3 hours. They, however, also observed the detection of viral RNA even in the samples which tested negative, the viability of which could not be ascertained. Similar findings in the convalescent phase had also been reported by Rothe C *et al.*[12] Consequently, it was deduced during the course of our study that it is beyond the capability of an RT-PCR test to accurately determine the complete inactivation of the viruses *in vivo* as it erroneously detects non-viable viral RNA and can provide falsely positive test results for variable periods of time even in the absence of the clinically viable virus and the resolution of clinical infection.

To precisely de-lineate the inactivation of SARS-CoV-2 by PvP-I, more sophisticated techniques such as serial viral cultures, viral titer using the dilution limit method on Vero cells (Viral endpoint assays), and so on are warranted, which were neither available nor authorized (by regulatory authorities) for use at the time of undertaking and execution of the study. Hence, only the trend of change in the mean viral load upon administration of PvP-I could be documented instead of inactivation and conversion of the samples. This has also been clearly demonstrated in the study by Guenezan J *et al.*[15] using both the above-mentioned methods simultaneously. Their study exhibited a 75% relative decrease in the mean viral titers between baseline and day 1 in the intervention group (PvP-I mouthwashes, gargles, nasal pulverization, and nasal ointment) and a 32% decrease in the control group (without any intervention) and reported the complete conversion of all the subjects, except one, to negative on viral titers by day 3. However, this effect was not evaluated immediately post intervention or within the previously demonstrated duration of bactericidal and virucidal action of PvP-I, that is, a minimum of 3 hours, and hence could not possibly be considered as the local de-colonization action of PvP-I in true sense.[10,16]

None of the study participants reported any adverse events or any side effects to the test agent, and 0.5% PvP-I was found to be very well tolerated by all the study subjects as has been previously demonstrated by Khan MM *et al.*[17] A review on the safety profile of PvP-I by Frank S *et al.*[18] also suggested its usage to be safe and without any adverse effects even for a duration of 5 months in the nasal cavity and 6 months in the oral cavity at concentrations of up to 1.25% and 2.5%, respectively. However, all the patients in the study by Guenezan J *et al.*[15] experienced unpleasant nasal tingling and had poor tolerance, and thus, in turn, questionable clinical applications. This is probably because of the increased strength (10%) of the ointment used and the quite over-zealous and repeated application protocol of the intervention agent.

This study, thus, shows a positive correlation with other such studies conducted previously and brings into light the use of 0.5% povidone-iodine nasal drops and oral gargles as a feasible option for use in diminishing the rapid transmission of COVID-19 and helping in curtailing the pandemic, all the while being well tolerable, inexpensive, readily available, and without any considerable side effects or adverse reactions.[3,5,6,10,15]

Limitations

A major limitation of this study is the inability to accurately determine the inactivation of the nasopharyngeal and oropharyngeal viral loads and segregate the viable and hence transmissible from the non-viable viruses in the samples testing positive for SARS-CoV-2. Also, studies with a larger sample size and more precise testing techniques, preferably multi-centric, are advisable for the generalizability of the results.

Conclusion

Although a clearly discernible statistically significant effect of povidone-iodine on SARS-CoV-2 for de-colonization in active cases could not be demonstrated in this study, it does depict a possible decreasing trend in the overall nasopharyngeal and oropharyngeal viral loads because of its virucidal effect. Thus,

routine use of PvP-I solution for decreasing nasal and oral viral loads can prove to be a vital adjunctive tool in the prophylaxis of SARS-CoV-2 and respiratory pathogens, in general. The study favors the use of PvP-I with a preventive rather than a curative intent.

Recommendation

Administration of PvP-I solution for local de-colonization of SARS-CoV-2 and other respiratory pathogens, in general, is a potentially low-cost, low-morbidity, and easily accessible vital auxiliary tool in decreasing the disease transmission alongside the use of routine PPE. This can be of substantial aid for the primary care physicians, especially for the practitioners in remote and resource-poor areas, for prevention against contracting the disease if administered to the patient before interacting or examining the patient or performing any procedure and to bring the overall disease burden in the community with its routine use.

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Conflicts of interest

There are no conflicts of interest.

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