Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) marked the year 2020 as the year of the highly infectious coronavirus disease-2019 (COVID-19) Pandemic.[1] The...
main diagnostic modality of COVID-19 has been Reverse Transcription Polymerase Chain Reaction (RT-PCR) and a rough approximation of the viral load is indicated by the Cycle threshold (Ct) value, which is a semi-quantitative measure, obtained through Real-time RT-PCR.\(^2\)

Due to relative ease and lesser invasiveness, nasopharyngeal and oropharyngeal swabs are the most common specimens collected for SARS-CoV-2 detection.\(^3,4\) Comparatively higher viral load has been detected in the nasopharynx than the oropharynx.\(^5\) Moreover, the nasal epithelium contains the maximum angiotensin-converting enzyme-2 (ACE-2) receptors in the body and SARS-CoV-2 makes its cellular entry through these receptors, with subsequent replication and transmission. This has been a basis for nasopharyngeal sample collection for diagnosis and use of face masks to cover the transmission portals (nose and mouth) and prevent the spread of COVID-19.\(^6,7\)

For protection of these portals of entry and transmission, Povidone Iodine (PVP-I) has been recommended as an effective anti-viral agent against SARS-CoV-2.\(^8\) Iodine in PVP-I is a known antiviral, antibacterial and fungicidal agent.\(^9\) PVP-I has shown efficacy against two coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV) causing SARS and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) causing the MERS epidemic.\(^10,11\) Recent studies have reported high virucidal activity of PVP-I, in-vitro and in-vivo, against SARS-CoV-2 within 30 s and 60 s of contact, respectively.\(^12\)

This study was conducted to assess the impact of PVP-I oral and nasal application on the SARS-CoV-2 viral load as indicated by Ct-values of rRT-PCR and to assess the correlation between nasopharyngeal and oropharyngeal sampling in terms of RT-PCR assay SARS-CoV-2 gene Ct values.

### Methods

#### Study design and participants

This study was a longitudinal (repeated measures) single-arm open-label interventional study with reliability analysis. The study was a validation of the diagnostic method used in the main study investigating the effect of oral and intra-nasal application of PVP-I against COVID-19.

The study site was located in a State in South India which had reported one of the highest rates of COVID-19 cases in the country.\(^13\) Study participants were laboratory-confirmed (RT-PCR) COVID-19 patients, aged 18 years and above. Patients with known allergy to any form of povidone iodine, history of thyroid disorders, pregnant or unconscious patients and patients on ventilator were excluded from the study. The study was conducted in June-August 2020.

With a threshold probability of rejecting the null hypothesis of 0.05 and a probability of failing to reject the null hypothesis under the alternative hypothesis of 0.2, a sample size of 10 was needed to prove a correlation coefficient of 0.8 between nasopharyngeal and oral samples.

#### Study procedure

Enrolment was done after obtaining written informed consent of COVID-19 patients. A pre-tested questionnaire in the local language was administered to the patients. Questions included demographic profile, travel history, contact with COVID-19 case, symptoms, comorbidities, date of positive report etc. Symptoms were documented in the symptom record sheet daily.

PVP-I bottles were provided to the participants with verbal and video-recorded instructions on dilution and usage. This was a commercially available iodine-based ‘mouthwash’ in India, a 2% solution with mint flavour, licensed for oral mucosal use.

Participants were asked to prepare fresh PVP-I solution daily by 1:1 dilution with water to yield a 1% solution. Intranasal application of PVP-I (0.3 ml) comprised external application in the anterior nares and along the walls of nasal cavity, as far as possible with cotton buds four times a day at six hourly intervals, preferably, 3-10 minutes after meals for a period of 7 days. This was according to the trough and peak action time of PVP-I applied locally over mucous membrane.

For oral gargle, 25 ml of the 1% solution was introduced into the oral cavity and used as a mouthwash whilst ensuring the solution was distributed throughout the oral cavity for 30 s and then gently gargled or held at the back of the throat for another 30 s before spitting out. The procedure was to be done four times a day, subsequent to- and for the same duration as the nasal application. Each patient was monitored telephonically on a daily basis by trained research personnel.

Clinical sample collection was done on Day-0, Day-3, Day-6, Day-9 of enrolment at three different timings: Hour-0 (five minutes before PVP-I use); Hour-2 (2 h after using PVP-I) and Hour-4 (4 h after using PVP-I) and only Hour-0 for Day-9.

#### Real-time reverse transcription polymerase chain reaction assay for SARS-CoV-2

RT-PCR assay was performed at the biosafety level-2 COVID-19 Diagnostic Laboratory of the study Institute. Under strict aseptic precautions, nasopharyngeal and oropharyngeal swabs were collected by trained research personnel in Viral Transport Medium (Poly Medicure Ltd.) and transported in cold chain of 2–4°C. Nucleic acids were isolated and purified using QIAamp Viral RNA Mini extraction kit. Purified nucleic acid including those of target genes— small envelope protein (E) and nucleocapsid protein (N) was directly amplified using TRUPCR® SARS-CoV-2 Kit (Genophyll Enterprises, mail@genophyll.com) based on rRT-PCR SARS-CoV-2 detection on QuantStudio™ 5 Real-Time PCR Instrument (HID Real-Time PCR Analysis Software v1.3 -Thermo Fisher scientific company). RT-PCR machine was calibrated and set threshold above the maximum
level of no Template control curve (random noise curve). Cycle threshold (Ct) cut-off value for positive test result was 36 and Ct-value cut-off of 37 was defined as negative result.

### Statistical analysis

Data analysis was done in STATA analysis software version 14.2 (StataCorp, College Station, TX). Data were summarized as mean (standard deviation) and median (inter-quartile range) for quantitative data and as frequency (percentages) for qualitative data. McNemar Test was applied for the paired nasopharyngeal and oropharyngeal samples for qualitative RT-PCR. Skilling Mack Test was used to study the association between PVP-I use (intra-day and inter-day) and E gene/N gene Ct values. A value of $P < 0.05$ was considered statistically significant. Pearson Correlation coefficients were calculated to assess concordance between the nasopharyngeal and oropharyngeal isolates and agreement was assessed using Bland-Altman plots in terms of two gene sets.

### Ethics

Prior ethical approval for the study was obtained from the Institutional Ethics Committee of the study institute (AIIMS/MG/IEC/2019-20/16). All procedures pertaining to protection of human participants were followed as per the Declaration of Helsinki.

### Results

#### Demographic and clinical characteristics of COVID-19 patients

Ten (male-9; female-1) COVID-19 cases were enrolled in the study. The mean (SD) age of the patients was 41.5 (8.82) years (range: 30 to 58 years). Two patients had recent travel history. There was no known close contact with COVID-19 case(s). Four patients were symptomatic (fever, cough, breathing difficulty, diarrhea, weakness); two patients were recently treated for tonsillitis and typhoid fever. Two patients had chronic diseases (hypertension, diabetes mellitus, bronchial asthma).

#### Qualitative result of SARS-CoV-2 RT-PCR assay

PVP-I was used for a week by the patients and on Day-8, there was neither PVP-I use nor sample collection. A total of 200 samples were tested for SARS-Cov-2 by RT-PCR. This comprised 10 nasopharyngeal and 10 oropharyngeal samples per patient, collected thrice each on Day-0, Day-3, Day-6 and once on Day-9. Six out of ten and five out of ten nasopharyngeal and oropharyngeal isolates of Day-9 respectively were RT-PCR positive. Results did not differ across days of testing for nasopharyngeal ($P = 0.687$) and oropharyngeal ($P = 0.219$) isolates [Table 1].

#### Cycle threshold (Ct) values of SARS-CoV-2 E gene and N gene on RT-PCR assay

Table 2 presents the hour-wise SARS-CoV-2 Ct values of $E$ gene and $N$ gene. Significant difference was found in $E$ gene Ct values between hours of nasopharyngeal sample collection on Day-0 ($P = 0.030$). For $N$ gene Ct values, significant difference was found between hours of oropharyngeal sample collection on Day-0 ($P = 0.011$) and Day-3 ($P = 0.022$).

Overall median (IQR) for $E$ gene Ct values of nasopharyngeal and oropharyngeal samples was 28.32 (22.00-31.78); $P = 0.076$ and 28.65 (25.84-31.85); $P = 0.218$, respectively. Overall median (IQR) for $N$ gene Ct values of nasopharyngeal and oropharyngeal swabs were 28.43 (22.08-32.11); $P = 0.077$ and 29.79 (26.95-33.13); $P = 0.364$, respectively.

Table 3 presents the $E$ gene and $N$ gene Ct values across sampling days. A gradual rise in the $E$ gene Ct values (nasopharyngeal) were detected at Hour-0 between Day-0 and Day-9 ($P = 0.005$). Although not statistically significant ($P = 0.308$), there was increase in the $E$ gene Ct values at Hour-2 from Day-0 to Day-6. $N$ gene Ct values were also higher at Hour-2 and Hour-4 of Day-6 as compared to previous sampling days, without statistically significant differences. The trend lines are displayed in Figure 1.

#### Correlation between nasopharyngeal and oral samples of SARS-CoV-2

In the correlation analysis between nasopharyngeal and oropharyngeal samples, concordance correlation coefficient for $E$ gene was 0.6178 (95% CI: 0.449-0.743) and [0.428 (95% CI: 0.212-0.603)] for $N$ gene. As depicted by Bland-Altman plot [Figure 2], mean difference between nasopharyngeal and oropharyngeal for $E$ gene and $N$ gene Ct values were -2.3 (-9.5%) and -2.0 (-8.2%), respectively. The differences established superiority of nasopharyngeal measurements in the range of Ct values for COVID-19 diagnosis. Ct values were lower in nasopharyngeal samples than oropharyngeal samples by a factor of 2.3 and 2.0 points. The regression line of differences showed that values were more prominently diagnostic at lower levels of Ct than higher values.

#### Discussion

This is one of the few in-vivo studies which assessed the impact of povidone iodine on the RT-PCR cycle threshold values of SARS-CoV-2 genes in COVID-19 patients. Of the ten COVID-19 patients enrolled in the study, six patients were asymptomatic. Asymptomatic viral shedding by SARS-CoV-2 infected cases has been reported earlier. The four symptomatic patients in our study had clinical manifestations and co-morbidities similar to those reported earlier among COVID-19 patients.

In this study, there was variability in the qualitative RT-PCR results across the sampling points. This is congruent with similar reports regarding qualitative RT-PCR which can vary greatly. Xiao et al. reported a positive third-time RT-PCR test in 30% of patients, despite previous two negative tests. Since SARS-CoV-2 virus-laboratory-patient dynamics influence RT-PCR results, cautious interpretation of results have been advocated. Moreover, prolonged viral shedding
Table 1: Distribution of RT-PCR qualitative result by site of sample collection

| Site      | Result | Day-0 (n=10) | Day-3 (n=9) | Day-6 (n=10) | Day-9 (n=10) | P*  |
|-----------|--------|--------------|-------------|--------------|--------------|-----|
| Nasal     | Positive | 8 8 9 6 6 5 | 5 6 6 5 | 6 6 6 5 | 0.687 |
| Nasal     | Negative | 2 2 1 3 3 4 | 5 5 4 4 | 4 4 5 5 | 0.219 |
| OralOral  | Positive | 9 9 7 5 5 5 | 5 3 5 5 | 5 7 5 5 | 0.219 |
| OralOral  | Negative | 1 1 3 4 4 5 | 5 7 5 5 | 5 7 5 5 | 0.219 |

Table 2: Intra-hour distribution of E gene and N gene Ct values

| Gene | Site                          | Day-0 Median (IQR) | Day-3 Median (IQR) | P*  |
|------|-------------------------------|--------------------|--------------------|-----|
| E    | Nasopharyngeal                | 22.01 (17.96-27.77) | 25.13 (21.99-30.01) | 0.030* |
|      | Oropharyngeal                 | 28.67 (26.8-36.79) | 28.75 (25.84-32.94) | 0.052 |
| N    | Nasopharyngeal                | 24.94 (15.4-31.63) | 28.98 (20.80-31.61) | 0.196 |
|      | Oropharyngeal                 | 30.78 (28.17-34.62) | 27.69 (26.99-34.10) | 0.011* |

Table 3: Ct values (E gene and N gene) across days by hour of sample collection

| Gene | Sample Timing | Day 0 | Day 3 | Day 6 | Day 9 | P*  |
|------|---------------|-------|-------|-------|-------|-----|
| E    | Hour 0        | 22.01 (17.96-27.77) | 25.59 (24.69-29.64) | 31.48 (27.98-32.50) | 30.94 (26.66-32.14) | 0.005* |
|      | Hour 2        | 25.13 (21.99-30.01) | 25.68 (21.56-29.33) | 34.18 (23.93-34.99) | NA                | 0.308 |
|      | Hour 4        | 26.78 (22.27-33.18) | 27.39 (19.76-27.50) | 24.90 (21.85-31.16) | NA                | 0.897 |
| N    | Hour 0        | 24.94 (15.49-31.63) | 25.74 (21.67-31.11) | 31.20 (29.83-33.41) | 29.89 (26.67-36.16) | 0.164 |
|      | Hour 2        | 28.98 (20.80-31.61) | 28.92 (23.51-30.66) | 26.94 (20.89-30.25) | NA                | 0.289 |
|      | Hour 4        | 28.43 (21.51-34.34) | 30.20 (26.30-36.80) | 26.97 (24.14-31.01) | NA                | 0.636 |

As reported earlier, nasopharyngeal samples were found to be relatively superior to oropharyngeal samples along with lower Ct values in most testing points, especially for N gene. Several other studies have also reported better viral detection from nasopharyngeal or nasal specimens. Liu et al. stated that inhibitory components in the oropharynx (close vicinity to the oral cavity) might attribute to lower SARS-CoV-2 detection in oropharyngeal samples.

Studies have reported the utility of Ct values in clinical progression of COVID-19. However, lack of association between Ct values and clinical course of COVID-19 has also been reported. In this study, a significant rise in the Ct values was observed for Hour-0 (prior to PVP-I usage for the day) across days of testing, which may be indicative of the natural course of SARS-CoV-2 infection and decline in viral load, irrespective of the positive qualitative results, as reported earlier. Another aspect in SARS-CoV-2 sample collection which is reinforced by our study, is the possibility of higher
yield of virus in the early part of the day or before washing, as reported earlier.\[24\]

Moreover, viral carriage and transmission by asymptomatic or convalescent COVID-19 cases through the nasal cavity and oropharynx have been reported.\[31,32\] In this study, 1% PVP-I was used. Similarly, studies have reported rapid inactivation of SARS-CoV-2 at concentrations ranging from 0.5% to 2.25% with intranasal safety concentrations reported to be 1.25% and recommendations for six hourly prophylactic usage of PVP-I.\[8,33\] Allaying apprehensions regarding PVP-I topical applications, several studies have reported low allergenic properties, low cytotoxicity, and no or minimal thyroid dysfunction with PVP-I usage.\[34-36\] Hence our study provides a direction in the usage of PVP-I 1% solution as an adjuvant therapy against COVID-19.

In this study, there was a significant difference in the Ct values between specific hours of testing after PVP-I usage. However, no consistent significant differences were found between successive days of testing. Although not statistically significant, higher Ct values were observed at Hour-2 for most of the samples. This points to the possibility of PVP-I action being optimal within...
2 h of usage, at a contact time of 30 s as done in our study. This finding supports recommendations for usage of PVP-I by health care workers and general public immediately pre- and post-close contact with COVID-19 cases.\[37\] PVP-I formulations as nasal sprays or oral rinses have been particularly recommended for those involved in aerosol-generating procedures such as surgical, otolaryngological and dental practice.\[38-40\]

Additionally, a large proportion of general public seek primary healthcare due to easier access, especially during the pandemic as healthcare facilities have either been converted to dedicated COVID-19 facilities or have placed restrictions on out-patient services. This study provides information to primary care physicians on the potential role of povidone iodine in COVID-19 as a protective measure, particularly among high-risk contacts in the community and as a treatment adjuvant for COVID-19 patients. The study also provides scientific research update on RT-PCR (variable results of the same patients at different testing points) and in-vivo PVP-I effect on SARS-CoV-2 cycle threshold values.

Study limitations include the small sample size of COVID-19 patients and testing at various clinical stages of the disease, although the participants were enrolled in the early stages of infection. Exposure could not be ascertained as participants could not recall or did not know if they were in close contact with a COVID-19 case. PVP-I usage was self-reported and it was not done under direct observation due to infectious nature of the disease. Lack of a control group is another limitation of our study. However, Hour-0 implied pre-PVP-I usage on all testing days so this may have validated the comparisons to some extent. Despite these limitations, our study provides unique insights into the paradigm of changes in Ct values of RT-PCR with PVP-I usage.

In conclusion, lower RT-PCR Ct values were found in Hour-0 samples across successive days, indicating higher viral load before PVP-I usage and decline in viral load as part of natural course of disease. Higher Ct values at Hour-2 for most of the samples indicate optimal action of PVP-I on the surface mucosa within 2 h of usage. Nasopharyngeal swab samples were found to be relatively superior to oropharyngeal samples in SARS-CoV-2 viral detection.

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Conflicts of interest
There are no conflicts of interest.

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