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Evaluation of virucidal efficacy of 0.5% Povidone iodine (PI), 0.2% Chlorhexidine (CHX) and 1.5% Hydrogen peroxide (H2O2) antiseptic rinse on tongue decontamination in SARS CoV-2 Patients

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ACE-II expression, Chlorhexidine, SARS CoV-2, viral cycle threshold.

Abstract:

Background: SARS CoV-2 spreads rapidly through respiratory droplets, saliva, or direct contact. Oral cavity acts as the gateway with tongue and oral mucosa showing increased expression of angiotensin converting enzyme-2(ACE-II) molecules onto which the virus binds. The simplest way to prevent the cross contamination there by reducing transfer is by adopting effective oral hygiene measures to reduce the viral load. Hence the present study aims to evaluate the efficacy of three different antiseptic rinse used in dental clinics in reducing the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) transfer.

Methods: The study was conducted on 32 mild symptomatic SARS CoV -2 Real time reverse transcription polymerase chain reaction (RT-PCR) positive patients (18 females and 14 males) with the mean age group of 40.3±12.7, who were advised isolation. Patients were grouped into four categories each consisting of 8 patients. Group A patients were provided with 0.5% of Povidone iodine (PI) mouth rinse, where Group B were advised 0.2% Chlorhexidine rinse (CHX), Group C were given 1.5% Hydrogen peroxide (H2O2) while the control group were advised water rinse. Tongue scrapings were collected using a sterile swab at the baseline, first week and at the end of second week. Samples were transferred to the viral transport media for the real time reverse transcription polymerase chain reaction to assess the presence of the virus along with the assessment of viral cycle threshold (Ct).

Results: A significant reduction was noted in all the three mouth rinses group except for the control. Statistically significant reduction (P value - 0.000) in the positivity rate was observed in 0.2% CHX group on the 7th day while the PI group fared better than the H2O2 group or control. At the end of 2 week however all the groups exhibited viral inactivity. Chlorhexidine 0.2% rinse group (n=8) showed greater reduction in the viral threshold with a better virucidal action from the early days of infectivity suggesting its effectiveness against SARS COV-2.

Conclusion: Within the limitation of the study it can be inferred that usage of 0.2% chlorhexidine mouth rinse is effective in reducing the SARS CoV-2 virus threshold and hence can be a potential aid in affected individuals in preventing further transmission of the virus.

Introduction:

SARS-CoV-2 previously known as 2019 Novel coronavirus belongs to the family Coronaviridae is responsible for the pandemic disease, COVID-19. The disease was first identified in Wuhan (China) and has spread all over the globe with 304 million confirmed cases and 5.4 million deaths have been reported as of January 2022.[1]

The South East Asia reported the highest increase in new cases while the European region reported the least.

Journal of Chemical Health Risks
www.jchr.org
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Patients with COVID-19 present with symptoms of fever, myalgia, dry cough, and respiratory distress. More than 14% of the people showed severe symptoms of the disease who required hospitalization with 5% of the people taking ICU admissions.[2]

Patients with various underlying systemic illnesses such as renal failure, cardiac disease, liver dysfunction are at a higher risk of developing complications such as severe acute respiratory syndrome, sepsis, and enter into a state of shock[3]. Cross infection takes place through droplet spread, nasal secretion by coughing or sneezing, or through direct contact with the patient, following which the virus can survive on various inanimate surfaces for a longer period of time.[4]

Oral cavity is a potential reservoir for the virus due to the presence of angiotensin-converting enzyme receptors (ACE-II) which act as a viral niche. This receptor is highly enriched in epithelial cells of the tongue compared to other oral tissues. The distribution and expression of ACE II molecules within the human body indicate the potential route for the viral entry and its multiplication. High ACE II expression has been reported in alveolar cells of the lungs, esophagus, enterocytes, myocardial cells, proximal convoluted tubules of the kidney. Hence, the organs exhibiting higher expression of the ACE II molecules show increased chances of viral replication and the disease severity.[5]

Xu et al revealed that dentists and dental procedures pose the highest risk of developing and spreading the COVID-19 infection. Aerosols produced during dental treatment act as a primary source of virus transmission into deeper organs such as the lungs. Further, when exhaled it could result in the community spread through sneezing, coughing, or through direct contact.[5]

Zou et al. have reported that ACE2 expression in cells of the tongue is comparatively higher than by type II alveolar cells of the lungs. Hence, 2019 novel COVID infection susceptibility is more in the tongue than the lungs.[6]

Therefore, effective oral hygiene measures using various antiseptic rinses could help in preventing the viral replication and the spread of the disease. Since many dental procedures generate aerosols, reducing the viral loads is of prime concern. Literature search regarding the control of spread of the novel coronavirus present in the aerosols did not yield significant results. However, mouthwashes containing various antiseptic agents have been proven effective in reducing other viral loads and spread of infection.[7]

The pathophysiology of periodontitis has also been attributed to the cytokine response which is seen in the patients diagnosed with COVID-19 in the form of the cytokine storm. Establishment of cytokine storm produces an immune-pathogenic damage leading to acute respiratory distress syndrome (ARDS) and further progresses to extensive tissue damage. Hence, COVID-19 shares a common cytokine expression profile as seen in the case of periodontitis where the host immune inflammatory response is compromised[8]. Antiseptics are the agents that act by preventing the growth of pathogenic microorganisms. Hua et al have reported the effectiveness of mouthwashes in patients on ventilator support who were undergoing treatment for pneumonia. Studies have evaluated the antiviral action of 0.2% Chlorhexidine, 0.5% Povidone iodine, 1.5% Hydrogen Peroxide, Cetylpyridinium Chloride, and Essential oils. However, the usage of these mouthwashes and its effectiveness during the active period of the novel coronavirus infection in controlling the spread of the infection needs to be investigated. Chlorhexidine 0.2% is considered as the gold standard chemical plaque control agent.[9] Eggers et al reported 1% Povidone iodine to possess the virucidal activity against MERS-CoV within 15 seconds after in-vitro exposure in a concentration of 0.23% which also has been shown to inactivate SARS-CoV, MERS-CoV, and influenza virus.[10]

Diluted Hydrogen peroxide has been used successfully as an oxidizing mouth rinse in cases of necrotizing ulcerative gingivitis due to the release of nascent oxygen, the anaerobic microflora is eliminated. However, it has been advocated as an interim mouth rinse not for long-term usage as studies have not substantiated its use on a regular basis.

The American Dental Association (ADA) has recommended the usage of preprocedural mouthwash Povidone iodine (PVP-I; 0.2%) before any oral procedures. The World Health Organization (WHO) has still not specified on the usage of mouth rinses, but they have been used in preventing various other viral infections. Hence, the aim of the present study was to evaluate the efficacy of three antiseptic mouth rinses Chlorhexidine 0.2%, 0.5% Povidone iodine, and 1.5% Hydrogen peroxide on tongue decontamination in reducing the SARS-CoV-2 virus transfer.

Materials and Methods:

The study was performed at Government District Hospital, FLU corner ward after obtaining consent from

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2475-2482 | ISSN:2251-6727

the concerned authority. Thirty-two symptomatic SARS-CoV-2 RT-PCR positive patients (18 Females and 14 Males) with a mean age of 40.3±12.7 years were enrolled for the study. Patients with positive RT-PCR who reported immediately within 48 hours after becoming symptomatic or had mild symptoms under quarantine center isolation were enrolled. After obtaining Institutional Ethical Clearance, patients who were vaccinated for COVID, pregnant and lactating mothers, or with any underlying systemic illness, smokers, or any modifying factors were excluded. Patients with severe symptoms or in the ICU, or who refused the usage of mouthwashes were also excluded.

The patients were randomly allocated into four categories. Group A patients were provided with 0.5% Povidone iodine mouth rinse, while Group B patients were provided with 0.2% Chlorhexidine rinse. Group C patients were given 1.5% Hydrogen peroxide while the control group were advised water rinse.

Patients used 10ml of solution as a mouthrinse, twice daily for 60 seconds, for a period of two weeks. Tongue scrapings were collected using a sterile swab at the baseline, first week, and at the end of two weeks to check for the presence of the virus and cycle threshold (Ct) using RT PCR.

Microbiological Parameters: SARS-CoV-2 viral detection was done using Meril COVID-19 One-step RT-PCR kit. Samples were collected using a sterile swab from the dorsum of the tongue. These swabs were transferred to the viral transport media (VTM) and transported to the GENETM laboratory maintaining a temperature of -70°C. VTM was used for RNA purification. The reaction mix was prepared using 9 µL of re-suspended master mix and 1 µL of ORF1ab/N/IC Primer and probe. 10 µL of this reaction mix was suspended into the wells of the PCR platform which was then amplified. COVID-19 RNA detection was done using ORF-1abgene and N gene, and the cycle threshold was recorded.

Statistical Analysis: The data was collected, coded, and fed into SPSS (IBM version-23) for statistical analysis. Descriptive statistics included mean and standard deviation. Inferential statistical tests included one-way ANOVA test followed by Post Hoc Tukey's test. The level of significance was set at 0.05 at a 95% confidence interval.

Results:

The study comprised 32 patients who tested RT-PCR positive at the baseline. Since all patients tested RT-PCR negative on the 14th day, comparison could not be made between these two time intervals. However, maximum changes were observed within the 7-day time period.

On intragroup comparison of the 7th day results, patients who used Povidone iodine mouthwash showed 25% (n=2) positive results, while the remaining 75% (n=6) tested negative on RT-PCR. However, 100% (n=8) of patients using 0.2% Chlorhexidine mouth rinse tested RT-PCR negative on the 7th day itself. The Hydrogen peroxide group showed a 50% reduction since the remaining 50% (n=4) were still RT-PCR positive at the end of 7 days. The control group exhibited 75% (n=6) of the patients to be RT-PCR positive.

The maximum reduction was noticed in Group B (Chlorhexidine group) with 100% clearance, followed by the Povidone iodine group and the Hydrogen peroxide group when compared to the control. All intragroup and intergroup comparisons were statistically significant with P values of 0.000 and 0.014, respectively.

The Ct values at the end of 7 days showed definitive changes. The control group exhibited 50% of the subjects with strong positive reports, while none of the other groups were strongly positive. However, 25% of the subjects in both the Povidone iodine group and the control group were moderately positive, while 50% of the Hydrogen peroxide group also remained moderately positive. The maximum cycle threshold was observed in the Chlorhexidine group (100%), followed by Povidone iodine (75%) and Hydrogen peroxide (50%) when compared to the control (25%). All the results were statistically highly significant with a P value of 0.003.

The mean Ct values of Group A were 22.0263, Group B were 19.9025, Group C were 22.2488, and Group D were 21.8713 at the baseline. There was an increase in Ct value in all groups. However, the maximum elevated levels were seen in Group B (35.00), followed by Group A (33.4713), Group C (31.3375), and Group D (25.4800). Elevated Ct values signify a decrease in viral load.

Maximum reduction within one week was noticed in the Chlorhexidine group (n=8), followed by the Povidone iodine and Hydrogen peroxide group when compared to the controls. All the results were statistically highly significant with a P value of 0.000. However, the control group showed a strong RT-PCR positive correlation for 50% of subjects at the end of 7 days and 25% to have moderate RT-PCR positive values.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2475-2482 | ISSN:2251-6727

		RT PCR			Chi squarevalue	Sig. (P value)
		BASELINE	7TH DAY	14TH DAY		
GROUP A	POSITIVE	8(100)	2(25)	0(0)	17.829	**0.000(HS)**
	NEGATIVE	0(0)	6(75)	8(100)		
GROUP B	POSITIVE	8(100)	0(0)	0(0)	24.000	**0.000(HS)**
	NEGATIVE	0(0)	8(100)	8(100)		
GROUP C	POSITIVE	8(100)	4(50)	0(0)	16.000	**0.000(HS)**
	NEGATIVE	0(0)	4(50)	8(100)		
GROUP D	POSITIVE	8(100)	6(75)	0(0)	17.829	**0.000(HS)**

TABLE 1: BASELINE – ALL THE SAMPLES IN ALL THE GROUPS ARE POSITIVE

AND 14TH DAY ALL WERE NEGATIVE – SO NO COMPARISON.
Statistically significant (P< 0.05), Statistically highly significant (P< 0.01), Non-Significant (P> 0.05).
RT PCR - Reverse Transcription Polymerase Chain Reaction
HS – Highly Significant

	GROUPA	GROUP B	GROUP C	GROUPD	CHI SQUARE VALUE	SIG. (P value)
POSITIVE	2(25)	0(0)	4(50)	6(75)	10.667	**0.014(S)**
NEGATIVE	6(75)	8(100)	4(50)	2(25)		

TABLE 2: AT 7TH DAY – COMPARISON BETWEEN ALL GROUPS

Statistically significant (P< 0.05), statistically highly significant (P< 0.01), Non-Significant (P> 0.05).
S – Significant

Baseline Ct	**Mean**	**Standarddeviation**	**F**	**Significance**
Group a	22.0263	1.53950	1.737	0.182(NS)
Group b	19.9025	1.90188		
Group c	22.2488	2.33067		
Group d	21.8713	3.19889		
7th Day Ct				
Group a	33.4713	2.86567	7.658	0.001(HS)
Group b	35.00	.000		
Group c	31.3375	3.95075		
Group d	25.4800	6.99953		

TABLE 3: AT 7TH DAY- CYCLE THRESHOLD COMPARISON

Statistically significant (P< 0.05), statistically highly significant (P< 0.01), Non-Significant (P> 0.05).
HS- Highly Significant

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2475-2482 | ISSN:2251-6727

		RT PCR			Chi square value	Sig. (P value)
		STRONG	MODERATE	NEGATIVE REPORT		
GROUP A	BASELINE	8(100)	0(0)	0(0)	27.429	**0.000(HS)**
	7TH DAY	0(0)	2(25)	6(75)		
	14TH DAY	0(0)	0(0)	8(100)		
GROUP B	BASELINE	8(100)	0(0)	0(0)	24.000	**0.000(HS)**
	7TH DAY	0(0)	8(100)	0(0)		
	14TH DAY	0(0)	0(0)	8(100)		
GROUP C	BASELINE	8(100)	0(0)	0(0)	32.000	**0.000(HS)**
	7TH DAY	0(0)	4(50)	4(50)		
	14TH DAY	0(0)	0(0)	8(100)		
GROUP D	BASELINE	6(75)	2(25)	0(0)	18.000	**0.001(HS)**
	7TH DAY	4(50)	2(25)	2(25)		
	14TH DAY	0(0)	0(0)	8(100)		

TABLE 4: 14TH DAY ALL WERE NEGATIVE SO NO COMPARISON

Statistically significant (P< 0.05), Statistically highly significant (P< 0.01), Non-significant (P> 0.05).
RT PCR - Reverse Transcription Polymerase Chain Reaction
HS – Highly Significant

Fig 1: sample collection at baseline

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2475-2482 | ISSN:2251-6727

Figure 2: sample collection after 7 days

Fig 3: Samples transferred to VTM

Figure 4: Various antiseptics used.

Discussion:

The outbreak of COVID-19 pandemic with its first wave, second wave and continued attacks have impacted the health and economy of millions of people worldwide. The exaggerated immune response serve as a tissue damaging factor for the oral tissues or other

Journal of Chemical Health Risks
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JCHR (2024) 14(2), 2475-2482 | ISSN:2251-6727

multi organ systems. The cytokine storm in strongly RT-PCR positive patients creates and emergency medical situation requiring hospital or ICU admission. The moderately symptomatic or positive patients who require home isolation are often ignored resulting in death due to sudden increase
in viral load.[1]

The oral tissues serve as a potential site for harbouring these viruses due to ACE-II receptors. Desquamated epithelial cells along with the virus may increase the infectivity of saliva also aerosols produced during the dental procedure may make these pathogens airborne or settle in the dental clinic thereby increasing the chance of cross infection.[4]

Hence studies have shown that usage of antiseptic mouth rinses can reduce the oro-pharyngeal load of SARS CoV-2, preventing cross transfer to a large extent.[11] However literature on pre-procedural mouth rinse for COVID patients are inconclusive, some suggesting Povidone iodine and Cetylpyridinum chloride to fare better than essential oil mouth rinses, while other have demonstrated no difference in effectiveness between Povidone iodine and Chlorhexidine
mouthwash.[12] This difference could be due to the variation in the test samples used such as saliva, plaque, tongue coating etc.

The present study included 32 RT-PCR positive patients who are mildly symptomatic and did not require ICU admission. Mildly symptomatic was defined as those patients who were RT-PCR positive and developed mild fever, cough, sore throat, shortness of breath and fatigue with SpO2 levels within 95% or higher.13Patients in ICU were excluded as it was not possible for them to use mouth rinses considering their acute stage. Similarly diabetic or immune-compromised patients were excluded as they could influence the outcome of the study. Hence patients diagnosed to be suffering from only SARS CoV-2 were included as samples.

The choice of antiseptics were made based on few previous studies on salivary samples.12 Pre-procedural rinse with Hydrogen peroxide have shown low viral concentration in aerosols, thereby reducing the chances of cross infection.[14]

The hypothesis that the dental biofilms harbour SARS CoV -2 RNA was first proved by Gomes et al.15 This observation is considered important because it can help prevent the spread of infection and cross contamination during the various dental procedures. A cross sectional study conducted by Estrich et al which has reported a prevalence rate of 0.9% of the dentists in developing the infection in United States. Hence the use of N-95 masks with strict protocol has to be followed by using personal protective equipments for the safety of both the dentists and the patients.[16]

Although studies have used saliva samples, the present study used tongue coating due to the concentration of ACE-II receptors on the tongue surface which act as niche for the virus. Hence assessment of viral concentration in these samples would be better than the salivary samples.

The present study showed that maximum reduction in the viral load was seen at the end of ^{7} days in all the groups. Due to increased immunological activity in the host there is a reduction in viral counts and elevated Ct values. This is similar to the findings of Walsh KA et al.[13]

The chlorhexidine group showed maximum reduction with 100% of patients testing negative on the 7th day and with an elevated Ct score (35.00). Chlorhexidine is a cationic bisbiguanide which is effective against a wide range of microorganisms including viruses and yeast. A recent study has demonstrated the invivo effectiveness of chlorhexidine mouth wash against SARS CoV-2 virus.

The use of chlorhexidine as a mouthwash or gel have also been effective in reducing the ventilator associated pneumonia from 24% to 18%.[17] This is in agreement with the findings of the present study.

Although Povidone iodine mouthwash was found to be less effective than Chlorhexidine it has 75% of patients tested negative on the 7th day. Povidone iodine has been found to inactivate many respiratory viruses including SARS CoV-1.12 The hydrogen peroxide group also showed reduction at the end of 7th day with mean Ct value of 31.3375. However lack of substantivity unlike Chlorhexidine could be attributed to the low performance.

A systemic review done by Herrera et al, Burton et al, Moosavi et al evaluated the role of the oral cavity in the transmission and pathogenicity of SARSCoV-2. They concluded that the oral viral load of SARS-CoV-2 has been associated with the severity of COVID-19, and thus, a reduction in the oral viral load could be associated with a decrease in the severity of the condition and transmission.[18,19,20]

An interesting finding was that the control group showed reduction in the viral loads, although lesser than that of experimental groups. This could be attributed to the immunity of the host controlling the viral replication. However it was observed that there was a slow reduction

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2475-2482 | ISSN:2251-6727

in the infectivity status of the host. This is similar to the findings of Walsh et al.[13] At the end of the study, after 2 weeks, all the patients tested negative suggesting the healing response of the host.

CONCLUSION:

Chlorhexidine, a widely used and readily available compound, has demonstrated efficacy against various human viruses. Our study concluded that 0.2% Chlorhexidine was more effective in reducing the viral load compared to Povidone iodine (PI) and Hydrogen peroxide (H2O2). However, further clinical studies with larger sample sizes are necessary to assess its safety and efficacy as an antiseptic mouth rinse during the active period of infection.

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