Effect of 1% Povidone Iodine Mouthwash/Gargle, Nasal and Eye Drop in COVID-19 patient

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ABSTRACT: Background: The sudden onset of COVID-19 began in late 2019 caused by a novel coronavirus (SARS-COV2) and on 11th March, WHO declared it to have developed pandemic status. There is still no specific treatment and vaccine available for COVID-19; causing wide spread health problem and concern of the globe. Povidone iodine (PVP-I) is an antiseptic that has been used for over 150 years. It is already proved that different concentration of PVP-I can deactivate COVID-19 virus. **Methodology:** In this randomized controlled clinical trial, out of 1113 patients 606 patients were enrolled and divided in 2 groups by randomization after taken consents. In Gr-A, 303 patients underwent mouthwash/gargle, nasal drops and eye drops with 1% povidone iodine 4 hourly for 4 weeks as well as symptomatic treatment according to need. In Gr-B 303 patients were advised mouthwash/gargle, nasal cavity and eye wash with lukewarm water 4 hourly for 4 weeks and symptomatic treatment according to need. RT-PCR test done every 3rd, 5th and 7th day and Thyroid hormone level (TSH,T_3, T_4, FT_4) at 4th week for follow up. **Results:** The group of patients used 1% PVP-I have shown tremendously reduced mortality, morbidity and hospital as well as financial burden in this covid situation. **Conclusion:** Administration of 1% PVP-I as mouthwash/gargle, nasal or eye drop is simple, rapid and cost effective in reduction of mortality and morbidity by COVID-19.

KEYWORDS: Povidone Iodine, 1Pq.s, COVID-19.

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Introduction

A strange situation has emerged among the people all over the world due to corona virus disease (COVID-19) due to its presence for uncertain time and severity of its consequences. Since December 2019, scientists and health-care workers are struggling for effective treatment plan and implementing strategies to control this pandemic. The nasal cavity, oropharynx and nasopharynx are the initial target cell of novel corona virus with the result saliva contains high viral load of COVID-19 with upto1.2 $X10^8$ infective copies/ml.[1,2,3] The saliva is an important diagnostic tool for rapid mass detection.[4] COVID-19 virus occupies host cells through two receptors: Angiotensin Converting Enzyme 2 (ACE_2) and CD_{147} (Basigen or EMMPRIN). Viral spike protein (SP) fixes to ACE_2 or CD_{147} of host cell causing viral invasion, replication and spreading to other cells.[5,6] Like RBCs and Type-II alveolar cells (AT_2) of lung. CD_{147} is also present in tear, alveolar tissues and retinal pigmented epithelium.[7] So some sort of upper respiratory tract infection is due to binding of COVID-19 virus with CD_{147} in ocular tissues then travel into nasal cavity via naso-lacrimal duct.[5,6] In case of COVID-19, initial interaction between its host receptor (ACE_2 or CD_{147}) and spike protein (SP) are the initiating event in establishment of causing human host infection.[8] A recent study done by Hou et al. shows that the ciliated cell with ACE_2 expressions are most susceptible to infection which are more in the upper than lower air way cells.[9] The study shows that a virus transmission pathway, which involves infection of ciliated cells of upper airway (nasal cavity) is the commonest site of infection followed by subsequent aspiration to lower airway and secondary to lungs. This process may play a role in systemic involvement and variable expression of clinical severity.[10,11,12] Iodine is an effective anti-septic agent since 1800s. Povidone Iodine was discovered in 1955 by H.A. Shelanski and M.V. Shelanski. It is a water soluble polymer polyvinyl pyrrotodon (PVP-I) and less toxic than tincture of iodine.[13] PVP-I is extensively used as a hand washing agent (as a 7.5% solution), for pre-procedure skin preparation (as a 10% solution), in ophthalmic surgery (as a 5% solution) and in oral surgery (as a 10% solution).[14,15,16] PVP-I is commercially available in Asia as a 1% w/v mouthwash for use every 2-4hourly. [17] The onset of antiseptic action of PVP-I starts when free form of iodine dissociate from the polymer complex which rapidly penetrates the microbes oxidizing the nucleic acid and its protein structures. PVP-I has higher virucidal activity than other commonly used anti-septic agents like chlorhexidine and benzalkonium chloride and shown to be active in vitro against SARS-COV (epidemic of 2002-03) &

MERS-COV (epidemic of 2012-13) virus.[18,19,20] COVID-19 Virus is highly homologous to SARS virus.[21] In vitro study on virucidal activity of povidone iodine against MERS & SARS virus show that the lowest concentration of povidone iodine to effective was 1% when used for 30 seconds, leading to a reduction of viral activity of ≥ 99.99%.[22] So, 1% PVP-I solution as mouthwash/gargle, nasal drop/spray and eye drop inactivate the heam agglutinin esterase activity as well as enhance absorption of ACE_2 as receptor of host cell.[23] Thus reduced the infectivity of host with systemic transmission and as well as cross infection.

Materials and Methods

Total 1113 patients from 1st February 2020 to 30th August 2020 in Bangladesh took treatment through telemedicine service of Anwar Khan Modern Medical College Hospital, Call A Doctor BD, Sebaghar. All patients were highly educated and belong to middle class family. They had very much hospital phobia in COVID-19 situation and wanted to take treatment at home isolation rather than in hospital. We used mobile calls, Viber, WhatsApp, e-mail and Zoom for communication and collection of data from patient or attending relative. RT-PCR positive patients who have done the test on 1st day of symptom (single or multiple symptoms – fever, body ache, headache, loss of smell, loss of taste, sore throat, diarrhea, skin rash, shortness of breath, redness of the eyes), age more than 10 years and less than 90 years were included in this study. Patients with history of allergy to povidone iodine, all form of thyroid diseases or on radioactive iodine treatment, known pregnancy, renal failure and malignancy were excluded. 606 patients were enrolled and divided in 2 groups by randomization after taken consents. In Gr-A, 303 patients underwent mouthwash/gargle, nasal drops and eye drops with 1% povidone iodine 4 hourly for 4 weeks as well as symptomatic treatment according to need. In Gr-B, 303 patients were advised mouthwash/gargle, nasal cavity and eye wash with lukewarm water 4 hourly for 4 weeks and symptomatic treatment according to need. RT-PCR test done every 3rd, 5th and 7th day and Thyroid hormone level (TSH, T_3, T_4, FT_4) at 4th week for follow up. Some patients required hospitalization were admitted in of Anwar Khan Modern Medical College Hospital. The study protocol was approved by the ethical committee of Anwar Khan Modern Medical College Hospital. Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 16. Quantitative data were expressed as means ±SD. 95% confidence interval was calculated and p value of <0.05 was considered as significance.

Preparation and Method of Application of 1% PVP-I –

10% PVP-I is found all over the country. But 1% commercially available PVP-I is found only in a few cities or town. Most of the 1% PVP-I was formed from 10% PVP-I in the following manner - Povidone Iodine 1P 10% v/w in purified water 1P q.s. Therefore, use 1 mL of PVP-I in 10mL of sterile water/purified water. 1% PVP-I is introduced into oral cavity as mouth wash. Care is taken to ensure the solution is distributed throughout the oral cavity for 30 seconds and then gently gargled or, held at the back of the throat for another 30 seconds before spitting out. Then 4-5 drops of 1% PVP-I is introduced to wash the nostrils by dropper and 2 drops in each eye. This application is done 4 hourly for 4 weeks.

Results

In the study, more affected are male (79.87 %, N- 484) than female (20.13%, N- 122). The differences were not statistically significant (P>0.05). More (39.93%) patients are in the 31-50 years age group, followed by 34.65% in the 51-70 years age group (Table -1). In group A (patients used PVP-I), only 2.64% (N-8) patient is RT-PCR positive on the 7th day whereas in group B (patients used lukewarm water), it is 70.30% (N-213) (Table 2, Gr- A & B) (p>0.05). Data of Table 3(Gr-A&B) shows that 3.30% (N-10) hospitalized patients of group A needed oxygen support (by mechanical ventilator and/or high flow nasal cannula and/or non rebreather mask and/or face mask and/or nasal cannula) but 20.79% (N-63) patients of group B needed oxygen support. Mortality rate is high 5.6% (N-17) in group B than 0.66% (N-2) in group A. The differences were statistically significant (P<0.05).

Table-1. Age and Sex Distributions of patients

Age Group(yrs)	Male		Female		Total	
11-30	**72**	11.88%	18	2.97%	90	14.85%
31-50	193	31.85%	49	8.09%	242	39.93%
51-70	167	27.56%	43	7.10%	210	34.65%
71-90	52	8.58%	12	1.98%	64	10.56%
	484	79.87%	122	20.13%	606	100%

Table-2. Gr-A(RT-PCR test result using PVP-I)

Age Group (yrs)	RT-PCR test positive on 3rd day		RT-PCR test positive on 5th day		RT-PCR test positive on 7th day	
	Male	Female	Male	Female	Male	Female
11-30	2	1	1	0	0	0
31-50	6	3	4	2	0	1
51-70	7	5	6	3	2	1
71-90	7	4	5	3	3	1
	22 (7.26%)	13 (4.29%)	16 (5.25%)	8 (2.64%)	5 (1.65%)	3 (0.99%)
	35 (11.55%)		24 (7.92%)		8 (2.64%)	

Table-2. Gr-B (RT-PCR test result using lukewarm water)

Age Group (yrs)	RT-PCR test positive on 3rd day		RT-PCR test positive on 5th day		RT-PCR test positive on 7th day	
	Male	Female	Male	Female	Male	Female
11-30	33	9	29	6	20	3
31-50	95	23	91	19	81	15
51-70	80	20	77	18	62	12
71-90	26	75	24	4	18	2
	235 (77.22%)	57(18.81%)	221(72.937%)	47(15.51%)	181(59.735%)	32(10.56%)
	291 (96.039 %)		268 (88.448%)		213 (70.297%)	

Table-3. Gr-A (Total outcome after using PVP-I)

Age Group (yrs)	Hospitalized		Hospitalized + Oxygen support		Death	
	Male	Female	Male	Female	Male	Female
11-30	0	0	0	0	0	0
31-50	1	0	0	0	0	0
51-70	0	0	4	1	1	0
71-90	1	0	3	2	1	0
	2 (0.66%)	0	7 (2.31%)	3 (0.99%)	2 (0.66%)	0
	2 (0.66%)		10(3.30%)		2 (0.66%)	

Table-3. Gr-B (Total outcome after using lukewarm water)

Age Group (yrs)	Hospitalized		Hospitalized + Oxygen support		Death	
	Male	Female	Male	Female	Male	Female
11-30	0	0	7	1	0	0
31-50	5	2	16	5	3	1
51-70	5	0	11	9	6	0
71-90	1	1	9	5	5	2
	11 (3.63%)	3 (0.99%)	43 (14.19%)	20 (6.60%)	14 (4.62%)	3(0.99%)
	14 (4.62%)		63 (20.79%)		17 (5.61%)	

Discussion

There are no established effective therapies or vaccines for COVID-19 infection still today, so treatment relies mostly on supportive care, oxygen support with or without mechanical ventilation and medication previously employed against SARS-Cov, MARS-Cov.[24]Povidone Iodine (PVP-I) is very much effective virucidal and well tolerable mouthwash/ gargle, nasal spray and eye drop than other antiseptics which working against SARC-Cov and MARS-Cov is already proven.[25,26] Free iodine release from aqueous solution of PVP-I which likely attack surface proteins of enveloped virus and destabilizes membrane fatty acid by reacting with unsaturated carbon bond. [27,28,29,30] It is already proved that binding with iodine to the lipid component of enveloped virus increases susceptibility over non enveloped viruses.[31] COVID-19 virus belongs to a family of enveloped, single-stranded RNA corona virus.[32] Some recent studies has shown that PVP-I inactivate MERS-Cov and SARS-Cov which has nearly identical genomes to COVID-19 virus.[33] Concentration of 0.23-1% PVP-I reduced infectivity below detectable level within 2 minutes.[34] In recent months, susceptibility to PVP-I solutions has been confirmed for COVID-19 virus. After 30 seconds, ≥ 99.99% virucidal activity against COVID-19 was found for a 1% PVP-I mouth wash and a 0.45% PVP-I throat spray.[35] COVID-19 viral load are high in nasal cavity, naso-oropharynx, lymphocyte of oral tissues, goblet and ciliated cells within respiratory epithelium of nose have the highest expression of ACE_2, the main receptor of COVID-19 virus and some accidental ocular exposure CD_{147}, also receptor of COVID-19 virus.[36] PVP-I of 0.5-10% solution inactivate the ACE_2 and CD_{147} receptor of host cell. In our study, patients of Gr-A (those who used 1% PVP-I) are tremendously improved over Gr-B (those who used only lukewarm water) in terms of RT-PCR test result, mortality, hospitalization with or without oxygen support (Table-2&3). In table-2, only 11.55% patient's show RT-PCR test positive in Gr-A on 3rd day where as 96.04% is positive in Gr-B. On the other hand, 2.64% patient is positive on 7th day in Gr-A and 70.30% positive in Gr-B. So, it is clear that 1% PVP-I can vigorously reduce the viral load in oral cavity, nasal cavity and naso-oropharynx. This information is also supported by an in vivo study done by Martinez Lams et al in June 2020; aimed to determine the influence of 1% PVP-I on COVID-19 positive patients. [37] They evaluated and compared the viral load of the saliva of

those patients after 1 minute use of 1% PVP-I and effects persisted for 3 hours. Another study done by Sarfaraz et al also support our study results.[37] In Table-3, Gr-A shows only 0.66% mortality over 5.61% of Gr-B and only 3.30% hospitalized patients need oxygen support in Gr-A in comparison to 20.79% in Gr-B. So the patients those who used 1% PVP–I have minimum mortality, morbidity and occupying minimum number of hospital bed causing less burden to health and financial sector of Bangladesh in COVID-19 pandemic situation. Hou et al recently demonstrated that COVD-19 virus initially infects ciliated cell of nasal cavity. The virus then spreads via nasal-oropharynx to lungs through micro aspiration and causes pulmonary infection which is then form further devastating systemic involvement via blood.[9] The use of 1% PVP-I as mouth wash/gargle, nasal and eye drop has also been recommended to reduced viral load in oral cavity, naso-oropharynx and thus to prevent systemic infection as well as accelerate recovery of these patients.[39,40] In Ader's study, 6 months use of daily 5% PVP-I mouthwash/rinse, nasal wash caused no change in serum T_3,T_4 or FT_4. [41] In this study, we found no change in serum TSH,T_3,T_4 or FT_4 after 4 weeks (4 times a day) use of 1% PVP-I. PVP-I is a broad spectrum antiseptic with no known resistance that has listed by WHO as an essential medicine. [42] PVP-I is broadly virucidal; a recently developed eye/nasal/oral formulation has been shown to rapidly deactivated COVID-19 virus. [43]

Conclusion

Administration of 1% PVP-I as mouthwash/gargle, nasal or eye drop is simple, rapid and cost effective in reduction of mortality and morbidity by COVID-19. In this horrible situation, simple use of 1% PVP-I can change the treatment modality of COVID-19 patient and reduce the hospital as well as financial burden of the globe.

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