



## Virucidal effect of povidone iodine on COVID-19 in the nasopharynx: an open-label randomized clinical trial

Mostafa Kamal Arefin<sup>1</sup> · S. K. Nurul Fattah Rumi<sup>1</sup> · A. K. M. Nasir Uddin<sup>1</sup> · Sultana Sahana Banu<sup>1</sup> · Mala Khan<sup>2</sup> · Ahsanul Kaiser<sup>3</sup> · Joybaer Anam Chowdhury<sup>4</sup> · Md. Abdullah Saeed Khan<sup>5</sup> · Mohammad Jahid Hasan<sup>5</sup>

Received: 14 April 2021 / Accepted: 10 May 2021 / Published online: 18 May 2021  
© Association of Otolaryngologists of India 2021

**Abstract** Povidone-iodine (PVP-I) is a time-tested antiseptic agent with excellent virucidal (99.99%) properties. Repurposing it against coronavirus disease-19 (COVID-19) is a relatively newer concept and has been sparsely tested in vivo. The most common route of entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the nasopharynx. Averting colonization of the virus could be one of the best options to reduce the incidence of infection. PVP-I gargle and mouthwash were found to be effective in vitro rapid inactivation against SARS-CoV-2 on a smaller scale (Hassandarvish et al. in *BDJ* 1–4, 2020, Pelletier et al. in *ENTJ* 1–5, 2020). However, efficacy in humans is lacking. To assess the virucidal effect of PVP-I against SARS-CoV-2 located in the nasopharynx was the objective of this parallel armed randomized clinical trial. We screened all RT-PCR-confirmed COVID-19 cases aged 18 years and above with symptoms. Written informed consent was obtained before

randomization. Nasopharyngeal clearance of SARS-CoV-2 was tested after single time application of PVP-I nasal irrigation (NI) at diluted concentrations of .4%, .5% and .6% and PVP-I nasal spray (NS) at diluted concentrations of .5% and .6%. All groups were compared to the corresponding controls (distilled water). The primary outcome was viral clearance in a repeat RT-PCR (qualitative), and the secondary outcome was the number of adverse events. Final data analysis was performed using the statistical software SPSS (Version 20). A total of 189 confirmed COVID-19 cases were randomized into seven groups: 27 patients in each group. Of all, 159 (84.1%) were male, and 30 (15.9%) were female. We observed a statistically significant proportion of nasopharyngeal clearance with all strengths of PVP-I NI and PVP-I NS compared to the corresponding controls. Additionally, 0.5% NI was significantly better than 0.5% NS for viral clearance ( $p = 0.018$ ) and had the highest nasopharyngeal clearance among all

✉ Mostafa Kamal Arefin  
arefin61dmc@gmail.com

S. K. Nurul Fattah Rumi  
rumi17dr@gmail.com

A. K. M. Nasir Uddin  
dmch@hospi.dghs.gov.bd

Sultana Sahana Banu  
sultana\_au@yahoo.com

Mala Khan  
malakhan\_07@yahoo.com

Ahsanul Kaiser  
ahsanulkaisertamal@gmail.com

Joybaer Anam Chowdhury  
joybaer6106@yahoo.com

Md. Abdullah Saeed Khan  
abdullahdmc@gmail.com

Mohammad Jahid Hasan  
dr.jahid61@gmail.com

<sup>1</sup> Dhaka Medical College Hospital, Dhaka, Bangladesh

<sup>2</sup> Bangladesh Reference Institute of Chemical Measurements (BRICM), Dhaka, Bangladesh

<sup>3</sup> Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh

<sup>4</sup> National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh

<sup>5</sup> Pi Research Consultancy Center, Dhaka, Bangladesh

**Table 1** Patient Demographics, baseline clinical characteristics and virucidal activity of PVI-P Nasal spray and mouth wash

	Nasal irrigation (NI)				<i>p</i> -value		
	.4% NI	.5% NI	.6% NI	Control-NI (CNI)	.4% NI v CNI	.5% NI v CNI	.6% NI v CNI
<i>Age group</i>							
18–30	4 (14.8)	7 (25.9)	3 (11.1)	3 (11.1)	0.787 <sup>a</sup>	0.548 <sup>a</sup>	0.750 <sup>a</sup>
31–40	6 (22.2)	9 (33.3)	5 (18.5)	9 (33.3)			
41–50	11 (40.7)	3 (11.1)	7 (25.9)	8 (29.6)			
51–60	6 (22.2)	6 (22.2)	8 (29.6)	5 (18.5)			
61–70	0	1 (3.7)	3 (11.1)	1 (3.7)			
> 70	0	1 (3.7)	1 (3.7)	1 (3.7)			
<i>Sex</i>							
Male	23 (85.2)	23 (85.2)	20 (74.1)	21 (77.8)	0.484 <sup>a</sup>	0.484 <sup>b</sup>	0.750 <sup>b</sup>
Female	4 (14.8)	4 (14.8)	7 (25.9)	6 (22.2)			
<i>Disease severity</i>							
Asymptomatic	1 (3.7)	2 (7.4)	2 (7.4)	0	1.00 <sup>a</sup>	0.075 <sup>a</sup>	0.781 <sup>a</sup>
Mild	12 (44.4)	6 (22.2)	12 (44.4)	12 (44.4)			
Moderate	14 (51.9)	19 (70.4)	12 (44.4)	14 (51.9)			
Severe	0	0	1 (3.7)	1 (3.7)			
<i>Co-morbidities</i>							
At least one	16 (59.3)	14 (51.9)	13 (48.1)	11 (40.7)	0.174 <sup>b</sup>	0.413 <sup>b</sup>	0.584 <sup>b</sup>
None	11 (40.7)	13 (48.1)	14 (51.9)	16 (59.3)			
<i>Disease duration (days)</i>	2.04 ± 0.72	1.92 ± 0.74	1.65 ± 0.63	1.85 ± 0.61	0.305 <sup>c</sup>	0.686 <sup>c</sup>	0.269 <sup>c</sup>
<i>Outcome</i>							
COVID Negative	18 (33.3)	25 (92.6)	23 (85.2)	8 (29.6)	<b>0.006<sup>b</sup></b>	<b>&lt; 0.001<sup>b</sup></b>	<b>0.018<sup>b</sup></b>
COVID Positive	9 (33.3)	2 (7.4)	4 (14.8)	19 (70.4)			
<i>Adverse event</i>							
Present	2 (7.4)	0	0	0	0.493 <sup>b</sup>	NA	NA
Absent	25 (92.6)	27 (100)	27 (100)	23 (100)			
	Nasal spray (NS)			Control-NS (CNS)	<i>p</i> -value		Total
	.5% NS	.6% NS			.5% NS v CNS	.6% NS v CNS	
<i>Age group</i>							
18–30	3 (11.1)	3 (11.1)	2 (7.4)	0.179 <sup>a</sup>	0.095 <sup>a</sup>	25 (13.2)	
31–40	6 (22.2)	8 (29.6)	13 (48.1)				
41–50	7 (25.9)	6 (22.2)	8 (29.6)				
51–60	9 (33.3)	5 (18.5)	3 (11.1)				
61–70	1 (3.7)	4 (14.8)	0				
> 70	1 (3.7)	1 (3.7)	1 (3.7)				
<i>Sex</i>							
Male	25 (92.6)	27 (100.0)	20 (74.1)	0.142 <sup>b</sup>	<b>0.010<sup>b</sup></b>	159 (84.1)	
Female	2 (7.4)	0	7 (25.9)				
<i>Disease severity</i>							
Asymptomatic	1 (3.7)	2 (7.4)	5 (18.5)	<b>&lt; 0.001<sup>b</sup></b>	<b>&lt; 0.001<sup>b</sup></b>	13 (6.9)	
Mild	9 (33.3)	7 (25.9)	22 (81.5)				
Moderate	17 (63.0)	17 (63.0)	0				
Severe	0	1 (3.7)	0				
<i>Co-morbidities</i>							
At least one	11 (40.7)	9 (33.)	17 (63.0)	0.102 <sup>b</sup>	<b>0.029<sup>b</sup></b>	91 (48.1)	
None	16 (59.3)	18 (66.7)	10 (37.0)				
<i>Disease duration (days)</i>	1.87 ± 0.54	1.92 ± 0.97	1.79 ± 0.78	0.668 <sup>c</sup>	0.626 <sup>c</sup>	1.86 ± 0.72	

**Table 1** continued

	Nasal spray (NS)			p-value		Total
	.5% NS	.6% NS	Control-NS (CNS)	.5% NS v CNS	.6% NS v CNS	
<i>Outcome</i>						
COVID Negative	18 (66.7)	22 (81.5)	2 (7.4)	<b>&lt; 0.001<sup>d</sup></b>	<b>&lt; 0.001<sup>e</sup></b>	116 (61.4)
COVID Positive	9 (33.3)	5 (18.5)	25 (92.6)			73 (38.6)
<i>Adverse event</i>						
Present	0	0	0	NA	NA	2 (1.1)
Absent	27 (100)	27 (100)	27 (100)			185 (98.9)

Bold indicates significant 'p' value < 0.05%

Comorbidities included Diabetes Mellitus, Hypertension, Bronchial Asthma and Ischemic Heart Disease

Outcome was defined as RT-PCR negativity for COVID after intervention

Only adverse event was 'Irritation'

<sup>a</sup>p-value was determined by Fisher Exact Test

<sup>b</sup>Chi-square Test

<sup>c</sup>Independent Samples *t* Test

<sup>d</sup>Multivariate Logistic Regression adjusting for Severity

<sup>e</sup>Severity and Comorbidity

strengths (n = 25, 92.6%). 0.6% NS is better than CNS and 0.5%NS in viral clearance. The only adverse event was nasal irritation recorded in two patients each in the 0.4% and 0.6% PVP-I NI groups (Tables 1 and 2). PVP-I NI and NS are proved as effective virucidal agent against SARS-CoV-2 in human body. Our recommendation is to use PVP-I in naopharynx (as well as oropharynx) to prevent COVID-19.

**Keywords** COVID-19 · Povidone Iodine · Nasal spray · Nasal Irrigation

## Introduction

Povidone-iodine (PVP-I) is a time-tested antiseptic agent with excellent virucidal (99.99%) properties. Repurposing it against coronavirus disease-19 (COVID-19) is a relatively newer concept and has been sparsely tested in vivo. The most common route of entry of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is the nasopharynx. Hence, it was targeted to prevent access and contamination of the nasopharynx by several protective measures, including facemasks. Averting colonization of the virus could be one of the best options to reduce the incidence of infection. PVP-I gargle and mouthwash were found to be effective in vitro rapid inactivation against SARS-CoV-2 on a smaller scale [1, 2]. However, efficacy in humans is lacking. To assess the virucidal effect of PVP-I against SARS-CoV-2 located in the nasopharynx was the objective of this parallel armed randomized clinical trial.

## Methods

This single-center, open-label randomized clinical trial with a 7-arm parallel-group design was approved by the ethical review committee of Dhaka Medical College, Bangladesh. (NCT Identifier number: NCT04549376). We screened all reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19 cases aged 18 years and above with symptoms. Written informed consent was obtained before randomization. Nasopharyngeal clearance of SARS-CoV-2 was tested after single time application of PVP-I nasal irrigation (NI) at diluted concentrations of 0.4%, 0.5% and 0.6% and PVP-I nasal spray (NS) at diluted concentrations of 0.5% and 0.6%. All groups were compared to the corresponding controls (distilled water). The primary outcome was viral clearance in a repeat RT-PCR (qualitative), and the secondary outcome was the number of adverse events. Final data analysis was performed using the statistical software SPSS (Version 20). The authors followed the Extension of the Consolidated Standards of Reporting Trials (CONSORT) 2010 guideline [3]. The study protocol was published elsewhere [4].

## Results

A total of 189 confirmed COVID-19 cases were randomized into seven groups: 27 patients in each group. All of them completed the study. Of all, 159 (84.1%) were male, and 30 (15.9%) were female. The average age of the participants was  $43.98 \pm 12.67$  years (SD), with the majority

**Table 2** Level of significance table for pair-wise comparisons of patient demographics, baseline clinical characteristics and virucidal activity of PVI-P Nasal spray and mouth wash

	0.4% NI v CNI	0.5% NI v CNI	0.6% NI v CNI	0.4% NI v 0.5% NI	0.4% NI v 0.6% NI	0.5% NI v 0.6% NI	0.5% NI v 0.6% NI	0.5% NS v CNS
Age*	0.787 <sup>a</sup>	0.548 <sup>a</sup>	0.75 <sup>a</sup>	0.117 <sup>a</sup>	0.424 <sup>a</sup>	0.349 <sup>a</sup>	0.349 <sup>a</sup>	0.179 <sup>a</sup>
Sex	0.484 <sup>a</sup>	0.484 <sup>b</sup>	0.75 <sup>b</sup>	1.000 <sup>a</sup>	0.311 <sup>b</sup>	0.311 <sup>b</sup>	0.311 <sup>b</sup>	0.142 <sup>a</sup>
Severity*	1.000 <sup>a</sup>	0.075 <sup>a</sup>	0.781 <sup>a</sup>	0.242 <sup>a</sup>	0.913 <sup>a</sup>	0.196 <sup>a</sup>	0.196 <sup>a</sup>	< <b>0.001</b> <sup>a</sup>
Comorbidity	0.174 <sup>b</sup>	0.413 <sup>b</sup>	0.584 <sup>b</sup>	0.584 <sup>b</sup>	0.413 <sup>b</sup>	0.785 <sup>b</sup>	0.785 <sup>b</sup>	0.102 <sup>b</sup>
Duration	0.305 <sup>c</sup>	0.686 <sup>c</sup>	0.269 <sup>c</sup>	0.572 <sup>c</sup>	0.045 <sup>c</sup>	0.165 <sup>c</sup>	0.165 <sup>c</sup>	0.668 <sup>c</sup>
Outcome	<b>0.006</b> <sup>b</sup>	< <b>0.001</b> <sup>b</sup>	< <b>0.001</b> <sup>b</sup>	<b>0.018</b> <sup>b</sup>	0.111 <sup>b</sup>	0.669 <sup>*</sup>	0.669 <sup>*</sup>	< <b>0.001</b> <sup>d</sup>
Adverse events	0.493	NA	NA	0.493	0.493	NA	NA	NA

  

	0.6% NS v CNS	0.5% NS v 0.6% NS	0.4% NI v 0.5% NS	0.4% NI v 0.6% NS	0.5% NI v 0.6% NS	0.5% NI v 0.6% NS	0.6% NI v 0.5% NS	0.6% NI v 0.5% NS	0.6% NI v 0.6% NS
Age*	0.095 <sup>a</sup>	0.682 <sup>a</sup>	0.683 <sup>a</sup>	0.683 <sup>a</sup>	0.461 <sup>a</sup>	0.484 <sup>a</sup>	0.968 <sup>a</sup>	0.968 <sup>a</sup>	0.936 <sup>a</sup>
Sex	<b>0.010</b> <sup>a</sup>	0.491 <sup>b</sup>	0.386 <sup>b</sup>	0.386 <sup>b</sup>	0.669 <sup>a</sup>	0.111 <sup>a</sup>	0.142 <sup>a</sup>	0.142 <sup>a</sup>	<b>0.010</b> <sup>a</sup>
Severity*	< <b>0.001</b> <sup>a</sup>	0.82 <sup>a</sup>	0.782 <sup>a</sup>	0.782 <sup>a</sup>	0.65 <sup>a</sup>	0.904 <sup>a</sup>	0.48 <sup>a</sup>	0.48 <sup>a</sup>	0.571 <sup>a</sup>
Comorbidity	<b>0.029</b> <sup>b</sup>	0.573 <sup>b</sup>	0.174 <sup>b</sup>	0.174 <sup>b</sup>	0.413 <sup>b</sup>	0.169 <sup>b</sup>	0.584 <sup>b</sup>	0.584 <sup>b</sup>	0.268 <sup>b</sup>
Duration	0.626 <sup>c</sup>	0.855 <sup>c</sup>	0.371 <sup>c</sup>	0.371 <sup>c</sup>	0.796 <sup>c</sup>	0.979 <sup>c</sup>	0.189 <sup>c</sup>	0.189 <sup>c</sup>	0.259 <sup>c</sup>
Outcome	< <b>0.001</b> <sup>e</sup>	0.214 <sup>b</sup>	1.000 <sup>b</sup>	1.000 <sup>b</sup>	<b>0.018</b> <sup>b</sup>	0.420 <sup>a</sup>	0.111 <sup>b</sup>	0.111 <sup>b</sup>	1.000 <sup>b</sup>
Adverse events	NA	NA	0.493	0.493	NA	NA	NA	NA	NA

Bold indicates significant 'p' value < 0.05%

<sup>a</sup>p-value was determined by Fisher Exact Test

<sup>b</sup>Chi-square Test<sup>b</sup>

<sup>c</sup>Independent Samples t Test

<sup>d</sup>Multivariate Logistic Regression adjusting for Severity

<sup>e</sup>Severity and Comorbidity

ranging from 31 to 40 years ( $n = 56$ , 29.60%). The PVP-I NS group had significantly higher proportions of severe patients than the control-NS (C-NS) group ( $p < 0.001$ ). The 0.6% NS group differed from the C-NS group by sex and the presence of comorbidities ( $p < 0.05$ ). Adjusting the differences, we observed a statistically significant proportion of nasopharyngeal clearance with all strengths of PVP-I NI and PVP-I NS compared to the corresponding controls. Additionally, 0.5% NI was significantly better than 0.5% NS for viral clearance ( $p = 0.018$ ) and had the highest nasopharyngeal clearance among all strengths ( $n = 25$ , 92.6%) and 0.6% NS is best among 0.5% NS and CNS. The only adverse event was nasal irritation recorded in two patients each in the 0.4% and 0.6% PVP-I NI groups (Tables 1 and 2).

## Discussion

Although in vitro testing of PVP-I solution revealed a considerable reduction in SARS-CoV-2 viral titers, its effect on humans was unclear [1]. Our study confirms the presumed effectiveness of PVP-I in nasopharyngeal clearance of SARS-CoV-2 among COVID-19 patients. Compared to controls, we noted viral clearance at two-fifth to three-fifth dilutions of PVP-I nasal irrigation and spray. Our findings agree with the first report of in vivo PVP-I mouthwash application [5]. In contrast, Guenezan et al. [6] observed no effect of PVP-I on nasopharyngeal viral loads. They reported unpleasant nasal tingling and transient elevation of thyroid stimulating hormone after povidone iodine administration. In contrast, we found nasal irritation in only two patients (1.1%). Our study's strength was testing different strengths of PVP-I nasal solution and comparing those with distilled water controls in a modest number of cases. However, our limitation was the inability to conduct viral quantification before and after intervention.

## Conclusion

In this study, a statistically significant proportion of nasopharyngeal clearance with all strengths of PVP-I NI and PVP-I NS (compared to the corresponding controls) is observed, so our recommendation is to use PVP-I prophylactically in nasopharynx as well as oropharynx (through which areas SARS-CoV-2 enters and resides for a while) for prevention of COVID-19.

**Acknowledgements** The authors acknowledge significant support from the Pi Research Consultancy Center, Dhaka, Bangladesh ([www.pircc.org](http://www.pircc.org)) in overall research activities. Also, thanks to the

BRICM for material support. The authors would like to thank all the clinical staff of the DMCH for their cordial assistance.

**Author contributions** MKA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conception of the research idea: MKA. Research design: MKA and MJH. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript: All authors. Statistical analysis: ASK, MKA and MJH. Administrative, technical, or material support: AKMNU, MK and SSB. Supervision: MKA, SKNFR, and MJH. The authors read and approved the final manuscript.

**Funding** The trial received research partial grant from BRICM.

**Data Availability** The corresponding author has access to the all-trial information, and the data will be available on reasonable request (contact: [dr.jahid61@gmail.com](mailto:dr.jahid61@gmail.com) or [arefin61dmc@gmail.com](mailto:arefin61dmc@gmail.com)).

## Declarations

**Conflict of interest** The authors declare that they have no competing interests.

**Ethics approval** The RCT protocol was approved by the Ethical Review Committee of Dhaka Medical College (Memo No: ERC-DMC/ECC/2020/93) on 23 May 2020.

**Trial registration** The trial protocol has been registered at ClinicalTrials.gov on September 16, 2020. NCT Identifier Number: NCT04549376. (<https://clinicaltrials.gov/ct2/show/NCT04549376>).

## References

- Hassandarvish P, Tiong V, Mohamed NA et al (2020) In vitro virucidal activity of povidone iodine gargle and mouthwash against SARS-CoV-2: implications for dental practice. *Br Dent J*. <https://doi.org/10.1038/s41415-020-2402-0>
- Pelletier JS, Tessema B, Frank S, Westover JB, Brown SM, Capriotti JA (2020) Efficacy of povidone-iodine nasal and oral antiseptic preparations against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). *Ear Nose Throat J*. <https://doi.org/10.1177/0145561320957237>
- Juszczak E, Altman DG, Hopewell S, Schulz K (2019) Reporting of multi-arm parallel-group randomized trials: extension of the CONSORT 2010 statement. *JAMA* 321(16):1610–1620. <https://doi.org/10.1001/jama.2019.3087>
- Hasan MJ, Rumi SKNF, Banu SS, Uddin AKMN, Islam MS, Arefin MK (2021) Virucidal effect of povidone iodine on COVID-19 in the nasopharynx: a structured summary of a study protocol for an open-label randomized clinical trial. *Trials* 22:2. <https://doi.org/10.1186/s13063-020-04963-2>
- Lamas LM, Dios PD, Rodríguez MTP et al (2020) Is povidone iodine mouthwash effective against SARS-CoV-2? First in vivo Tests Oral Dis. <https://doi.org/10.1111/odi.13526>
- Guenezan J, Garcia M, Strasters D et al (2021) Povidone iodine mouthwash, gargle, and nasal spray to reduce nasopharyngeal viral load in patients with COVID-19. *JAMA-Otolaryngol Neck Surg* 9(6):1871. <https://doi.org/10.1001/jamaoto.2020.5490>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.