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Effect of the povidone iodine, hypertonic alkaline solution and saline nasal lavage on nasopharyngeal viral load in COVID-19

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Abstract

Objective: The present study aimed to investigate the in vivo activity of nasal irrigation (NI) with saline, NI with povidone–iodine (PVP–I) 1%, NI with a mix of hypertonic alkaline and PVP–I 1% against Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).

Design: This study was a prospective randomised clinical trial.

Setting: A multicenter study involving tertiary care centres.

Participants: The study included adult outpatients whose qualitative SARS-CoV-2 RT-PCR tests in nasopharyngeal swabs were positive. One hundred twenty patients were divided into four equal groups. Standard COVID-19 treatment was given to Group 1, NI containing saline was added to patients' treatment in Group 2, NI containing 1% PVP–I solution was added to patients' treatment in Group 3, and NI containing 1% PVP–I solution and the hypertonic alkaline solution was added to patients' treatment in Group 4.

Main Outcome Measures: On the first day of diagnosis (Day 0), nasopharyngeal swab samples were taken, on the third and fifth days the nasopharyngeal viral load (NVL) reduction in quantitative RT-PCR test was calculated.

Results: Between the zeroth to third days and zeroth to fifth days, the NVL reduction was significant in all groups ($p < .05$). In paired comparisons of groups, the NVL decrease in Group 4 in the first 3 days was significantly lower than all groups ($p < .05$). The NVL decrease in Groups 3 and 4 in the first 5 days were significantly lower than Group 1 ($p < .05$).

Conclusion: This study revealed that the use of NI of 1% PVP–I and the hypertonic alkaline solution mixture was more effective in reducing NVL.

KEYWORDS
COVID-19, hypertonic alkaline solution, nasopharyngeal viral load, povidone–iodine

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1 | INTRODUCTION

The causative pathogen of COVID-19 is severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) binds to the angiotensin-converting enzyme-2 (ACE-2) receptors of the respiratory epithelium with the S protein.[1] ACE-2 receptor is produced in high density in the nasal and nasopharyngeal mucosa and these regions are very important for the replication and infection of the virus.[2,3] In addition, it was determined that SARS-CoV-2, especially the S protein, was affected by environmental conditions.[4] Therefore, treatments targeting the nose and nasopharynx may prevent the development of disease by preventing the binding of SARS-CoV-2 and/or alleviate the COVID-19 progression by reducing the viral load.

Nasal irrigation (NI) is a proven preventive and/or therapeutic non-pharmacological method that can be applied with different solutions, reduces inflammation and removes microorganisms such as bacteria and viruses with its mechanical and chemical properties.[5] In previous studies, solutions with different contents and different concentrations have been used in the management of COVID-19 disease with the NI method.[6–8] Among these NI ingredients, there are known solutions such as saline and povidone–iodine (PVP–I) that have been used for a long time, as well as new solutions such as the hypertonic alkaline solution based on Lake Van (12 g/L sodium chloride, 2 g/L sodium sulphate, 0.8 g/L potassium chloride, 0.1 g/L Calcium chloride dihydrate, 1.1 g/L magnesium sulphate heptahydrate and 4 g/L sodium bicarbonate, pH = 9).[6,7]

The aim of this study was to investigate the in vivo activity of NI with saline, NI with PVP–I 1% (PNI), NI with hypertonic alkaline (HANI) and PNI 1% and hypertonic alkaline solution (PVP + HANI) against SARS-CoV-2.

Key points

- Nasal irrigation (NI) can be applied with different solutions, reduces inflammation and removes microorganisms.
- Povidone–iodine (PVP–I) mixtures prepared in different forms and concentrations are effective against Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).
- NI with a hypertonic alkaline solution has been shown to reduce the nasopharyngeal viral load of SARS-CoV-2.
- In this study, the activity of NI with saline, PVP–I 1%, and a mix of hypertonic alkaline and PVP–I 1% were investigated against SARS-CoV-2.
- This study showed that PVP–I 1% and hypertonic alkaline-PVP–I 1% mixture were effective against SARS-CoV-2. Besides the mixture is more effective than PVP–I.

2 | MATERIALS AND METHODS

This prospective randomised controlled clinical trial was approved by the Ethics Committee of Istanbul Aydın University (decision date: 21 April 2021 and decision no: 2021/456) and conducted on patients who applied to Istanbul Training and Research Hospital, Cerrahpasa Medical Faculty Hospital and Medical Faculty Hospital of Istanbul Aydın University between September 2021 and October 2021. Informed consent forms were signed by all subjects.

Subjects, who were administered to the emergency on the first day of symptoms started, were diagnosed with COVID-19. The outpatient subjects, according to the criteria in the COVID-19 guideline of the Turkish Ministry of Health were included in the present study.[9] Patients under 18 years old or over 60 years old, patients with psychiatric and/or neurologic diseases, patients with cancer or cancer treatment history, patients with chronic diseases such as hepatitis, kidney disease and patients with PVP–I allergy were excluded from the study.

At least 30 SARS-CoV-2 infected patients were included in each study group because the minimal subject number for a parametric test was 30.

The participants were randomised by using randomisation software to either control or intervention groups; subjects were separated 1:1 into the study arms. The subjects were coded with a computer-generated random number to provide blindness. In our study team, the researchers who collected data and analysed the collected data were different people. It was not known by the data collectors, which drug was given to which patient. The teams that analysed the data did not know the patient groups.

Standard COVID-19 treatment (Favipiravir 2 × 1600 mg loading dose on the first day +2 × 600 mg maintenance dose for 4 days) was given to Group 1 (control), NI containing isotonic (saline) solution was added to patients' treatment in Group 2 (saline), NI containing 1% PVP–I solution was added to patients' treatment in Group 3 (PVP–I group) and NI containing 1% PVP–I solution prepared with the hypertonic alkaline solution, was added to patients' treatment in Group 4 (PVP–I + HANI). NI was carried out with a continuous nasal spray with sun-proof white tubes, stored at room temperature. The continuous nasal sprays were used four times a day at 6-h intervals. All subjects were educated about how to perform NI. The symptoms of the patients were questioned on the first and last day of the study using the visual analogue scale.

Nasopharyngeal swab samples were taken from subjects whose RT-qPCR test resulted positive for SARS-CoV-2, on the initial day of diagnosis (Day 0), the third and fifth days. Six hours afterward NI, nasopharyngeal swab samples were taken by an expert otorhinolaryngologist. Nasopharyngeal swabs for each sampling were preserved in 2 mL of the viral transport medium (vNAT Transfer Tube, Bioeksen Ltd., Turkey) and stored at 4°C until the qPCR experiment. The viral loads were measured by Bio-Speedy Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Double Gene RT-qPCR Kit (Bioeksen Ltd., Turkey) following the manufacturer's recommendations using the CFX96 real-time PCR detection system (Bio-rad, USA). The RT-qPCR detection kit targets the E and RdRP genes of the SARS-CoV-2 genome. A positive result was defined when the Ct value is ≤35 cycles. The Ct values of each sample were further used for statistical analyses. Viral loads in swab samples were projected to RNA copies per 2 mL.

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TABLE 1 Demographic data and symptoms of patients.

Parameters		Group 1 ($n = 30$)	Group 2 ($n = 30$)	Group 3 ($n = 30$)	Group 4 ($n = 30$)	p
Sex	Male n (%)	12 (40%)	12 (40%)	11(36.7%)	13(43.3%)	.964*
	Female n (%)	18 (60%)	18 (60%)	19(63.3%)	17(56.7%)	
Age	Mean ± SD (Median)	37.33 ± 9.93 (36.5)	42.10 ± 14.29 (47)	39.40 ± 12.81 (395)	40.13 ± 12.32 (39.5)	.607**

	Group 1 Median (Q1–Q3)		Group 2 Median (Q1–Q3)		Group 3 Median (Q1–Q3)		Group 4 Median (Q1–Q3)		p**	
Symptoms	Day 0	Day 5	Day 0	Day 5	Day 0	Day 5	Day 0	Day 5	Day 0	Day 5
Fatigue	4 (1–5)	1 (0–3)	3 (2–4.25)	0 (0–0)	3 (.75–5)	0 (0–0)	2 (1–5)	0 (0–0)	.812	.196
Miyalgia	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–2)	0 (0–0)	1 (0–1.25)	0 (0–0)	0 (0–0,25)	.217	.393
Fever	0 (0–2.25)	0 (0–3)	0 (0–1)	0 (0–2)	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–2)	.482	.765
Cough	0 (0–1)	0 (0–0)	0 (0–2)	0 (0–0)	1 (0–1.25)	0 (0–0)	0 (0–0.25)	0 (0–0)	.48	.392
Sputum	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.562	.393
Headache	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.393	.392
Sore throat	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.217	.251
Diarrhoea	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.898	1
Nausea	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.898	1
Runny nose	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.78	.874
Nasal congestion	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–2)	0 (0–1.25)	0 (0–0)	0 (0–0)	.597	.656
Taste disorder	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0.25)	0 (0–0)	.100	.701
Smell disorder	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	.940	.940

Note: Pearson chi-square test, value = .278; df = 3, *p > 0.05; Kruskal–Wallis test, **p > 0.05.

SPSS 23.0 was used for statistical analysis. The Kolmogorov–Smirnov test and Levene's tests were used to analyse the normal distribution and homogeneity of the data. The data were not normally distributed. The statistical analyses were performed with the Pearson chi-square test, the Kruskal-Wallis test, the Friedman test and the Mann–Whitney U test. The significance level was determined as $p < .05$.

3 | RESULTS

The demographic data and symptoms of patients were given in Table 1. The study groups were statistically similar according to the age and gender of the subjects ($p > .05$; Table 1). All subjects completed the study. No significant difference was found between the groups according to the initial and last symptoms ($p > .05$; Table 1). There were no adverse effects in regard to using NI such as epistaxis and burning.

The median values of nasopharyngeal viral loads (NVLs) were 133 625 805 (min: 1 233 575–max: 11 423 754 590) in Group 1, 16 0 88 122(min: 867 034–max: 14 055 518 620) in Group 2, 207 580 634 (min: 1 296 686–max: 1 465 129 301)in Group 3, 238 101 474 (min: 5 278 084–max: 19 475 541 727) in Group 4 on Day 0. There was no statistically significant difference according to the initial (zeroth) NVL density (Kruskal–Wallis test, $p = .107$).

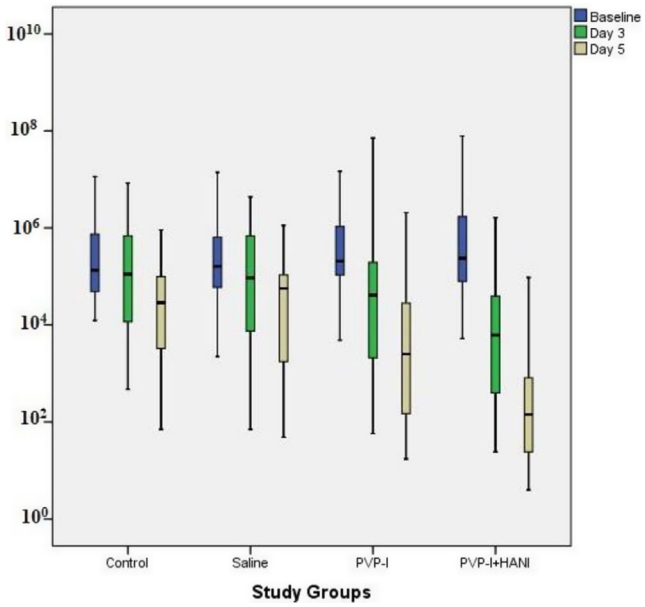

FIGURE 1 The median values of nasopharyngeal viral loads on study days. HANI, nasal irrigation with hypertonic alkaline; PVP–I, povidone–iodine.

The median values of NVLs were 111 296 836 (min: 470 527–max: 8 417 708 503) in Group 1, 93 777 119 (min: 70 307–max: 4 344 176 287) in Group 2, 59 418 531 (min: 57 296–max:

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TABLE 2 The evaluation of nasopharyngeal viral load (NVL) change in groups.

Study day	NVL change				p
	Group 1 median (min–max)	Group 2 median (min–max)	Group 3 median (min–max)	Group 4 median (min–max)	
Zeroth to third day	20 160.338 (−8 318 505.412–10 530 128.66)	53 629.7 (−3 785 342.91–11 509 614.315)	112 922.151 (−68 232 012.38–14 634 794.5)	218 382.452 (5243.303–194 227 576.31)	.001*
Third to fifth day	9217.224 (−36 746.346–8 352 558.801)	65 848.197 (−606 856.42–4 000 125.55)	203 264.925 (1239.39–14 651 194.509)	238 067.609 (5272.192–194 675 186.787)	.266
Zeroth to fifth day	34 418.015 (−71 576.56–11 398 204.91)	128 853.623 (−604 196.473–12 937 992.195)	203 264.925 (1239.390–14 651 194.509)	238 067.608 (5272.192–194 675 186.78)	.005*

Note: Kruskal-Wallis Test *$p < .05$.

7 140 937 038) in Group 3, 6 244 346 (min: 24 164–max: 1 616 018 293) in Group 4 on the third day. On the third day of the treatment, there was a significant difference in the groups in terms of NVL (Kruskal–Wallis test, $p = .005$). The median values of NVLs were 28 995 441 (min: 70 117–max: 912 987) in Group 1, 56 428 119 (min: 48 091–max: 1 117 525 424) in Group 2, 2 521 293 (min: 17 296–max: 2 080 423 244) in Group 3, 159 437 (min: 3977–max: 401 932 862) in Group 4 on the fifth day. On the fifth day of the treatment, there was a significant difference in the groups in terms of NVL (Kruskal–Wallis test, $p = .0001$). In the evaluation performed within the groups, it was seen that the decrease in NVL was statistically significant in all groups (Friedman test, $p = .0000001$ for each group; Figure 1).

In the evaluation of the NVL change, there was a significant difference between zeroth to third day and zeroth to fifth day ($p < .05$; Table 2). In paired comparisons of groups, the NVL change in Group 4 in the first 3 days was significantly lower than in all groups ($p < .05$; Table 3). In paired comparisons of groups, the NVL changes in Groups 3 and 4 in the first 5 days were significantly lower than in Group 1 ($p < .05$; Table 3).

There was no significant difference according to other comparisons ($p > .05$; Tables 1 and 2).

4 | DISCUSSION

The nasal cavity is covered by the cells, which express ACE-2 and TMPRSS-2 are responsible for facilitating SARSCoV-2 to enter the host cells and SARS-CoV-2 utilises the S1 spike glycoprotein for attachment to the host target cells.[10] The environmental changes, such as pH and tonicity, affect the structural proteins of the virus, especially the S protein and the infectivity of the virus.[4]

There are two suppositions regarding the transmission of SARS-CoV-2: inhalation of infected droplets into the lung or the presence of a viral inoculum in the nose and the aspiration of micro aspirates from both nasopharynx and oropharynx into the lungs.[11] Studies have revealed that due to the high expression of ACE-2 receptor on goblet cells and respiratory epithelium, the viral load is the highest in the nasal cavity, nasopharynx and oropharynx, which are regarded as the first entry of the virus into the body.[12,13] In previous clinical research, the viral replication ratio that was detected in the samples taken from the nasal cavity are higher than the rate that was detected in the samples taken from the epithelium of the large respiratory tracts. These outcomes suggested that the dominant site of viral replication, accumulation, and entrance into the human body is the nasal cavity, in the early stages of COVID-19.[3]

The nasal mucosa is one of the first lines of the human body's defence against any respiratory pathogen. Because NI supplies fluidity and clearance of respiratory secretions, it was considered the inhibited factor for transmission of SARS-CoV-2 human to human and the spread of the virus to the lower airways.[14,15] Its mechanisms were both mechanical intervention and removal of inflammatory mediators.[16] Some in vitro studies reported that the S

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TABLE 3 Subgroup analyses of the change in virus loads within groups.

	$p_{Group\ 1-2}$	$p_{Group\ 1-3}$	$p_{Group\ 1-4}$	$p_{Group\ 2-3}$	$p_{Group\ 2-4}$	$p_{Group\ 3-4}$
Zeroth to third day	.69	.135	0,0001*	.294	.003*	.02*
Zeroth to fifth day	.077	.007*	0,001*	.315	.092	.383

Note: Mann–Whitney test *$p < .05$.

protein of SARS-CoV-2 is affected by different ranges of pH and environmental tonicity.[17]

Different solutions with different contents and different concentrations have been used as NI in order to the management of the COVID-19 pandemic. Carrouel et al. revealed that using NI and mouth rinse which contain the agents b-cyclodextrins and flavonoids reduce the viral load of SARS-CoV-2 in the upper respiratory tract.[18] Yılmaz et al. showed HANI solution with a 9.3 pH value creates a hyperosmolar environment in the nasal region and reduces the NVL of SARS-CoV-2. during the first 3 days, in the early stage of the disease.[6] A high salt concentration of extracellular space creates a hyperosmotic environment so it will inhibit the entry of the SARS-CoV-2 into the cell. The virus-receptor interaction, in other words, the interaction between the S protein and ACE-2, is disrupted as a result of the conformational changes in the protein.[6]

PVP–I is another agent that is widely used as a preoperative skin antiseptic and mouth rinse. In previous studies, it has been revealed that PVP–I facilitates the removal of microorganisms. The most potent metabolites of PVP–I are molecular I_2 and hypoiodous acid. Hypoiodous acid oxidises amino acids, nucleic acids and cell membranes.[19] Because of the oxidation of cell surface receptors, PVP–I prevents the attachment of viruses to host cells.[20]

Since the beginning of the COVID-19 epidemic, many studies have been carried out in order to break the effect of the epidemic. Considering the effect of NVL on the course of the disease, various experiences were presented in order to provide local control. The effectiveness of PVP–I mixtures prepared in different forms, nasal spray, gargle and mouthwash, and at different concentrations, 0.4%, 0.5%, 0.6% and 1% against SARS-CoV-2 has been demonstrated by various studies.[7,21,22] These studies indicated that PVP–I reduced the viral load of SARS-CoV-2 by showing a virucidal effect, and PVP–I solutions were defined as an effective method of reducing the viral load of SARS-CoV-2.[23,24] The effects of PVP–I on SARS-CoV-2 have been demonstrated by in vivo and in vitro studies.[23,24]

Mixtures containing different proportions of PVP–I have been used in previous studies. In this study, we used the mixture of PVP–I containing 1% PVP–I, which has shown in vivo effectiveness in previous studies, and mixed with the hypertonic alkaline solution as a solvent, which has been shown to have a positive effect on SARS-CoV-2.[7,21–24] The NVL reduction seen in the PVP–I group of this study supports the existing literature. In addition, in vivo additive or synergistic effects of PVP–I with a hypertonic alkaline solution were shown in this study. The decrease in NVL during the first 3 days in the group that applied PNI was significantly higher than in all other groups. In addition, the decrease in NVL observed in the first 5 days was significantly higher in the PVP–I and PVP–I + HANI groups compared to the control group. This study was shown that 1% PVP–I and hypertonic alkaline NI may use with a significant decrease in viral load.

There are some limitations of our study showing the effectiveness of an untested mixture on SARS-CoV-2. The first of these limitations is that the NVL we detected using the RT-qPCR test does not only express live viruses. The RT-qPCR test is based on nucleic acid quantification and cannot distinguish between live viruses and dead viruses. The second limitation is that we do not know whether the patients were using their medications optimally because they were in home isolation. However, there are previous studies showing that patients' adherence to drug use increases during the COVID-19 pandemic. In the literature rare cases of thyroid dysfunction, aspiration pneumonia, anaphylaxis, contact dermatitis and oedema have been reported due to PVP–I use. Liver and kidney toxicity has been demonstrated in high-dose ingestion.[25] In this study thyroid, liver or kidney functions did not evaluate by blood tests but according to the questionnaire, patients did not complain of any allergic symptoms like contact dermatitis, oedema or anaphylaxis. Our last and most important limitation is the lack of in vitro studies on the effects and side effects of the mixture of PVP–I and HANI we used in our study. However, no side effects related to drug use were observed in any of the patients included in our study.

5 | CONCLUSION

This study reported that the use of hypertonic alkaline NI together with 1% PVP–I was more effective in decreasing NVL in the early period. The decreased NVL may reduce the carriage of infectious SARS-CoV-2 in patients. 1% PVP–I and hypertonic alkaline NI may be safely used to prevent transmission during the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

Designed the study: Aysegul Batioglu-Karaaltin, Ozgur Yigit, Dogan Cakan, Ozer Akgul, and Hasan Ahmet Ozdogan. *Collected the data*: Enes Yigit, Yetkin Zeki Yilmaz, Kays-ı Burak Cakir, Gamze Ciftci, Nihal Seden Boyoğlu, Abdurrahman Cagliyan, Efe Can, Ozgur Dikme, Yalcin Hacioglu, Ilker Inanc Balkan and Ozgur Enver. *Wrote the main text*: Aysegul Batioglu-Karaaltin, Ozgur Yigit, Dogan Cakan, Ozer Akgul, Hasan Ahmet Ozdogan, Enes Yigit, Yetkin Zeki Yilmaz, Kays-ı Burak Cakir,Gamze Ciftci, Nihal Seden Boyoğlu, Abdurrahman Cagliyan, Efe Can, Ozgur Dikme, Yalcin Hacioglu, Ilker Inanc Balkan and Ozgur Enver. *Statistical analysis*: Dogan Cakan, Aysegul Batioglu-Karaaltin,-Ozgur Yigit, Ozer Akgul and Hasan Ahmet Ozdogan. *Literature search*: Enes Yigit, Yetkin Zeki Yilmaz, Kays-ı Burak Cakir, Gamze Ciftci, Nihal Seden Boyoğlu, Abdurrahman Cagliyan, Efe Can, Ozgur Dikme, Yalcin

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CONFLICT OF INTEREST

None of the authors has any conflict of interest or otherwise.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/coa.14056.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Istanbul Aydın University Ethics Committee (decision date: 21 April 2021, decision no: 2021/456).

PATIENT CONSENT

Informed consent forms were signed by all subjects.

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