Neutral Electrolyzed Water (SES) for Nasopharyngeal and Oropharyngeal Rinses Prevented COVID-19 in Front-Line Health Professionals: A Randomized, Open-Label, Controlled Trial in a General Hospital in Mexico City.

Rafael Gutiérrez-García

General Hospital Enrique Cabrera

Juan Carlos De la Cerda-Ángeles

General Hospital Enrique Cabrera

Ariana Cabrera-Licona

Esteripharma SA de CV

Iván Delgado-Enciso

Universidad de Colima Faculty of Medicine: Universidad de Colima Facultad de Medicina

Nicolás Mervitch-Sigal

Esteripharma Mexico SA de CV

Brenda Paz-Michel (✉ bpaz@esteripharma.com.mx)

Esteripharma <https://orcid.org/0000-0001-7137-6505>

Research article

Keywords: COVID-19, SARS-CoV-2, neutral electrolyzed water (SES), nasal rinses, mouthwashes, prophylaxis

Posted Date: July 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-701671/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has destabilized society all around the world and is predicted to take a long time to be overcome. The worldwide efforts that healthcare professionals are making is well known, and the high risk of illness and death that front-line staff experience on a daily basis is a reality as well. Despite well-defined protocols for the use of personal protective equipment, many nurses and doctors are still getting sick and dying. It is well known that vaccination is still faraway to be achieved worldwide and that new variants are emerging, so additional protective measures must be explored. This study investigated the effectivity of a neutral electrolyzed water (SES) to reduce the risk of COVID-19 disease in front-line medical staff, when it was used for nasopharyngeal and oropharyngeal rinses (prophylactic protocol).

Methods: A prospective open-label, randomized controlled clinical trial was performed in front-line medical staff from the general hospital Enrique Cabrera in México City. One hundred and seventy volunteers were enrolled and equally divided in control group and SES group. All members of the trial wore the adequate personal protection equipment at all times while performing their duties, as required by standard COVID-19 safety protocols. Additionally, the SES group participants followed a prophylactic protocol with SES (oral and nasal rinses, three times a day for 4 weeks). All participants were monitored for COVID-19 symptoms and disease in a time-frame of 4 weeks and the incidence of illness per group was registered. The relative risk of disease, associated with each treatment was calculated.

Results: The presence of COVID-19 positive cases, in the group that received the nasal and oral rinses with SES was 1.2%, while in the group that did not do the SES rinses (control group), it was 12.7% ($p = 0.0039$ and $RR = 0.09405$; 95%, CI of 0.01231-0.7183). The prophylactic protocol was demonstrated as a protective factor for developing the disease.

Conclusions: Nasal and oral rinses with SES may be an efficient alternative to reinforce the protective measures against COVID-19 disease and should be further investigated.

Trial registration: RPCEC00000357. Retrospectively registered, March, 16, 2021. <https://rpcec.sld.cu/en/trials/RPCEC00000357-En/revisions/5137/view>

Background

SARS-CoV-2; the novel virus in the coronavirus family, is an enveloped single-stranded positive-sense RNA virus that primarily infects the upper respiratory tract. This infection generally causes the COVID-19 disease which has reached pandemic status. Common COVID-19 symptoms include dry cough, dyspnea, headache, fever and fatigue [1]. Complications can lead to respiratory failure and death; in such a way that at the time of writing this article, COVID-19 have caused more than 108.4M of cases and 2.3M of deaths in 219 territories worldwide [2]. Health workers have experienced high mortality due to COVID-19, Mexico being the highest with 3,284 deaths, and followed by USA, UK, Brazil and Russia [3, 4]. Even though front-line medical staff are being vaccinated, a specific effective therapy, as well as mass vaccination remain distant goals, with challenging problems such as the appearance of SARS-CoV-2 mutations [5]. Prophylactic treatments using aerosolized combination of medication have been explored with promising results to reduce illness in medical staff [6, 7], however these may not be accessible in all countries. Additional measures such as prophylaxis with nasopharyngeal and oropharyngeal rinses are a low explored option to mitigate the impact of multiple exposures to this virus [8–14]. Recently, the virucidal effect of acidic electrolyzed water (EW); a broad-spectrum antiseptic, over SARS-CoV-2 in *vitro* has been reported, and it has been postulated that EW may be a safe and accessible option for cleaning oral and nasal cavities to avoid COVID-19 infection [15, 16]. Neutral electrolyzed water (SES) (pH 6.5–7.5) in particular, is an interesting candidate since it is safe to be applied in the nasal and oral mucosa, and because its virucidal action on nonenveloped and enveloped viruses has been demonstrated [17–19]. In the present work, the effect of using SES with 0.0015% of reactive species of chlorine and oxygen was studied as a prophylactic protocol (nasopharyngeal and oropharyngeal rinses), to reduce the risk of COVID-19 disease in front-line medical staff, through a prospective open-label randomized controlled trial, conducted in a Mexican COVID-19 hospital.

Methods

Study design

A prospective, randomized 2-arm, parallel group, open-label clinical trial was conducted from September to November 2020. The aim of the study was to compare the prophylactic effect of using SES, through nasal and oral rinses, together with the use of personal protective equipment (PPE), versus using only PPE in COVID-19 front-line healthcare professionals in the General Hospital “Dr. Enrique Cabrera Cosío” in Mexico City, to prevent the COVID-19 disease. The study was approved by the research ethics committee of the Health Ministry of Mexico City (August 31, 2020), and was conducted in accordance with the ethical international standards established in the Declaration of Helsinki. A written informed consent was obtained from each participant before the study. The present clinical trial was registered as PREVECOVID-19: RPCEC00000357 in the Cuban Public Registry of Clinical Trials (RPCEC) database.

Study Subjects

To participate in the study, the criterion was to be COVID-19 front-line medical staff (nurses and physicians, males or females) from the General Hospital Enrique Cabrera in México City. The exclusion criteria were: medical staff presenting previous or current SARS-CoV-2 infection confirmed by an RT-PCR test; medical staff using any kind of nasal or oral sanitizer at the moment of recruitment or at any time in the past 2 weeks; taking any antiviral medicine at the moment of recruitment or at any time in the past 3 months; and/or participating in another clinical study. Additionally, the following elimination criteria were used: medical staff that voluntarily decided to suspend the prophylactic treatment or to abandon the study, medical staff who presented two or more symptoms associated with COVID-19 disease (*vide infra*) and that were confirmed as COVID-19 positive by RT-PCR within the first 14 days of their recruitment, and medical staff that at some point of the study presented with severe oral or nasal irritability, attributable to the administration of the SES.

Nurses and physicians were invited to participate through an invitation letter. Said invitation letter was given to the leaders of the nursing department and other relevant healthcare departments, so they could distribute the information. Interested medical staff in participating were provided with the details of the study and with the informed consent. Immediately after their recruitment (read and signed informed consent), each participating physician or nurse took one of two identical tokens that were placed inside an opaque plastic container. One token was labeled “with SES” (treatment group) and the other “without SES” (control group). Thus, all the participants were randomized between the two groups, until conforming two groups of 85 members each. All participants provided their medical history, including information about diabetes, obesity, hypertension and/or any other disease. All medical staff enrolled in the study were working an average of 25 hours a week in the COVID-19 front-line care of the hospital and all of them were wearing the corresponding PPE (i.e., surgical uniform, N95 mask, eye-sealing glasses and plastic wallet, disposable cap, latex gloves, rubber footwear for hospital use and disposable shoe covers), while working. Additionally, third level care health professionals wore a full protective mask, Dermacare®, overalls with zipper, and an integrated hood with elastic hand and ankle cuffs, double disposable boot covers and double latex gloves. Likewise, all medical staff had frequent hand washing with liquid soap (2% chlorhexidine gluconate) and hand disinfection (0.05% chlorhexidine gluconate and 60–80% ethyl alcohol). Additionally, disinfection of secondary uniform and footwear (80% ethyl alcohol) and bath at the end of the working day were routinely performed. All members of the treatment group were given directions on how to use the SES as nose rinses and mouthwashes, as well as provided with bottles containing the product. All participants were instructed to immediately inform their leader and the monitor of the study, if any COVID-19 symptoms (*vide supra*) were experienced during the study, and to be tested for SARS-CoV-2 by RT-PCT (nasopharyngeal swab) in the hospital laboratory. The follow up of each healthcare professional started once they were included in the protocol and finished 4 weeks later.

Prophylactic Protocol With Neutral Electrolyzed Water (Ses)

All treatment group individuals were provided with a document indicating a detailed description of how to perform the prophylactic protocol (Table 1), as well as with: 1) four plastic flasks with 30 mL of SES each, including a valve to be used for the nasal spray, and 2) four plastic flasks with 240 mL of SES each, including a graduated cap to be used for mouthwashes.

Table 1
Prophylactic protocol with SES for nasopharyngeal and oropharyngeal rinses.

	Nasal Cavity Rinses (EsteriFlu®)	Oral Cavity Rinses (ESTERICIDE® Bucofaríngeo)
How to use	<ul style="list-style-type: none">• Four vertical sprays in each nostril.• It should be inhaled deeply at the time of each spray.	<ul style="list-style-type: none">• 10 mL as mouthwash and gargle, during 60 seconds.• Spit out.
Frequency	<ul style="list-style-type: none">• Three times a day	

The SES formula (pH 6.5–7.5) has 0.0015% of active species of chlorine and oxygen and was provided by Esteripharma S.A. de C.V with the commercial product names ESTERICIDE® Bucofaríngeo (COFEPRIS registration no. 1003C2013 SSA) and EsteriFlu® (COFEPRIS registration no. 308C2015 SSA). Nasopharyngeal rinses were performed by applying four sprayings (approximately 0.4 mL) of SES (EsteriFlu®) to each nostril using the nasal valve, three times a day. Oropharyngeal rinses were performed by gargling 10 mL of SES, during 60 seconds, three times a day. All participants were informed of the importance of following the protocol and of the correct way of doing nasal sprays and mouthwashes, as well as of immediately reporting any possible side effects attributable to the use of the SES (*vide supra*).

Diagnosis Criteria, Outcome Measures And Follow-up

The primary endpoint was the number of healthcare professionals, nurses, or physicians, with COVID-19 disease confirmed by RT-PCR, between the 14th day since their recruitment and the 28th day of follow up. As part of the COVID-19 diagnosis criteria, all participants were instructed to immediately report to their leader and to their monitor of the protocol when they had at least two of the following COVID-19 signs and symptoms: dry cough, fever > 37.5°C, headache, myalgia, arthralgia, rhinorrhea, conjunctivitis, pharyngodynia, odynophagia. It is important to mention that all participants were trained medical staff from the front-line of a COVID-19 hospital, and all of them were previously trained to identify and report symptoms, as part of the intrinsic safety protocols of the hospital and the National Ministry of Health (Secretaría de Salud). All the healthcare professionals that had symptoms were immediately isolated and tested for SARS-CoV-2 with an RT-PCR test (nasopharyngeal swab) in order to confirm or reject the COVID-19 diagnosis. Individuals with suspicious symptoms were instructed to immediately report to the hospital laboratory; a

nasopharyngeal sample was taken there and transported with the BIOLOGIX® system, applicable for the collection and transportation of clinical virus samples. SARS-CoV-2 virus detection was carried out by RT-PCR, following the protocols specified by the Institute of Diagnosis and Epidemiological Reference (INDRE), and the health ministry of the country [20, 21]. Results were directly reported to tested individuals 48 to 72 hours after sampling through an official email. All the COVID-19 positive medical staff stayed at home and had disease treatment independent of this clinical trial.

The secondary endpoint was the number of healthcare professionals that presented adverse effects (irritation, pain, redness, numbness, bleeding) potentially attributable to the use of the SES; all members of the protocol were instructed to immediately suspend the prophylactic protocol and to report to the main researcher of any moderate or severe potential side effects.

Members of both, control and treatment groups, were followed up weekly through a phone call, during four weeks, checking for COVID-19 symptoms and/or confirmation of SARS-CoV-2 infection, as well as potential side effects, as communicated by each participant to the main researcher of the study. All participants were followed up for 4 weeks or until they were confirmed as COVID-19 positive. Hospital epidemiology department collected the data and monitored the program.

Blinding

Only the researchers that performed the statistical analyses were blinded.

Sample Size

The sample size calculation was based on the number of front-line healthcare professionals that had a confirmed COVID-19 disease by RT-PCR within a period of one month, despite the use of personal protection equipment (PPE). The sample size was calculated considering that 29% of such professionals may develop the COVID-19 disease, according to previous reports from Mexican hospitals [22] and considering that the prophylactic protocol with SES may reduce the incidence of the disease by 70%. Fifty-seven patients for each group were needed to reach the required power (0.8), when the statistical analysis was performed at the level of the one-tailed alpha (0.05). At the end of the study, the statistical power for detecting a difference between the two groups was calculated (one-tailed alpha = 0.05), using the number of patients with disease confirmation, resulting in 86%.

Statistical analysis

Categorical variables were described in percentages (%), and continuous variables were expressed in mean $\pm$ standard deviation. Comparisons for the proportions of categorical variables were conducted using the Fisher exact test. Data with normal distribution (e.g., age) was compared between groups, using the Student's t test. Relative risk (RR) analysis, with 95% CI for associations between the use of the prophylactic protocol and the development of COVID-19 disease, was used. A $p < 0.05$ was considered statistically significant. The GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com) was used for all statistical analyses. Sample size and statistical power were calculated using the online calculator software by HyLown Consulting LLC (Atlanta, GA, USA) to Compare 2 Proportions: 2-Sample, 1-Sided for a one-tailed test [23].

Results

170 healthcare volunteer professionals were randomized in control or prophylactic protocol group, each with 85 individuals. Six individuals were withdrawn from the control group since they presented with COVID-19 disease (symptoms and confirmation by RT-PCR test) within the first fourteen days since their recruitment and one individual from the prophylactic protocol group. The remaining participants were followed up two additional weeks checking for COVID-19 symptoms and conformation of the disease by RT-PCR (Fig. 1).

Healthcare professionals from both groups had similar baseline characteristics. There were 79 individuals in the control group; 53 nurses (67.1%) and 26 physicians (32.9%); while there were 84 individuals in the prophylactic protocol group; 56 nurses (66.7%) and 28 physicians (33.3%). As for gender, the control group had 72.2% women, and the prophylactic protocol group had 75.0%, with no significant differences between the groups regarding gender ($p = 0.7242$) or type of profession ($p = 1$). The age means showed statistical difference ($p = 0.0360$) between the two groups, with 40.94 ± 7.74 in the control group and 43.73 ± 9.01 in the prophylactic protocol group; particularly in the age group of 30–39 years old, where there were 29 individuals in the control group in this age range and 15 ($p = 0.0081$) in the SES group.

Comorbidities were observed in individuals from both groups, 16.5% in the control group and 29.8% in the prophylactic protocol group. The relevant comorbidities observed in the control group and the prophylaxis group were obesity [11.4% and 15.5%, respectively ($p = 0.4976$)], diabetes [3.8% and 6.0%, respectively ($p = 0.7207$)], and hypertension [5.1% and 8.3%, respectively ($p = 0.5367$)]. Other diseases with less importance for the purpose of this study were present in 7.6% of the control group participants, versus 8.3% in the SES-treatment group, without statistical significance ($p = 0.0631$) (Table 2).

Table 2
General characteristics of the medical staff enrolled in the clinical trial.

General characteristics	Control N (%)	Prophylactic protocol with SES N (%)	P value
Profession			1
<i>Nurses</i>	53 (67.1%)	56 (66.7%)	
<i>Doctors</i>	26 (32.9%)	28 (33.3%)	
Gender			0.7242
Male	22 (27.8%)	21 (25.0%)	
Female	57 (72.2%)	63 (75.0%)	
Age	40.94 ± 7.74	43.73 ± 9.01	0.0360*
20–29	6 (7.6%)	7 (8.3%)	0.0081**
30–39	29 (36.7%)	15 (17.8%)	
40–49	37 (46.8%)	44 (52.4%)	
50–59	5 (6.3%)	13 (15.5%)	
60–63	2 (2.5%)	5 (6.0%)	
Comorbidities	13 (16.5%)	25 (29.8%)	0.0631
Obesity	9 (11.4%)	13 (15.5%)	
Diabetes	3 (3.8%)	5 (6.0%)	
Hypertension	4 (5.1%)	7 (8.3%)	
Other diseases ^a	6 (7.6%)	7 (8.3%)	
Statistically significant values according to Student's T-Test: *p = 0.05, **p = 0.01; ^a Other diseases; control group: vitiligo, obstructive sleep apnea syndrome, hypothyroidism, arthritis, irritable bowel syndrome, gastroesophageal reflux; prophylactic protocol group: hypothyroidism, arthritis, breast cancer in remission, irritable bowel syndrome, allergic rhinitis, peripheral vascular insufficiency, arrhythmia.			

From the 163 volunteers that were followed up during two additional weeks, 10 individuals (12.7%) from the control group were COVID-19 confirmed by presence of symptoms and SARS-CoV-2 RT-PCT test, whereas only 1 (1.2%) was confirmed in the prophylaxis protocol group. The difference in the incidence between the two groups was statistically significant with a p-value of 0.0039. The relative risk (RR) was of 0.09405, with a 95% CI of 0.01231–0.7183, indicating a protective factor against COVID-19 disease in individuals that followed the prophylactic protocol with neutral electrolyzed water (Table 3), without any side effects.

Table 3
Relative Risk association between the general characteristics of COVID-19 individuals and group type.

General Characteristics	Control N (%)	Prophylactic protocol with SES N (%)	P value	RR	95% CI
Medical staff COVID-19 positive	10 (12.7%)	1 (1.2%)	0.0039**	0.09405	0.01231–0.7183
Occupation					
Nurses	10 (100%)	1 (100%)	0.0034**	0.09464	0.01254–0.7145
Physicians	0	0	-	-	-
Gender					
Male	2 (20%)	0	0.4884	0	-
Female	8 (80%)	1 (100%)	0.0131*	0.1131	0.01458-0.8770
Age	38.10 ± 5.26	43	-	-	-
20–29	1 (10.0%)	0	0.4615	-	-
30–39	4 (40.0%)	0	0.2822	-	-
40–49	5 (50.0%)	1 (100%)	0.0880	-	-
50–59	0	0			
60–63	0	0			
Comorbidities					
Obesity	0	0			
Diabetes	0	0			
Hypertension	0	1	1	-	-
Others ^a	0	1	1	-	-
Statistically significant values: *p = 0.05, **p = 0.01; ^a Hypothyroidism					

All the positive individuals in the control or prophylaxis protocol groups were nurses, 10 in the control group and 1 in the prophylactic protocol group with SES. Regarding gender, the only one infected individual in the prophylactic protocol group was female, as well as 80% of the positive medical staff in the control group. Only two men in the control group were positive to SARS-CoV2 and none in the SES group, but this was not statistically significant ($p = 0.4884$) (Table 3). Regarding age, the only one confirmed infected individual in the prophylactic protocol group was 43 years old, while in the control group the mean age of positive individuals was 38.1 ± 5.3 years old. No statistical significance was observed between developing COVID-19 disease and having a comorbidity. The group that followed the prophylactic protocol with SES had a lower incidence of COVID-19 positive cases and this effect was independent of age, gender, occupation, and former health status (Table 3).

Discussion

This prospective open-label randomized controlled trial was conducted to determine if there is a relationship between performing nasopharyngeal and oropharyngeal rinses with neutral electrolyzed water (SES; 0.0015% of reactive species of chlorine and oxygen), additional to wearing the appropriated PPE, and decreasing the risk of COVID-19 disease in front-line medical staff from a Mexican COVID-19 hospital. Results showed that indeed, the group that followed the prophylactic protocol with SES, had a significant decrease in the incidence of COVID-19, with only 1.2% of reported cases; in comparison with the control group, where 18.8% of individuals got the disease. This result allows us to postulate that the proposed prophylactic protocol of nasal and oral rinses with SES was effective in reducing the viral load in the upper respiratory tract and acting as a protective factor, by reducing the probability of developing the disease. Recently, it has been reported that nasal goblet and ciliated cells are a likely initial invasion site and reservoir of SARS-CoV-2 virus because these cells have a high expression of ACE2 and TMRPSS2; it was also determined that salivary glands, epithelial cells of the tongue and fibroblasts of oral mucosa express ACE2, explaining that both nasopharynx and oropharynx have the highest viral loads [24–27]. Additionally, it has been demonstrated *in vitro* that acidic electrolyzed water had a virucidal effect on SARS-CoV-2 [16], while neutral electrolyzed water showed similar virucidal activity against the respiratory influenza viruses H5N1 and H9N2, and over gastrointestinal noroviruses [17–19]. Interestingly, in the case of influenza virus, no viral particles and proteins were detected after SES exposure and it has been postulated that the REDOX

potential of SES, breaks chemical bonds and causes changes in surface proteins, destruction of the viral envelope, inactivation of viral enzymes, and destruction of viral nucleic acids [28]. This may explain the low incidence of SARS-CoV-2 positive cases in the group that followed the prophylactic protocol, suggesting that when exposed, the rinses not only reduced the viral load by dragging, but also by inactivating viral particles, and thus preventing their union with cellular receptors and the infection, given that viral proteins are susceptible to denaturalization [28]. In this regard, other substances with oxidizing potential have been proposed for oropharyngeal washes and even in dilutions for irrigation of the nose, but their irritant effect on mucous membranes is discussed [8–14]. Therefore, the use of SES for these purposes has the advantage of not being irritating and having an effective oxidant potential against viral particles; it should be noted that no individual using SES reported related side effects, therefore they did not discontinue its use.

The proposed scheme for using SES three times a day required that the rinses were made at the beginning of the day, at midday and at the end of the day, trying to cover the entire active day of the individuals and not just the working day, so it is possible that the rinses with electrolyzed water may effectively reduce the risk of infection even when containment measures are lowered. A more detailed study about this should be carried out to corroborate this point, especially considering the exposure and protective conditions of the regular population, in order to demonstrate the utility of the SES in preventing COVID-19 disease at this level. Additionally, the use of SES by sick people may help to locally inactivate the viral loads in mouth and nose, and thus to reduce the transmission rates. With respect to this point, it has been reported that the administration of SES to ambulatory patients by nebulization, in combination with conventional therapy, reduced the disease progression and improved the signs and symptoms after 24–72 hours of the first administration [29]. So, this report agrees with the hypothesis of an efficient inactivation of the virus, in the mouth and respiratory tract. In the present study, only one third of the population from each group was of physicians, and none of them got sick. Additionally, it was observed that the highest number of COVID-19 positive individuals were female nurses from the control group; this is in agreement with other studies that describe a high incidence of SARS-CoV-2 infection in nurses, since they spend more time with patients than physicians do [30]. Other studies about the risk of infection considered populations with similar gender proportions and concluded that the probability of getting infected is equal for both sexes [31, 32]. So, for this study we conclude that the highest incidence in the female population was due to the higher percentage (> 70%) of enrolled individuals being women.

On the other hand, recent epidemiological studies showed that COVID-19 patients had a mean age in the mid-40s [32], and in agreement with observations in their study, the infected individuals of both groups belong to this age group. However, the proportion between the two groups is quite different allowing to hypothesize that the use of SES may reduce the risk of contagion.

Finally, with respect to comorbidities, it is clear that hypertension, diabetes, and obesity, increase the risk of infection and severity of the COVID-19 disease [33]. Since the Mexican population has a high prevalence of said comorbidities, in this study we evaluated if there was an increased risk of disease in individuals with said preexisting conditions, despite the use of SES. Results showed no increased risk of contracting the disease that could be associated with comorbidities. However, the sample size of volunteers with such comorbidities was not big enough, so in order to establish if the use of SES can reduce the risk of infection in these individuals, a bigger sample must be analyzed.

Our study has some limitations, first, the lack of a control group treated with a placebo, such as saline solution. Secondly, the lack of -PCR tests and the consequent impossibility to analyze, at least once a week, all of the participants in order to identify asymptomatic but infected cases. Nevertheless, this study provides sufficient evidence to postulate that SES with 0.0015% of active species of chlorine and oxygen is useful to prevent the COVID-19 disease. When SES is administered as a nasal spray and as a mouthwash, additional to PPE, it may improve the protection against the COVID-19 disease, as it has been proved in this study and due to its known potential to inactivate viruses, such as the SARS-CoV-2. It is urgent to develop more studies, especially considering the daily activities of the general population, in order to demonstrate that neutral electrolyzed water is safe and effective to improve personal protection, and potentially to reduce the risk of contagion and transmission rates in the general population all over the world.

Conclusions

Nasopharyngeal and oropharyngeal rinses with SES may be an efficient alternative to reinforce the protective measures against COVID-19 disease and should be further investigated.

Abbreviations

SES: Neutral electrolyzed water, PPE: Personal protective equipment, RR: Relative Risk.

Declarations

Ethics approval and consent to participate

The study was approved by the research ethics committee of the ministry of health of Mexico City in accordance with the ethical international standards established in the Declaration of Helsinki. Each participant gave their informed consent, and data was processed according to national and international data protection laws.

Consent for publication

Not applicable

Availability of data and materials

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

Competing of interests

The authors Rafael Gutiérrez-García, Juan C. De la Cerda-Ángeles and Iván Delgado-Enciso declare no conflict of interest; Ariana Cabrera-Licona, Nicolas Mervitch-Sigal and Brenda A. Paz-Michel declare to work at Esteripharma company but did not participate in the decision to publish the results of the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

RGG designed the study and carried out data acquisition, JCA carried out data acquisition; ACL carried out data analysis; IDE carried out data analysis and interpretation; NMS helped with the validation and supply of the neutral electrolyzed water used in the study; BPM participated in the design of the study. All authors helped to prepare the manuscript and approved it for submission.

Acknowledgments

To Esteripharma company for providing the SES for the study, as Esteriflu® and Estericide® Bucofaríngeo products. To Vishlai Pineda Urbina for the professional translation services.

References

1. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. *Front Cell Infect Microbiol.* 2020;10:724. <https://doi.org/10.3389/fcimb.2020.587269>.
2. Worldometers C, Update (Live): 108,451,551 Cases and 2,383,004 Deaths from COVID-19 Virus Pandemic - Worldometer. 2021. <https://www.worldometers.info/coronavirus/>. Accessed 12 Feb 2021.
3. Amnesty International. Mapping health worker deaths from COVID-19. 2020. <https://www.amnesty.org/en/latest/news/2020/09/mapping-covid19-health-worker-deaths/>. Accessed 8 Feb 2021.
4. Secretaria de Salud. Personal de Salud COVID-19 MÉXICO. 2021. https://www.gob.mx/cms/uploads/attachment/file/616869/COVID-19_Personal_de_Salud_2021.02.15.pdf. Accessed 8 Feb 2021.
5. Thomson EC, Rosen LE, Shepherd JG, Spreafico R, da Silva Filipe A, Wojcechowskyj JA, et al. Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity. *Cell.* 2021. <https://doi.org/10.1016/j.cell.2021.01.037>.
6. Liu X, Liu Y, Wang L, Hu L, Liu D, Li J. Analysis of the prophylactic effect of thymosin drugs on COVID-19 for 435 medical staff: A hospital-based retrospective study. *J Med Virol.* 2021;93:1573–80. <https://doi.org/10.1002/jmv.26492>.
7. Dubina MV, Gomonova VV, Taraskina AE, Vasilyeva NV, Sayganov SA. Pathogenesis-based preexposure prophylaxis associated with a low risk of SARS-CoV-2 infection in healthcare workers at a designated COVID-19 hospital: a pilot study. *BMC Infect Dis.* 2021;21:536. <https://doi.org/10.1186/s12879-021-06241-1>.
8. Cegolon L, Javanbakht M, Mastrangelo G. Nasal disinfection for the prevention and control of COVID-19: A scoping review on potential chemopreventive agents. *Int J Hyg Environ Health.* 2020;230:113605. <https://doi.org/10.1016/j.ijheh.2020.113605>.
9. O'Donnell VB, Thomas D, Stanton R, Maillard J-Y, Murphy RC, Jones SA, et al. Potential Role of Oral Rinses Targeting the Viral Lipid Envelope in SARS-CoV-2 Infection. *Function.* 2020;1. <https://doi.org/10.1093/function/zqaa002>.
10. Carrouel F, Conte MP, Fisher J, Gonçalves LS, Dussart C, Llodra JC, et al. COVID-19: A Recommendation to Examine the Effect of Mouthrinses with β -Cyclodextrin Combined with Citrox in Preventing Infection and Progression. *J Clin Med.* 2020;9:1126. <https://doi.org/10.3390/jcm9041126>.
11. Bidra AS, Pelletier JS, Westover JB, Frank S, Brown SM, Tessema B. Rapid In-Vitro Inactivation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Using Povidone-Iodine Oral Antiseptic Rinse. *J Prosthodont.* 2020;29:529–33. <https://doi.org/10.1111/jopr.13209>.
12. Caruso AA, Del Prete A, Lazzarino AI. Hydrogen peroxide and viral infections: A literature review with research hypothesis definition in relation to the current covid-19 pandemic. *Med Hypotheses.* 2020;144:109910. <https://doi.org/10.1016/j.mehy.2020.109910>.
13. Meyers C, Robison R, Milici J, Alam S, Quillen D, Goldenberg D, et al. Lowering the transmission and spread of human coronavirus. *J Med Virol.* 2021;93:1605–12. <https://doi.org/10.1002/jmv.26514>.
14. Seneviratne CJ, Balan P, Ko KKK, Udawatte NS, Lai D, Ng DHL, et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial in Singapore. *Infection.* 2021;49:305–11. <https://doi.org/10.1007/s15010-020-01563-9>.

15. Yan P, Daliri EBM, Oh DH. New clinical applications of electrolyzed water: A review. *Microorganisms*. 2021;9:1–21. <https://doi.org/10.3390/microorganisms9010136>.
16. Takeda Y, Uchiumi H, Matsuda S, Ogata H. Acidic electrolyzed water potentially inactivates SARS-CoV-2 depending on the amount of free available chlorine contacting with the virus. *Biochem Biophys Res Commun*. 2020;530:1–3. <https://doi.org/10.1016/j.bbrc.2020.07.029>.
17. Cabello GC, Rosete ODP, Manjarrez ZME. Efecto de una solución electrolizada de superoxidación con pH neutro sobre la infección del virus de influenza A en células MDCK. *Rev Inst Nal Enfer Respi Mex*. 2009;22:280–7.
18. Moorman E, Montazeri N, Jaykus LA. Efficacy of neutral electrolyzed water for inactivation of human norovirus. *Appl Environ Microbiol*. 2017;83. <https://doi.org/10.1128/AEM.00653-17>.
19. Tamaki S, Bui VN, Ngo LH, Ogawa H, Imai K. Virucidal effect of acidic electrolyzed water and neutral electrolyzed water on avian influenza viruses. *Arch Virol*. 2014;159:405–12. <https://doi.org/10.1007/s00705-013-1840-2>.
20. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance*. 2020;25:2000045. <https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045>.
21. den Brink van. “Dr. Manuel Martínez Báez” (InDRE) CRITERIOS PARA LA ACEPTACIÓN DE PRUEBAS MOLECULARES ÚTILES PARA EL DIAGNÓSTICO DE SARS-cov-2 DURANTE LA CONTINGENCIA DE COVID-19 EN MÉXICO. 2020. https://www.gob.mx/cms/uploads/attachment/file/547178/Criterios_para_la_aceptacion_de_pruebas_moleculares_para_el_diagnostico_de_SARS-CoV-2.pdf. Accessed 15 Feb 2021.
22. Del-Carpio-Orantes L, Garcés-Gracia E, Ortiz-Espinoza C, et al. Médicos de primera línea de atención infectados por COVID-19 durante un brote hospitalario en Veracruz, México. *Med Int Mex*. 2020;36:781–8.
23. HyLown Consulting LLC. Power and Sample Size Calculators Compare 2 Proportions: 2-Sample, 1-Sided Calculator: 1. 2013. <http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-1-Sided>. Accessed 6 May 2021.
24. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26:681–7. <https://doi.org/10.1038/s41591-020-0868-6>.
25. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020;382:1177–9. <https://doi.org/10.1056/nejmc2001737>.
26. To KKW, Tsang OTY, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis*. 2020;20:565–74. [https://doi.org/10.1016/S1473-3099\(20\)30196-1](https://doi.org/10.1016/S1473-3099(20)30196-1).
27. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12:1–5. <https://doi.org/10.1038/s41368-020-0074-x>.
28. Morita C, Sano K, Morimatsu S, Kiura H, Goto T, Kohno T, et al. Disinfection potential of electrolyzed solutions containing sodium chloride at low concentrations. *J Virol Methods*. 2000;85:163–74. [https://doi.org/10.1016/S0166-0934\(99\)00165-2](https://doi.org/10.1016/S0166-0934(99)00165-2).
29. Delgado-Enciso I, Paz-García J, Barajas-Saucedo CE, Mokay-Ramírez KA, Meza-Robles C, Lopez-Flores R, et al. Patient-Reported Health Outcomes After Treatment of COVID-19 with Nebulized and/or Intravenous Neutral Electrolyzed Saline Combined with Usual Medical Care Versus Usual Medical care alone: A Randomized, Open-Label, Controlled Trial. *Res Sq*. 2020. 10:rs.3.rs-68403. <https://doi.org/10.21203/rs.3.rs-68403/v1>. [Preprint] September.
30. Liu SY, Kang XL, Wang CH, Chu H, Jen HJ, Lai HJ, et al. Protection procedures and preventions against the spread of coronavirus disease 2019 in healthcare settings for nursing personnel: Lessons from Taiwan. *Aust Crit Care*. 2020. <https://doi.org/10.1016/j.aucc.2020.10.006>.
31. Peckham H, de Groot NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ICU admission. *Nat Commun*. 2020;11:1–10. <https://doi.org/10.1038/s41467-020-19741-6>.
32. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol*. 2021;93:1449–58. <https://doi.org/10.1002/jmv.26424>.
33. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. *J Infect Public Health*. 2020;13:1833–9. <https://doi.org/10.1016/j.jiph.2020.07.014>.

Figures

Figure 1

Flow Diagram showing the number of screened, included, eliminated, and analyzed patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SESCONSORTBMC160621.doc](#)