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The Efficacy of Nitric Oxide Generating Lozenges on Outcome in Newly Diagnosed COVID-19 Patients of African American and Hispanic Origin

A Randomized Clinical Trial

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Running head: Efficacy of Nitric Oxide Generating Lozenges in Newly Diagnosed COVID-19

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Highlights

- Efficacy and safety of Nitric Oxide (NO) lozenges was evaluated in symptomatic COVID-19 outpatients.
- Patients self-identified as Hispanic or African American at high risk were studied.
- NO lozenges did not mitigate disease severity.
- NO lozenges did not reduce hospitalization, ICU admission or death.
- NO lozenges were well tolerated.

Abstract

BACKGROUND: The study was initiated in 2020 to test the efficacy of a nitric oxide generating lozenge (NOL) in outpatients with newly diagnosed COVID-19 to mitigate disease severity. The study enrolled high risk patients, African American and Latino.

METHODS: This was a randomized, double blinded, prospective, placebo controlled trial. The primary endpoint was hospitalization, ICU admission, intubation, dialysis and death. The secondary endpoints were time to symptom resolution and the effect on oxygen saturation. Patients ages 50-85 with recent COVID-19 diagnosis with at least one risk factor were recruited. Patients were randomized either to active treatment or placebo using block randomization. Blood pressure and oxygen saturation (SpO2) was measured before and after the first dose and each AM thereafter.

RESULTS: A total 840 patients was planned, half in the lozenge and placebo groups. An interim review of data was pre-specified. After 524 patients the composite endpoint occurred in 6 patients, 3 (1.1%) in each group. The time to symptom resolution was one

day shorter on active treatment (8.7±6.6 versus 9.8±6.8 days) (p=0.3). There was no change in SpO2 on placebo (0.0±2.0%) and no significant change on treatment (0.14±0.9%), p=0.3. All events occurred in the first year (2020).

CONCLUSIONS: This study did not find a benefit of NOL therapy in COVID-19 patients and was terminated for futility. NOL treatment did not reduce mortality, hospitalization, intubation or a reduction in symptoms duration. The study did find the NO lozenges were well tolerated in high risk patients without reported side effects.

Key words: COVID-19; Nitric Oxide; Nitric Oxide Generating Lozenges; Efficacy

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, China. It causes a severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2) and by early 2020 became a pandemic. The virus spread to Europe and then to the USA. The first case in the USA was identified in March 2020. According to the CDC, by the end of 2022, there were over 100 million documented cases of COVID-19 with more than 1 million (1,088,481) deaths in the United States.[1] The virus mutates frequently and variants have developed with different transmissibility and ability to cause varying frequency of disease, hospitalization and death. Three waves of COVID-19 have occurred in the USA and a fourth wave may be developing in Europe.

In 2020, during the first wave, there were no proven treatment options, as well as no vaccines. The population was naïve for SARS-CoV-2. The virus proved to be very infectious causing sever COVID-19 illness with high rate of hospitalizations and death. Early reports from China indicated that complications were more common in hospitalized patients with cardiac disease. Patients with cardiac injury had a higher mortality than those without cardiac disease (51.2% versus 4.5%, $p < .001$).[2] It became apparent that a number of underlying medical conditions can increase the risk of severe COVID-19-associated illness, including chronic kidney disease, chronic obstructive pulmonary disease (COPD), atherosclerotic heart disease, diabetes, and obesity.[3]

In 2020, due to lack of effective treatment, efforts were undertaken to mitigate the disease severity and prevent hospitalization, mechanical ventilation and death. Attempts were made to repurpose a number of generic drugs to treat COVID-19 illness, to reduce

the severity of the disease. Studies were also initiated that employed inhaled nitric oxide to treat intubated patients.[4]

Inhaled nitric oxide has been shown to be effective and has an approved indication to manage and treat hypoxic respiratory failure or persistent pulmonary hypertension in term and near-term neonates.[5,6] However, nitric oxide is not approved in the U.S. to treat adult respiratory distress syndrome (ARDS) In a randomized, double-blind, parallel study in patients with various etiologies of ARDS acute improvements in oxygenation were observed, but there was no effect of nitric oxide on the primary endpoint of days alive or days off ventilator support.[6] Off label use of nitric oxide as a rescue therapy has been employed in ARDS with refractory hypoxemia and pulmonary hypertension, [7,8,9] as well as in the management of oxygenation and pulmonary hypertension during lung or heart transplantation, and as a treatment for acute right ventricular failure after cardiotomy and cardiopulmonary bypass.[10,11] Based on a meta-analysis, inhaled nitric oxide was not associated with a mortality benefit in patients with ARDS, but it had a transient positive effect on oxygenation. Based on these observations it was felt NO therapy may benefit patients with COVID precipitated ARDS.[9] Studies have been initiated with inhaled nitric oxide for the management of moderate to severe ARDS in patients with COVID-19. A search of ClinicalTrials.gov shows that 22 studies have been registered treating COVID-19 with inhaled nitic oxide. The results of these studies were not known at the time of the initiation of this study. Results of controlled clinical trials on NO both retrospective and observational have been published. Most report that inhaled nitric oxide improves oxygenation in critically ill patients with COVID-19, but conflicting results have been reported in terms of a

mortality benefit.[6,12,13,14,15,16,17]

Nitric oxide is produced in the human body and found in many different kinds of cells and organ systems. It is considered one of the most protective molecules in man.[18] Acute respiratory distress syndrome (ARDS) is a severe late complication with COVID-19 which can also result in pulmonary hypertension and increased intrapulmonary shunting of blood from hypoventilated regions.[19] Nitric oxide plays a role in maintaining the integrity of vascular system and has the capability to produce pulmonary vasodilation by relaxation of smooth muscle cells that increases blood flow.[13,19,20] Furthermore, NO has been shown to be necessary for efficient oxygen delivery by hemoglobin especially during periods of hypoxia.[21] Nitric oxide has a beneficial effect on immune system, and has anti-viral activity. NO was reported to alter the surface protein of SARS-CoV-1 (spike protein) preventing attachment to the ACE2 receptor, blocking entry into cell.[22] Nitric oxide also decreases the propensity of blood to clot, [23] a problem leading to multi-system damage in patients with severe COVID-19 illness. Considering all these factors it was hypothesized that increasing NO levels in patients with COVID-19 would have a salutatory benefit.

In this study, a unique method was used to increase the patient's nitric oxide level by employing a novel nitric oxide generating lozenge using sodium nitrite as the active pharmaceutical ingredient.

This clinical trial aimed to test the efficacy of the nitric oxide lozenge in outpatients with newly diagnosed COVID-19 in preventing progression of disease, reducing the need for hospitalization, mechanical ventilation and decreasing death. The study was initiated in 2020, during the first wave of the COVID-19 pandemic.

METHODS

Trial Design

This study was a randomized, double blinded, prospective, placebo controlled clinical trial conducted under an Investigational New Drug Application (IND# 150758). The Study was approved by Solution IRB (Yarnell, AZ) and registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04601077). The study was performed in the United States and involved 30 screening centers that initially screened the patients and then the patients were followed by a Central Coordinating Center which contacted the patients 2 to 3 times a week for 30 days. The objective of the study was to determine the safety and efficacy of NOviricid™, an orally disintegrating sodium nitrite lozenge (30 mg) that generates NO in patients (not hospitalized) with a diagnosis of COVID-19. The study drug and placebo were provided by the sponsor, Nitric Oxide Innovations, LLC.

The NO lozenge dose was selected on the basis of the lack of significant side effects with a 20 mg supplement dose and the prior anti-hypertensive activity of a 30 mg lozenge dose.

The study had two phases. The first phase was a pilot study including 100 patients and aimed to evaluate the safety and tolerability of NOviricid™. Because no signal suggesting a safety concern was seen in this phase, the study continued to the second phase. The primary objective of the second phase was to determine the

effectiveness of the sodium nitrite lozenge in reducing the composite primary endpoint of hospitalization, intubation, ICU admission, dialysis and death in patients with a diagnosis of COVID-19. The secondary efficacy endpoints included the effect of treatment on time to symptom resolution and the effect of treatment on oxygen saturation compared to placebo. Per protocol, patients of the pilot study were included in the second phase of the trial. The pilot study was identical to the continuation trial in terms of entry criteria and data collection.

Study population

The selection of the study population was based on the desire to enrich the study population with high risk patients for hospitalization and death. Reports from the U.S. database compiled by CDC reported mortality from COVID-19 to have a racial disparity.[24] A disproportionate number of COVID-19 fatalities among African Americans and Hispanics has been reported. African Americans have a high incidence of comorbidities including pre-existing and often untreated cardiovascular conditions.[25] The Hispanic population also has a high incidence of comorbidities such as diabetes and hypertension and is also at higher risk for hospitalization and death than the Caucasian population as noted in a CDC report (03/06/2021) Table 1.[26]

The original protocol aimed to enroll African American patients only. However, the enrolment was slower than projected. The protocol was amended to include Hispanic patients who were also at higher risk. Thus, the final target population included self-identified African American and Hispanic patients. To be eligible for this study, the patient had to give voluntary written informed consent to participate in the study; self

identify as African American or Hispanic; age 50-85 with recent COVID-19 diagnosis (positive PCR testing, or other FDA approved rapid testing within 72 hours); being symptomatic (fever, cough, shortness of breath, weakness, or other flu-like symptoms); having at least one risk factor (history of hypertension (BP> 140/90), congestive heart failure, angina, prior myocardial infarction (MI), coronary artery disease diagnosed by angiography with at least one significantly occluded vessel, diabetes mellitus, obesity, or smoking (for at least 5 years); and agreeing to comply with study procedures (recording oximeter and blood pressure readings in a diary and responding to calls 3 times per week for follow up).

The exclusion criteria included: Females who were pregnant, breastfeeding or planned to become pregnant during the course of the study. Patients unresponsive or unable to take medications by mouth (NPO). Individuals who are cognitively impaired and/or who are unable to give informed consent. Blood pressure below 110 mmHg systolic and 60 mmHg diastolic on entry into study. History of syncope or symptoms of orthostatic hypotension. History of methemoglobinemia.

Sample Size

It was estimated that 420 patients in each of the two study groups would provide 80% power to show a 20% decrease in the primary composite endpoint with the active treatment to be statistically significant at a two-sided alpha error of 0.05 ($p<0.05$). Enrolment of a total 840 patients was planned, 420 in the nitrite (NO) group and 420 in the placebo group.

Study Procedures

Randomization

At screening, patients upon diagnosis of COVID-19 were asked to participate in the study, read and then sign the Informed Consent. This was followed by a brief review of medical history, concomitant therapies, and eligibility based on the inclusion and exclusion criteria. If the patient was eligible for the study, the patient was randomized either to active treatment or placebo using block randomization. The sodium nitrite lozenge and placebo tablets looked identical and the containers were coded. The patients and study personnel were blinded to the identity of the study drugs.

Interventions

Subjects were given a supply of study drug for 30 days (60 lozenges) and were instructed to take one lozenge twice daily approximately 12 hours apart. If a dose was missed, the next dose was to be taken at the next regular scheduled interval. Patients were instructed not to take more than 2 lozenges per day. The first dose of study drug was taken with 1 hour of observation to determine if hypotension developed. Blood pressure and oxygen saturation was measured before and after the first dose. Data collected during the screening were entered into the electronic case report form. Before leaving the screening site, each patient received a portable pulse oximeter, an automated blood pressure monitor, an electronic thermometer and were trained how to use the equipment. A study diary was also provided to record oxygen saturation, blood pressure and body temperature daily. Furthermore, the patients were instructed to

record problems with the study drug use, changes in concomitant therapies, and any side effects or changes in their current condition. Participants were called at least twice a week by the study center and at 30 days. Patient's diary readings and any follow up information were entered in the patient's record and then into the master electronic data file. Patients were also asked to contact the study center, or ask a family member to contact the study center for a change in their condition. If the patient was admitted to hospital they were asked to provide the hospital name for follow up contact or ask a friend or relative to do so.

At the end of 30 days, the patients were asked to return any unused study drug and their diary in a prepaid return envelope.

Data analysis

An interim review of data was pre-specified. This included evaluating the primary composite endpoint. Categorical data were analyzed by Chi Square test or Fisher exact test. Continuous variables were analyzed by independent sample t test. A two-sided p value of <0.05 was considered to be statistically significant.

Study Medication

An NO generating lozenge was utilized in this study. In normal individuals 20 mg lozenge generates 15 ppm NO concentration. Administered every 12 hours based on blood pressure effects seen in hypertensive patients lasting 8-10 hours.

RESULTS

Study Population and Outcomes

At the time of interim analysis, a total of 524 patients have been enrolled. Study drugs were coded as Study Drug A and Study Drug B. A blinded analysis was performed for the primary composite endpoint. A total of 261 patient were randomized to Study Drug A and 263 to Study Drug B. The composite primary endpoint occurred in 6 patients, 3 were on Study Drug A and 3 were on Study Drug B, with a frequency of 1.1% of the patients in each group. Thus, the two study drugs (active treatment and placebo) showed no difference on the composite efficacy endpoint. Based on this observation, a decision was made to stop and unblind the study. The study was analyzed according the protocol, with the primary and secondary endpoints evaluated. Patient demographics are shown in Table 2.

The time to symptom resolution was one day shorter in the patients receiving the active treatment (8.7± 6.6 versus 9.8 ± 6.8 days) but this difference was not statistically significant (p=0.3). Regarding the effect of the study drug on oxygen saturation measured a (SpO2) using a hand held oximeter, before and after the first dose of the study drug, there was no change with placebo (0.0 ± 2.0%) while there was a small but nonsignificant increase with the nitrite lozenge (0.14 ± 0.9%), p=0.3 (Table 3), (Supplementary source data available online). The systolic blood pressure decreased after the sodium nitrite lozenge (-0.4 ± 5.5 mm Hg) but the decrease was less than that seen after placebo (-1.6 ± 6 mm Hg), p=0.02. Neither caused an unsafe drop in blood pressure.

All primary composite endpoints occurred in the first year of the study (2020), and none

in 2021 and 2022. The study was terminated due to futility.

Adverse Events

No signs of toxicity of sodium nitrite and nitric oxide were reported.

DISCUSSION

Coronavirus Disease 2019 (COVID-19) quickly became a worldwide pandemic affecting millions of people. This study was undertaken when SARS-CoV-2 a more virulent strain was present than the currently prevalent omicron variant. Reports from China and subsequently Europe and the U.S. found older patients with underlying cardiovascular disease more susceptible to severe infection with a higher mortality. Patients with diabetes and obesity were at higher risk. Early on as the disease progressed in the U.S. hypertension, ASHD, diabetes and obesity all were conditions that were associated with more severe COVID with increased hospitalization and death.[3] Additionally, African American and Latino patients were reported to have more severe disease with a higher mortality.[24,26]

Corona virus possesses a spike protein that is employed by the virus to enter cells using the angiotensin converting enzyme 2 receptor (ACE2). Nitric Oxide (NO) has been reported to alter the virus surface protein of SARS-1 spike protein making attachment to the ACE2 receptor more difficult, impeding entrance into cells.[22] Additionally NO has been reported to prevent replication of the SARS CoV-2 virus in vitro.[27] In addition NO has been reported to improve patient oxygenation.[9,21,28] Additional possible benefits of NO therapy are to improve vascular function[18] and to

cause endothelial relaxation.[19,29] NO has also been reported to decrease blood coagulation.[23] Since hypoxia, vascular dysfunction, and blood clots have all been reported to be adversities in patients with COVID, improvement in these conditions was thought to offer potential benefits to patients and thus improve outcomes.

NO is naturally produced gas in man [11] and found in many different varieties of cells. NO is the endothelial derived relaxing factor (EDRF) first described by Furchgott in 1980.[19,29] NO is produced by at least two different pathways in man. One is though the oxidation of L-arginine by nitric oxide synthase (NOS).[30] A second pathway is a step wise reduction of inorganic nitrate to nitrite to NO.[31] This reductive pathway is dependent upon oral nitrate reducing bacteria.[32] The orally administered nitrite lozenge used in this study bypasses microbial breakdown progressing to a direct reduction of nitrite to NO.

The company Nitric Oxide Innovations (NOI) has developed a novel nitric oxide generating lozenge using sodium nitrite as the active pharmaceutical ingredient. Using ascorbic acid and hawthorn berry, the sodium nitrite is reduced to nitric oxide in the oral cavity generating 20-40 ppm NO gas as the lozenge dissolves over 5-6 minutes. The lozenge offers the ability to deliver NO efficiently in patients outside a hospital or medical facility. This study was undertaken in a high-risk population to determine if an oral NO treatment could modify the disease process reducing the composite endpoint of death, hospitalization, intensive care unit admission or intubation. We also hypothesized that NO therapy would improve oxygenation and shorten the duration of symptomatic disease.

Unfortunately, an interim analysis revealed no difference in the primary outcome between treated and untreated patients. There was no significant difference in oxygenation and no significant difference in symptom duration. All deaths and hospitalizations were noted early in the study. As the omicron variant became dominant in the U.S. there were no deaths or hospitalizations noted. The changing characteristics of the disease led to a situation where far larger numbers of patients would be needed to have an event rate that was initially utilized to determine the sample size of the study that could potentially show a 20% difference between treated and non-treated patients. In a rapidly evolving disease process studying efficacy of a treatment becomes quite difficult. A study must be initiated quickly and rapidly enroll patients. While obtaining IRB approval and FDA permission to proceed was quickly obtained, it was very slow to initiate study sites and enter African American patients during the initial stages of the pandemic. These observations and the difficulties seen with so many other studies suggest the need to develop platforms to facilitate investigation of potential therapeutic agents during a pandemic that creates a national emergency.

The current results with the 30 mg lozenge dose administered twice daily does not exclude the possibility of a higher more frequently administered dose of nitrite being effective though a much larger study would be needed.

Limitations

This study looked at one dosage of the NO releasing lozenge. It is possible that higher more frequent dosing could have been effective, Furthermore the study treated

outpatients only. Patients hospitalized with severe COVID have very different pathophysiology and could very well respond to NO inhalation therapy.

Conclusions

The current study did not find a benefit of NO lozenge therapy in COVID-19 patients. The study did find the NO lozenges were well tolerated without reported side effects. Signs of toxicity of sodium nitrite and nitric oxide include hypotension headaches, cyanosis, and methemoglobinemia, none of which were observed. The safety of the therapy suggests that NO releasing lozenges may be useful in other disease states that could benefit by increasing NO levels.

Declaration of Competing Interest

Thank you for consideration of our paper for publication in American Journal of Medicine. This letter should confirm that I serve as Founder and CEO of Nitric Oxide Innovations, the company that develops and markets nitric oxide-based therapeutics, including Noviricid. Please let me know if you need any additional information.

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APPENDIX

Screening Centers: Trust Care Health, Ridgeland, MS; Premier Urgent Care and Occ-Health CTR, Chicago, IL; Ruan Medical Group, Houston, TX; Regenerative Spine & Pain Specialists, Fayetteville, GA; LA Universal Research Center, Los Angeles, CA; Dean Medical, Inc., Lakeland, FL; Dr. Bahrami's Group, Miami, FL; Wellness Clinic and Healthcare Consulting, PLLC, Camden, AR; Dr. Andrea McCall's Group, Queens Village, NY; Sunrise Research Institute, Sunrise, FL; RMP Health Solution, Inc., Little Rock, AR; Future Clinical Research. Miami, FL; Universal Axon Homestead, LLC, Homestead, FL, Innovation Clinical Trials, Palmetto Bay, FL; Homestead Research Institute, Inc., Homestead, FL; Affinity Clinical Research, LLC., Tampa FL;Clinical Research of Brandon #1, Brandon, FL, Clinical Research of Brandon #2. Tampa, FL;

Houston Clinical Research Associates, Houston, TX; NuoVida Research Center, Miami, FL; LinQ Research, LLC, Pearland, TX; HCRA/Majid Shah, MD, Houston, TX; BCSD Research, Inc., Miami, FL; Small Giants Research, LLC, Miami, Florida; USPA Advance Concept Medical Research Group, LLC, South Miami, FL; MG Research Center, Inc., Miami, FL; Angels Clinical Center , Miami, FL; Comprehensive Medical & Research Center (CMRC), Plantation, FL; Blessed Health Care, Department of Clinical Trials, Miami, FL.

REFERENCES

1. CDC COVID Data Tracker. Available at:

https://covid.cdc.gov/covid-data-tracker/#datatracker-home

Last acessed: 01 02 2023

2. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810.

3. CDC COVID Data Tracker./ Underlying Medical Conditions. Available at:

https://covid.cdc.gov/covid-data-tracker/#underlying-med-conditions

Last acessed: 01 02 2023

4. Writing Committee for the REMAP-CAP Investigators; Higgins AM, Berry LR, Lorenzi E, Murthy S, et al. Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial. JAMA. 2023;329(1):39-51.

5. Witek J, Lakhkar AD. Nitric Oxide. 2022 Sep 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available at:

https://www.ncbi.nlm.nih.gov/books/NBK554485/

Last acessed: 01 02 2023

6. INOMAX (nitric oxide) gas, for inhalation. FDA approved label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020845s016s017lbl.pdf Last acessed: 01 02 2023

7. Welker C, Huang J, Gil IJN, Ramakrishna H. 2021 Acute Respiratory Distress Syndrome Update, With Coronavirus Disease 2019 Focus. J Cardiothorac Vasc Anesth. 2022;36(4):1188-1195.

8. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled nitric oxide in ARDS study group. Crit Care Med. 1998;26:15–23.

9. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev. 2016;2016:CD002787.

10. Benedetto M, Romano R, Baca G, et al. Inhaled nitric oxide in cardiac surgery: Evidence or tradition? Nitric Oxide. 2015;49:67-79.

11. Schmid ER, Bürki C, Engel MH, Schmidlin D, Tornic M, Seifert B. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. Anesth Analg. 1999;89(5):1108-1115.

12. Al Sulaiman K, Korayem GB, Altebainawi AF, et al. Evaluation of inhaled nitric oxide (iNO) treatment for moderate-to-severe ARDS in critically ill patients with COVID-19: a multicenter cohort study. Crit Care. 2022;26(1):304

13. Bagate F, Tuffet S, Masi P, Perier F, et al. A. Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. Ann Intensive Care. 2020;10(1):151

14. Lotz C, Muellenbach RM, Meybohm P, et al. Effects of inhaled nitric oxide in COVID-19-induced ARDS - Is it worthwhile? Acta Anaesthesiol Scand. 2021;65(5):629-632.

15. Garfield B, McFadyen C, Briar C, et al. Potential for personalised application of inhaled nitric oxide in COVID-19 pneumonia. Br J Anaesth. 2021;126(2):e72-e75.

16. Alqahtani JS, Aldhahir AM, Al Ghamdi SS, et al. Inhaled Nitric Oxide for Clinical Management of COVID-19: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022;19(19):12803

17. Vives M, Gascó I, Pla G, et al. Inhaled Nitric Oxide in Acute Severe Pulmonary Hypertension and Severe Acute Respiratory Distress Syndrome Secondary to COVID-19 Pneumonia: A Case Report. Am J Case Rep. 2022;23:e937147.

18. Moncada S, Higgs EA. The discovery of nitric oxide and its role in vascular biology. Br J Pharmacol. 2006;147 (Suppl 1):S193-201.

19. Ignarro LJ. Inhaled NO and COVID-19. Br J Pharmacol. 2020;177(16):3848-3849.

20. Ferrari M, Santini A, Protti A, et al. Inhaled nitric oxide in mechanically ventilated patients with COVID-19. J Crit Care. 2020;60:159-160.

21. Zhang R, Hess DT, Qian Z, et al. Hemoglobin βCys93 is essential for cardiovascular function and integrated response to hypoxia. Proc Natl Acad Sci U S A. 2015;112(20):6425-6430.

22. Akerström S, Gunalan V, Keng CT, Tan YJ, Mirazimi A. Dual effect of nitric oxide on SARS-CoV replication: viral RNA production and palmitoylation of the S protein are affected. Virology. 2009;395(1):1-9.

23. Radomski MW, Palmer RM, Moncada S. The anti-aggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. Br J Pharmacol. 1987;92(3):639-646.

24. Yancy CW. COVID-19 and African Americans. JAMA. 2020;323(19):1891-1892

25. Carnethon MR, Pu J, Howard G, et al. Cardiovascular Health in African Americans: A Scientific Statement from the American Heart Association. Circulation. 2017;136(21):e393-e423.

26. CDC COVID Data Tracker/ COVID-19 Weekly Cases and Deaths per 100,000 Population by Age, Race/Ethnicity, and Sex. Available at: https://covid.cdc.gov/covid-data-tracker/#demographicsovertime Last accessed 01/02/2023

27. Akaberi D, Krambrich J, Ling J, et al. Å. Mitigation of the replication of SARS-CoV-2 by nitric oxide in vitro. Redox Biol. 2020;37:101734.

28. Allen BW, Stamler JS, Piantadosi CA. Hemoglobin, nitric oxide and molecular mechanisms of hypoxic vasodilation. Trends Mol Med. 2009;15(10):452-60

29. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature. 1980;288(5789):373-6.

30. Marletta MA, Yoon PS, Iyengar R, Leaf CD, Wishnok JS. Macrophage oxidation of L-arginine to nitrite and nitrate: nitric oxide is an intermediate. Biochemistry. 1988;27(24):8706-11.

31. McKnight GM, Smith LM, Drummond RS, Duncan CW, Golden M, Benjamin N. Chemical synthesis of nitric oxide in the stomach from dietary nitrate in humans. Gut. 1997;40(2):211-4.

32. Bryan NS, Tribble G, Angelov N. Oral Microbiome and Nitric Oxide: the Missing Link in the Management of Blood Pressure. Curr Hypertens Rep. 2017;19(4):33

Table 1. Racial Disparity in Negative Outcomes of COVID-19 Among African Americans and Hispanics

	African Americans [X]	Hispanics [X]
Cases	1.1	1.3
Hospitalization	2.9	3.1
Death	1.9	2.3

(X) In excess compared to Caucasians

Table 2. Patient Demographics

	Sodium Nitrite Lozenge	Placebo	P value
N	261	263	0.871
Female	150 (57.5%)	166 (63%)	0.187
Male	111 (42.5%)	87 (37%)	0.187
African American	71 (27%)	71 (27%)	0.958
Hispanic	190 (73%)	192 (73%)	0.958
Systolic BP (mmHg)	131.6±11.9	133.5±13.6	0.087
Diastolic BP (mmHg)	80.4±8,9	81.4±7.9	0.186
SpO2 (%)	95.9±2.4	95.6±3.1	0.224

BP: Blood Pressure; SpO2: Saturation of Peripheral Oxygen, data given as mean ± SD

Table 3. Results

	Sodium Nitrite Lozenge	Placebo	P value
Composite endpoint (n) (%)	3 (1.1%)	3 (1.1%)	1.00
Symptom duration (days)	8.7 ± 6.6	9.8 ± 6.8	0.30
Change in O2 saturation (%)	0.14 ± 0.9	0 ± 2%	0.30