

Transcutaneous Vagus Nerve Stimulation is Associated with Lower Mechanical Ventilation and Mortality in COVID-19 Patients: An interim Safety Analysis

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Abstract

Objective: To evaluate the safety and efficacy of transcutaneous vagus nerve stimulation in preventing respiratory failure and improving survival in hospitalized COVID-19 patients.

Design, Setting, and Participants: Interim analysis of an ongoing single-arm, uncontrolled open-label, observational trial to assess the transcutaneous vagus nerve stimulation (tVNS) in hospitalized SARS-CoV-2 infected subjects. Eligible subjects are 18 years old or older requiring hospitalization for COVID-19 pneumonia.

Results: The 25 subjects enrolled with a mean age of 52.2 (22-80). Mechanical ventilation was required in only 2 (8%) cases. One survived and 1 one died. Although 4 (16%) of the 25 hospitalized subjects died, only 1 (4%) was attributed to respiratory failure. Relative to other reported COVID-19 hospitalization outcomes data, our mortality rate of 16% (4 of 25) is lower than many other reported cohorts 10.2% – 50%. Only 8% (2 of 25) of subjects required mechanical ventilation comparing favorably to 7.4%-79% of subjects requiring mechanical ventilation in other cohorts. Adverse events associated with tVNS occurred in only 2 subjects (8%) and consisted of reversible oral paresthesia and orthostatic hypotension.

Conclusion and Relevance: In this interim report of tVNS in COVID-19 pneumonia, patients had a low rate of adverse events, infrequent use of mechanical ventilation, and a high rate of survival. Several other studies have shown a wide range of in hospital mortality (14-50%) and the requirement of mechanical ventilation (7-79%). The interim analysis found the mortality rate and the frequency of mechanical ventilation to be less than almost all other large COVID-19 cohorts. Only mild and self-limiting adverse events tVNS occurred in 2 subjects highlighting the safety of vagus stimulation. The study is slated to enroll a minimum of 50 subjects.

Trial Registration: ClinicalTrials.gov Identifier: NTC04379037

Keywords: Vagus Nerve Stimulation, VNS, SARS-CoV-2, COVID-19, Mechanical Ventilation, Mortality, Cytokine Storm, Cytokine Release Syndrome

Abbreviations:

VNS: Vagus Nerve Stimulation

CRS: Cytokine Release Syndrome

IL: Interleukin

TNF: Tumor Necrosis Factor

CAP: Cholinergic Anti-inflammatory Pathway

ARDS: Acute Respiratory Distress Syndrome

Introduction

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues and thousands of individuals are dying daily from COVID-19 worldwide, a more effective therapeutic option is essential. Infection with SARS-CoV-2 is characterized by a dramatic cytokine storm in some patients with COVID-19 [1]. Often referred to as Cytokine Release Syndrome (CRS), this storm is due to the release of high levels of pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF), chemokines by respiratory epithelial, dendritic cells, and macrophages. The surge of pro-inflammatory cytokines has the potential to contribute to the multitude of pathological changes seen in severe COVID-19 patients (Figure 1).

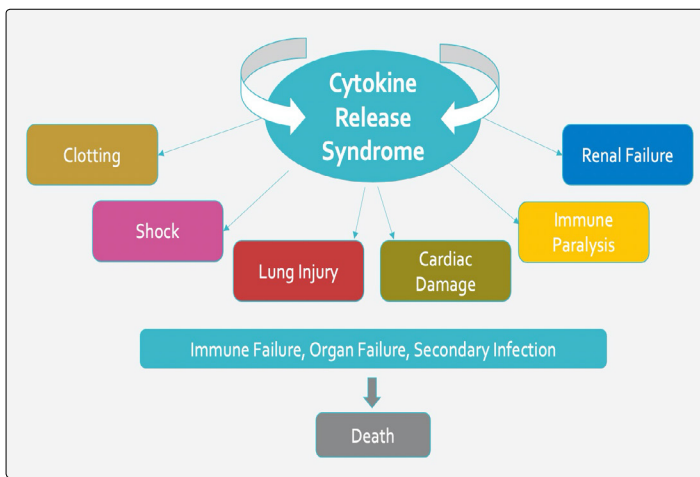


Figure 1: Potential negative impact of cytokine release syndrome.

We hypothesize that CRS can be dampened with a subsequent improvement in the patient's clinical outcome by activating the vagal-driven cholinergic anti-inflammatory pathway (CAP).

The CAP is a neural reflex capable of decreasing the release pro-inflammatory cytokines and is modulated by the vagus nerve. Electric neuromodulation of the vagus nerve inhibits the synthesis of TNF during endotoxemia, ischemia/reperfusion injury, hemorrhagic shock, septic peritonitis, and other excessive cytokine disorders [2-6].

Vagus nerve stimulation (VNS) has the potential to play an important role in the management of patients with SARS-CoV-2 infection [6]. The vagus nerve widely innervates multiple organs, especially the lungs and gastrointestinal tract. When the electrical stimulation is applied transcutaneously at the ear (taVNS), afferent fibers are stimulated thereby activating the central autonomic network and resulting in activation of the efferent fibers of both the right and left vagus nerves as well as sympathetic fibers within the spinal cord and potential activation of the HPA axis. The cumulative effect of taVNS is the improvement of the inflammatory modulation [6]. taVNS therapy is uncomplicated, safe, inexpensive and treatment might suppress the CRS enough to improve the clinical course in COVID-19 patients with symptoms severe enough to require hospitalization. (Figure 2)

An observational trial was designed to explore the safety and potential benefit of transcutaneous auricular vagus nerve stimulation in hospitalized patients infected with COVID-19. An interim safety and efficacy analyses were performed after enrollment of the first 25 patients.

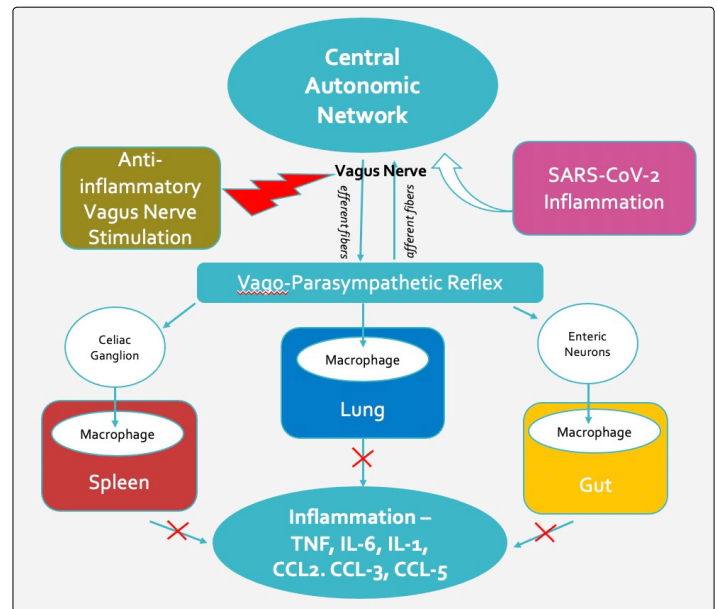


Figure 2: Potential beneficial effect of vagus nerve stimulation in COVID-19 patients.

Methods

Study Design and Participants

This is an open-label, an observational trial designed to see if taVNS stimulation was safe and might improve clinical outcomes for patients hospitalized with COVID-19 pneumonia. The protocol was approved by the ethical committee of Hospital Zonal Virgen del Carmen de Zárate, Zárate, Buenos Aires, Argentina. Written informed consent was obtained from all individuals before enrollment.

Eligible subjects are 18 years old or older, have a positive or presumed positive test for SARS-CoV-2, and require hospitalization for symptoms consistent with COVID-19 pneumonia. Study enrollment began in July 2020 with a planned minimal enrollment of 50 subjects. The interim analysis was performed after 25 patients were enrolled in the study.

Inclusion Criteria:

1. Patient older than 18 years of age
2. Tested positive or suspected/presumed positive for SARS-CoV-2 infection
3. Patients requiring hospital admission with evidence of pneumonia and/or pneumopathy
4. Patients showing fever or respiratory symptoms with radiological findings of pneumonia or pneumopathy
5. Respiratory distress (≥ 30 breaths/min) or Oxygen saturation $\leq 93\%$ at rest in ambient air; or oxygen saturation $\leq 97\%$ with $O_2 > 5L/min$.

6. The patient provides signed and witnessed Informed Consent

Exclusion Criteria:

1. Already enrolled in an experimental trial for SARS-CoV-2 or COVID-19 therapy
2. Potentially life-threatening heart rhythm
3. Pregnancy or potential pregnancy
4. Current implantation of an electrical and/or neurostimulator device, including but not limited to a cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant
5. History of an aneurysm, intracranial hemorrhage, brain tumors, or significant head trauma
6. Belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with the follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled, and prisoner)

Intervention with Vagus Nerve Stimulation

After obtaining written consent, patients were assigned to receive 5 minutes of transcutaneous vagus nerve stimulation (tVNS) with an electronic neuromodulation device (Vitality Smart cable, Nemechek Technologies, Figure 3). Stimulation parameters are 10 Hz, 800uS with the voltage set at 10v below the perception threshold) and was applied every 6 hours for up to 14 days.



Figure 3: Vitality Smartcable

The electrical stimulation was delivered through a small clip that makes contact within the concha and the back of the ear (Figure 4). The ear and the clip contact points are cleaned with an alcohol

swab before each treatment. After placement of the clip, the voltage was slowly increased until the subject could perceive the current. The voltage was set just below the level of perception by slowly reducing the current until it was no longer detectable by the subject.



Figure 4: Concha Clip Placement

All other therapies (antivirals, steroids, immunoglobulin) as determined by the managing physician were allowed.

Outcomes Measures

Primary outcome measures are as follows:

1. **Survival without the need of mechanical ventilation at day 14. [time frame: 14 days from symptom onset] is to be considered a positive outcome.**
 1. Patients in need of mechanical ventilator utilization (including non-invasive Ventilation, NVI), or death will be considered a negative outcome.
 2. New do not resuscitate (DNR) orders will be considered a negative event at the date of the DNR.
2. **Survival [time frame: 14 days]**
 1. Overall survival
3. **Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48 h) at day 14 [time frame: 14 days].**
 1. Death or DNR order will be considered a competing negative event.

Results

Study Participants

Between July 7 and August 25, 25 subjects (17 men and 8 women) with a mean age of 52 years (22-80) were enrolled in the study.

The majority of subjects had comorbidities that included hypertension (60%), diabetes (28%), cardiovascular disease (8%), obesity (16%), and chronic kidney disease (8%) (Table 1).

Eighteen subjects (72%) were treated with tVNS 4 times per day for 5 minutes while an additional 7 subjects (28%) received tVNS only twice daily during their hospital stay.

In addition to tVNS, all subjects received oxygen and dexamethasone and 4 subjects (16%) received hyperimmune globulin as the only other forms of an investigational therapy for COVID-19. The mean oxygen saturation level on admission was 93.4% [range 87-98%] and oxygen saturation levels reached a low mean of 89.9% [range 83-97] during the hospitalization.

Table 1: Comparison of survivors and non-survivors.

	Survivors (%)	Non-Survivors (%)
Of Total Patients	21 (84)	4 (16)
Rec'd VNS	21 (100)	4 (100)
Admission O2 sat%, Mean	85-97% [mean 93.4]	87-98% [mean 93.7]
No Mech. Vent.	20 (95.2)	3 (75)
Rec'd Mech. Vent.	1 (4.7)	1 (25)
Co-Morbidity		
Obesity	4 (19)	-
Diabetes Mellitus	5 (23.8)	2 (50)
Hypertension	14 (66.7)	2 (50)
CAD/CVA	2 (9.5)	-
Renal	2 (9.5)	-
Asthma/COPD	2 (9.5)	1 (25)
HIV	-	1 (25)

Survival

Of the initial 25 subjects treated with tVNS, 84% (n=21) survived with only 4.8% (n=1) of the survivors requiring mechanical ventilation. Of the 4 non-survivors, only 2 died from respiratory failure felt to be attributed to COVID-19 pneumonia and only 1 of the 2 received mechanical ventilation. The other 2 non-survivors died from diabetic ketoacidosis and bacterial septicemia felt to be related to advanced AIDS. (Table 1)

Of the 21 survivors, 95.2% (n=20) did so without the need for mechanical ventilation. There was no significant difference in the oxygen saturation levels at the time of admission between survivors on non-survivors. Survivors had more comorbid diagnoses than non-survivors, but the numbers are too small to draw any statistical conclusions.

Mechanical Ventilation

Patients treated with tVNS had a very low need for mechanical

ventilation. Of all 25 subjects, only 2 (8%) received mechanical ventilation; 1 survived and the other did not. Of subjects not receiving mechanical ventilation, overall survival was 86.9%. (Table 2) There was no significant difference in the oxygen saturation levels at the time of admission between survivors on non-survivors.

Both survivors and non-survivors had comorbid diagnoses, but a higher number of comorbid conditions were seen in those not requiring mechanical ventilation.

Table 2: Comparison of patients requiring or not requiring mechanical ventilation.

	Mechanical Ventilation (%)	Non-Mechanical Ventilation (%)	Total (%)
All Patients	2 (8)	23 (92)	25
Survival - Day 14	1 (4.8)	20 (86.9)	21 (84)
Mortality	1 (50)	3 (13)	4 (16)
Admission O2 sat%	98%, 95%, [mean 96.5%]	85-97% [mean 93.4]	
Co-Morbidity			
Obesity	-	4 (17.4)	4 (16)
Diabetes Mellitus	-	7 (30.4)	7 (28)
Hypertension	2 (25)	14 (60.8)	16 (64)
CAD/CVA	-	2 (8.7)	2 (8)
Renal	-	2 (8.7)	2 (8)
Asthma/COPD	1 (12.5)	2 (8.7)	3 (12)

Adverse Events

Adverse events associated with tVNS occurred in only 2 subjects (8%) and consisted of oral paresthesia and orthostatic hypotension. Both of which resolved spontaneously and did not occur with the use of a lower voltage during subsequent treatments with vagal stimulation. Both patients with AE from tVNS survived.

Determination of outcome by gender, age, obesity, geographic region, and the presence of obesity or any other comorbid condition was not possible because of the small numbers of patients in the interim analysis.

Comparison to Other Cohorts

A control group is ideally used to provide a relative standard against which therapy is compared. Because of the outbreak of SARS-CoV-2 among hospital staff and the rapidly escalating number of SARS-CoV-2 cases arriving within the hospital, the study was modified to limited staff contact with infected patients unless clinically necessary and the control group was eliminated from the study.

As part of interim safety and efficacy analysis, a comparison to other reported cohort data on overall mortality and the frequency of mechanical ventilation is outlined. The data is stratified according to the number of hospitalized subjects reported for

each cohort.

Although our preliminary analysis details only treated patients, one can see that overall mortality is either lower or similar to other reported cohorts when vagus nerve stimulation is incorporated in the treatment regimen. (Table 3)

Table 3: Comparison of mortality and mechanical ventilation rates among other published cohorts.

Cohort	Number of Hospitalized Patients	Overall Mortality (%)	Require Mechanical Ventilation
Seattle, U.S. ⁸	24	12 (50%)	18 (75%)
Argentina - VNS	25	4 (16%)	2 (8%)
China ⁹	191	54 (28.2%)	32 (16.6%)
New York, U.S. ⁷	257	1010 (39%)	203 (79%)
New York, U.S. ¹¹	393	40 (10.2%)	130 (33%)
Louisiana, U.S. ¹⁰	1382	325 (23.5%)	364 (26.3%)
New York, U.S. ¹²	1999	292 (14.6%)	445 (22.2%)
United Kingdom ¹³	6678	2212 (33.1%)	497 (7.4%)
United States ¹⁴	11721	2514 (21.5%)	1967 (16.8%)

Regarding mechanical ventilation, the addition of vagus nerve stimulation early in the course of hospitalization was also associated with significantly fewer patients requiring mechanical ventilation when compared to these other cohorts.

Discussion

Electrical stimulation of the vagus nerve is capable of modulating the working point of the inflammatory response in a wide variety of potentially lethal medical conditions (endotoxemia, ischemia/reperfusion injury, hemorrhagic shock, septic peritonitis) [6-14]. Transcutaneous vagus nerve stimulation (tVNS) is a safe, rapid and technically simple process that if used early in the hospitalization potentially could improve the clinical outcome of COVID-19 patients.

Our study uses vagus nerve stimulation in COVID-19 in hospitalized patients requiring oxygen support or having respiratory distress early in the course of their hospitalization. After an analysis of the first 25 patients, tVNS is proving to be well tolerated and not seem to have any negative impact on mortality nor increase the need for mechanical ventilation.

More importantly when compared to other COVID-19 pneumonia cohorts, tVNS may improve both overall mortality and reduce the incidence of ARDS and mechanical ventilation. We believe it is imperative that all potential therapies against COVID-19 be thoroughly evaluated

The study is moving forward with a total enrollment of 50 subjects and we will publish these final results once all subjects have been

treated.

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