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Non-invasive Vagus Nerve Stimulation for COVID-19: Results From a Randomized Controlled Trial (SAVIOR I)

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Abstract

Background

Severe coronavirus disease 2019 (COVID-19) is characterized, in part, by an excessive inflammatory response. Evidence from animal and human studies suggests that vagus nerve stimulation can lead to reduced levels of various biomarkers of inflammation. We conducted a prospective randomized controlled study (SAVIOR-I) to assess the feasibility, efficacy, and safety of non-invasive vagus nerve stimulation (nVNS) for the treatment of respiratory symptoms and inflammatory markers among patients who were hospitalized for COVID-19 (ClinicalTrials.gov identifier: NCT04368156).

Methods

Participants were randomly assigned in a 1:1 allocation to receive either the standard of care (SoC) alone or nVNS therapy plus the SoC. The nVNS group received 2 consecutive 2-min doses of nVNS 3 times daily as prophylaxis. Efficacy and safety were evaluated *via* the incidence of specific clinical events, inflammatory biomarker levels, and the occurrence of adverse events.

Results

Of the 110 participants who were enrolled and randomly assigned, 97 (nVNS, $n = 47$; SoC, $n = 50$) had sufficient available data and comprised the evaluable population. C-reactive protein (CRP) levels decreased from baseline to a significantly greater degree in the nVNS group than in the SoC group at day 5 and overall (i.e., all postbaseline data points collected through day 5, combined). Procalcitonin level also showed significantly greater decreases from baseline to day 5 in the nVNS group than in the SoC group. D-dimer levels were decreased from baseline for the nVNS group and increased from baseline for the SoC group at day 5 and overall, although the difference between the treatment groups did not reach statistical significance. No significant treatment differences were seen for clinical respiratory outcomes or any of the other biochemical markers evaluated. No serious nVNS-related adverse events occurred during the study.

Conclusions

nVNS therapy led to significant reductions in levels of inflammatory markers, specifically CRP and procalcitonin. Because nVNS has multiple mechanisms of action that may be relevant to COVID-19, additional research into its potential use earlier in the course of COVID-19 and its potential to mitigate some of the symptoms associated with post-acute sequelae of COVID-19 is warranted.

Keywords: COVID-19, coronavirus, non-invasive vagus nerve stimulation, neuromodulation, respiratory symptoms, randomized control trial, biomarkers, inflammation