

# Oxygen saturation improved with nitrate-based nutritional formula in patients with COVID-19

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## Abstract

In this open-label case series trial, we evaluated the effects of a nitrate-based nutritional formula on oxygen saturation (SpO<sub>2</sub>) and patient-reported outcomes in individuals with coronavirus disease 2019 (COVID-19). Five adult patients (three men and two women, age 39.6 ± 6.9 years) with a positive COVID-19 test result, breathing difficulties, and SpO<sub>2</sub> ≤ 95%, who were free from other pulmonary and cardiovascular conditions, were recruited for this study. Participants were assigned to receive a multi-component nutritional formula (containing 1200 mg of potassium nitrate, 200 mg of magnesium, 50 mg of zinc, and 1000 mg of citric acid) every 4 hours during the 48-hour monitoring period. In all participants, SpO<sub>2</sub> improved immediately after administration of the nutritional formula, from 1 to 7 percentage points (mean increase 3.6 ± 2.7 points; 95% confidence interval 0.3 to 7.0). SpO<sub>2</sub> remained above baseline values throughout the monitoring interval, with values persisting over threshold values (>92%) for all patients and at each time point during the 48 hours. No patients reported any side effects of the intervention. These promising and rather unexpected results call for immediate, well-sampled, mechanistic randomized controlled trials to validate our findings.

## Keywords

Coronavirus disease 2019, nitrate, oxygen saturation, patient outcome, nutritional formula, respiratory

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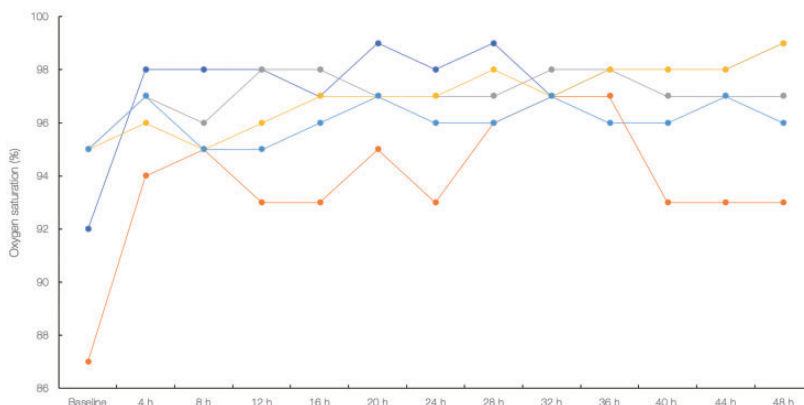
Coronavirus disease (COVID-19) is a novel respiratory infectious disease caused by a newly identified strain of coronavirus. Serious cases of COVID-19 are often characterized by respiratory distress and low oxygen saturation ( $\text{SpO}_2$ ).<sup>1</sup> Several therapeutic options are now available to tackle low  $\text{SpO}_2$  in hypoxemic patients with COVID-19,<sup>2</sup> yet most of these patients require advanced instrumentation and in-hospital supervision. Although nutritional ingredients have been shown to improve tissue oxygenation in HIV infection,<sup>3</sup> no studies to date have evaluated their effects in the population with COVID-19 infection or with respect to blood oxygen levels. Still, promising effects of nitrate-based nutritional formula have been demonstrated in other pulmonary diseases, including cystic fibrosis,<sup>4</sup> pulmonary arterial hypertension,<sup>5</sup> and acute respiratory failure,<sup>6</sup> although no indices of blood  $\text{SpO}_2$  levels have been measured in the above studies. In this open-label case series trial, we evaluated the effects of a nitrate-based nutritional formula on peripheral  $\text{SpO}_2$  and patient-reported outcomes in individuals with COVID-19 infection.

Written informed consent was obtained from all patients. The study protocol was approved by the institutional review board at the University of Novi Sad

(46-06-01/2020-1/1), and the study was performed in accordance with the principles laid out in the Declaration of Helsinki.

Five adult patients (three men and two women, age  $39.6 \pm 6.9$  years) with positive COVID-19 test results, breathing difficulties, and  $\text{SpO}_2 \leq 95\%$ , who were free from other pulmonary and cardiovascular conditions, were recruited in this study. The participants were assigned to receive a multi-component nutritional formula (containing 1200 mg of potassium nitrate, 200 mg of magnesium, 50 mg of zinc, and 1000 mg of citric acid) every 4 hours during the 48-hour monitoring period. No other treatments for improvement in  $\text{SpO}_2$  were administered during the trial.  $\text{SpO}_2$  and patient-reported outcomes were evaluated at baseline (pre-intervention) and at each 4-hour time point throughout the trial.

In all participants,  $\text{SpO}_2$  improved immediately after administration of the nutritional formula, from 1 to 7 percentage points (mean increase  $3.6 \pm 2.7$  points; 95% confidence interval 0.3 to 7.0).  $\text{SpO}_2$  remained above baseline values throughout the monitoring interval, with values persisting over threshold values ( $>92\%$ ) for all patients and at each time point during the 48 hours (see Figure 1). This was accompanied by a reduction in cough, breathing



**Figure 1.** Individual changes in oxygen saturation during the trial. Each color represents a different patient.

difficulties, and chest pain in one patient (women, age 39 years), attenuated diarrhea in another patient (man, age 38 years), and a decrease in fatigue and headache in a third patient (women, age 35 years). No patients reported any side effects of the intervention.

The favorable effects of the potassium nitrate-based nutritional formula administered in this preliminary trial among patients with COVID-19 might be owing to the formula-driven instant production of nitric oxide that stimulates vasodilation and better oxygen delivery to the peripheral tissues,<sup>3</sup> and/or a contraction of the spleen, which serves as a dynamic red blood cell reservoir that can be mobilized and facilitate oxygen transport.<sup>7</sup> The immediate effects of the multi-component formula were rather surprising, as dietary nitrate requires at least an hour to show any known biological effects in humans, with the peak effect usually reported after 180 minutes.<sup>4-6</sup> In addition, this nitrate-based nutritional formula appears to be comparable to conventional therapy in treating low SpO<sub>2</sub> caused by COVID-19. The increase in oxygen concentrations seen in patients with COVID-19 on oxygen therapy (1–6 L/minute) was approximately 4% with each liter of O<sub>2</sub> per minute,<sup>8</sup> which is similar to findings reported in our trial (mean SpO<sub>2</sub> increase = 3.6%). These promising and rather unexpected results call for immediate, well-sampled, mechanistic randomized controlled trials to validate our findings. If confirmed, a nutritional formula containing nitrates might emerge as a convenient and competitive solution that improves low SpO<sub>2</sub> in COVID-19, which can perhaps enable the management of some patients outside of the hospital.

### Authors' contributions

All authors had access to the data and had a role in writing this manuscript.


### Declaration of conflicting interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SMO, AM, and PD declare no conflicts of interest. AN is an employee of ThermoLife International LLC, who developed the nutritional formula used in this study.

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