



Hyperbaric oxygen therapy to reverse post-COVID cognitive impairment

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Received: 26 July 2022 / Accepted: 20 August 2022 / Published online: 26 August 2022
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We compliment García-Grimshaw et al. [1] for performing and reporting their prospective study, which developed a multivariate causal model to investigate the relationships between hypoxemia severity at hospital admission and several COVID-19-associated variables, and their effects on post-COVID cognitive performance, in patients hospitalized with COVID-19. From the study [1], a positive direct relationship was observed between the partial pressure of arterial oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio on admission and post-COVID cognitive performance ($\beta=0.24$, $P=0.010$). In addition, COVID-19 patients with hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg) demonstrated significantly poorer post-COVID cognitive performance compared to their counterparts who were without hypoxemia ($\text{PaO}_2/\text{FiO}_2 > 300$ mmHg) at hospital admission.

The authors did not discuss the clinical implications of these findings in the article. Since the study [1] highlights the central role of hypoxemia in the pathophysiology of post-COVID cognitive impairment in patients with COVID-19, we believe the intervention to post-COVID cognitive impairment should be based on the improvement of tissue oxygenation, which can be directly achieved by oxygen therapy. Early oxygen therapy in patients with COVID-19 may be beneficial to prevent the development of post-COVID cognitive impairment, but most commonly, patients with COVID-19 receive oxygen therapy in the later stage of the disease upon presentation in the healthcare facilities, where tissue

hypoxia has already occurred [2]. Therefore, the research focus should be placed on restoration of tissue oxygenation after the development of tissue hypoxia, which can be achieved with hyperbaric oxygen therapy.

Hyperbaric oxygen therapy involves inhaling 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA), which aims to enhance the amount of oxygen dissolved in the body tissues. Even before the COVID-19 pandemic, evidence has been accumulated about the neuroplasticity effects of hyperbaric oxygen therapy, where the combined action of hyperoxia and hyperbaric pressure can improve tissue oxygenation by activating both oxygen- and pressure-sensitive genes [3]. It is evidenced that hyperbaric oxygen therapy, which explicitly utilizes the hyperoxic-hypoxic paradox through constant fluctuation in both pressure and oxygen concentrations, can induce gene expression and metabolic pathways involved in brain tissue regeneration. These pathways can promote neurogenesis and angiogenesis in injured brain tissue.

Hyperbaric oxygen therapy has been trialed in patients with COVID-19 with some success. In a case report [4] of a patient with post-COVID cognitive impairment, hyperbaric oxygen therapy led to improvements in brain perfusion and integrity of white matter brain microstructure, which are indicative of angiogenesis and neurogenesis, respectively. The patient also demonstrated improvement in cognitive performance after hyperbaric oxygen therapy [4]. Recently, a small-scale randomized controlled trial [5] of hyperbaric oxygen therapy in patients suffering from post-COVID-19 condition adds to the growing positive evidence of the intervention. There was a significant group-by-time interaction in the cognitive performance in patients randomized to hyperbaric oxygen therapy compared to patients randomized to sham therapy, which was accompanied by significant improvement in brain MRI perfusion and microstructural changes in frontal, parietal, and limbic regions of the brain involved in cognitive roles [5].

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Based on the discovery that hypoxemia is the main driver of post-COVID cognitive impairment in patients with COVID-19, we believe larger scale trials should be performed to investigate the use of hyperbaric oxygen therapy in patients suffering from post-COVID cognitive impairment, especially when evidence to date has been reassuring. In fact, interventions for the post-COVID condition should not be sidelined since the post-COVID condition has been associated with deterioration in the quality of life, particularly the frail elderly patients who are more susceptible to post-COVID cognitive impairment [6].

Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

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