Recovery of Four COVID-19 Patients via Ozonated Autohemotherapy

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an en-\v{v}olved RNA betacoronavirus,\(^1\) that has spread globally since December 2019. As of July 22, 2020, more than 14,000,000 confirmed cases and 607,781 deaths from COVID-19 have been reported to the World Health Orga\n\v{n}ization from 216 areas and territories.\(^2\) Patients with more prominent lab\r\ary abnormalities may develop acute respiratory distress syndrome (ARDS), which potentially leads to multiple organ failure and death.\(^1,3\) Howev\r\er, at present, there are no regulatory approved antiviral medicines, vaccines, or specific clinical treatments for COVID-19.

Ozonated autohemotherapy has been reported to improve blood flow and tissue oxygenation to vital organs (Figure 1).\(^4\)–\(^6\) It also appears to stimulate the innate immune system by inducing the activation of nuclear factor activated T-cells (NFAT) and Activated Protein-1 (AP-1) signaling pathways,\(^5\) be\\nsides being a strong anti-inflammatory and antioxidant molecule.\(^5\) Early studies on severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have shown increased amounts of proinflammatory cytokines and extensive lung damage in both SARS-CoV and MERS-CoV patients.\(^6,7\) These findings indicate that ozonated autohemotherapy may be a new strategy to treat patients infected with betacoronaviruses. Therefore, we present, for the first time, a case series of 4 patients with different disease severities for whom ozonated autohemotherapy was performed once a day to stimulate antioxidative and anti-inflammatory fields and pleural effusion. While the patient was resting in bed, arterial blood gas analysis showed a partial pressure of arterial oxygen (PaO\(2\)) of 106 mm Hg, respectively. After 3 more treatments on 2 consecutive days, blood analysis showed a partial pressure of arterial oxygen (PaO\(2\)) to the fraction of inspired oxygen (FiO\(2\)) (PaO\(2\)/FiO\(2\) [P/F] ratio) of 80 mm Hg. Ozonated autohemotherapy was administered to improve oxygen delivery and correct the hypoxemia. Ten minutes after the ozonated autohemotherapy was initiated, the P/F ratio increased to 192 mm Hg. The arterial blood gas analysis was tested at 2 h and 9 h after the first session of ozonated autohemotherapy, and the measured P/F ratios were 118 mm Hg and 106 mm Hg, respectively. After 3 more treatments on 2 consecutive days, the chest X-ray image showed improvement of the pulmonary lesions, and there were further improvements after all 9 treatment sessions had been completed (Figure S1). In patient 2 (severe) and patients 3 and 4 (moderate disease), P/F ratios were within the normal range. Ozonated autohemotherapy was performed once a day to stimulate antioxidative and anti-inflammatory responses. The clinical symptoms of these 3 patients were continually monitored, and the ozonated treatments were stopped and they were switched to oral medication and symptomatic treatment when their symptoms diminished. However, their P/F ratios did not improve markedly with the ozonated autohemotherapy treatments, but they did decrease. The exact therapeutic mechanism, antiviral effects, and the population in which this therapy is suitable for use should be further studied. This may help in
the complete utilization of ozonated autohemotherapy treatment in COVID-19 patients.

Furthermore, the younger sibling of our critically ill patient 1 (patient 5, a 53-year-old man), was diagnosed with COVID-19 and admitted to our hospital along with patient 1. Like patient 1, patient 5 was also treated with antiviral agents and steroids, but developed severe ARDS with a P/F ratio of 82 and a CT score of 6/20 on hospital day 7 (Figure S2). Patient 5 was then admitted to the ICU and received mechanical ventilation (MV) through an endotracheal tube and was on extracorporeal membrane oxygenation (ECMO) support. After 11 days of ECMO support, the refractory hypoxemia was resolved. Patient 5 continued treatment with MV until it was withdrawn on hospital day 29. After spending 18 days in the ICU, patient 5 was transferred to the COVID-19 general ward. He was then officially discharged to his home after spending a total of 56 days in the hospital. In this case series, these 2 critically ill patients (1 and 5) were siblings. They contracted the virus together and were admitted to the same hospital on the same day and received the same antiretroviral therapy. However, different lung protection treatments, ozonated autohemotherapy and ECMO, respectively, were initiated. The length of stay in the ICU (10 days) and length of stay in the hospital (30 days) were both significantly shorter for patient 1, who was treated with ozonated autohemotherapy. Furthermore, the overall medical cost for patient 1 was $15,467 USD, but for his younger sibling patient 5 with ECMO and MV treatment, the overall hospitalization cost was $139,935 USD.

The combination of ozonated autohemotherapy with antiretroviral therapy in this case series of 4 patients with COVID-19 with varied disease severities led to improvement of the expression of infection-related biomarkers, which may have resulted from the stimulation of the innate immune system by ozone. All 4 patients who received ozonated autohemotherapy, including the critically ill patient 1, patient 2 (severe), and patients 3 and 4 (moderate), were discharged from the hospital, and their durations of hospitalization were 30, 18, 13, and 27 days, respectively. All patients revisited the hospital after 1 month, and their CT scans showed that most of the lung lesions had resolved (Figures S1 and S3). Overall, there were no abnormalities in the follow-up visit after ozonated autohemotherapy administration, indicating that it is a safe treatment for COVID-19 patients.

We, thus, report the successful use of ozonated autohemotherapy to treat 4 COVID-19 patients, including 1 critically ill patient. Although the exact mechanism of action of ozonated autohemotherapy is less well characterized, amelioration of inflammation and tissue damage could play critical roles. Furthermore, ozonated autohemotherapy is not only a safe procedure without reperfusion damage but also a much more economical and practical treatment, and this may, thus, benefit the global COVID-19 patient population with refractory hypoxemia.

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SUPPLEMENTAL INFORMATION
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