Therapeutic plasma exchange as a rescue therapy in patients with coronavirus disease 2019: a case series

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Introduction In December 2019, a group of patients with pneumonia was suddenly reported in Wuhan, Hubei, China. Chinese etiologists attributed these cases to a new virus belonging to the Betacoronavirus genus. This enveloped virus has positive-sense RNA and belongs to the Coronaviridae family. On January 12, 2020, the World Health Organization named this new virus the “2019-novel coronavirus” (2019-nCoV). The first cases in Iran were reported in Qom in February 2020, and soon after, positive cases increased rapidly all over Iran.

This infection has a wide range of clinical manifestations which usually include cough, fever, shortness of breath, and impairment of smell and taste. Coronavirus is one of the pathogens that mainly affect the respiratory system. Most patients experience lymphopenia and thrombocytopenia.

The immune response is crucial for controlling and removing coronavirus disease 2019 (COVID-19), but the uncontrolled response of the immune system to the virus can also play an emerged role in the pathogenesis of the disease. In critically ill patients, elevated levels of proinflammatory cytokines including interleukin (IL) 2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon γ-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and tumor necrosis factor α have been reported, and a cytokine storm may play a significant role in the pathogenesis of severe acute respiratory syndrome virus 2. Moreover, it can lead to complications such as acute respiratory distress syndrome (ARDS), respiratory failure, shock, and death.

Hence, effective treatment should include a strategy to suppress the inflammatory response, stop virus replication, and remove pre-made cytokines. Therapeutic plasma exchange seems to be an attractive strategy to solve this problem. In 2009, Patel et al. used therapeutic plasmapheresis to treat 3 children infected with who did not respond to traditional therapy. In this case series, it was reported that, with the elimination of the cytokine storm, acute lung injury was controlled and all 3 children survived.

We report a case series of 8 patients with COVID-19, who were in septic shock stage and had ARDS, undergoing therapeutic plasmapheresis, corticosteroid therapy, and interferon administration.
Chest computed tomography (CT) scans of patient no. 2 and no. 7 are shown in Supplementary material, Figure S1 and S2.

Regarding these findings, in order to suppress the cytokine storm, patients were treated with plasmapheresis. The plasmapheresis protocol was 2 l of filtration daily, compensated with 4 units of fresh-frozen plasma, 5 vials of albumin, and one or two 10–20 CC calcium gluconate (20%), depending on the patient's serum calcium level. The remaining volume was replaced with normal saline, according to the patient volume status.

Plasmapheresis has potential side effects, including nonplasma fluid replacement complications, red blood cell reactions to plasma donors, and complications during apheresis. Replacing fluids can cause hypocalcemia; this will be followed by symptoms such as paresthesia, nausea and vomiting, muscle cramps, chest pain, hypotension, and, in extreme cases, tetany or arrhythmias such as QT prolongation. Replacement with nonplasma fluids can also cause hypokalemia, decreased coagulation factors, and immunoglobulins; and the reaction of red blood cells to donor plasma may lead to anaphylactic shock.

We would have stopped plasmapheresis if there had been any change in the patient's condition or if we had observed any red flags (eg, dyspnea, seizures, chest pain, hypotension not responsive to 1 or 2 fluid boluses). Patients' vital signs were checked every 10 to 15 minutes during apheresis. With careful monitoring, none of the patients had any side effects from plasmapheresis.

Our first experience was patient no. 1, who unfortunately died. The cause of the patient's death, in our opinion, was the late onset of plasmapheresis and the patient's critical condition. We attempted to start plasmapheresis earlier in the other 7 patients, if they showed hypoxemia despite corticosteroid therapy. Patients' respiratory status improved dramatically after plasmapheresis. Patients no. 2 to no. 8 were hospitalized between 8 to 22 days after the onset of symptoms and were discharged after partial remission. We described the demographic information and clinical status of these patients before and after plasmapheresis in Table 1. Chest CT of patients no. 2 and no. 7 after plasmapheresis are shown in Supplementary material, Figure S3 and S4.

At 2-week follow-up, 5 patients had no clinical issues and 2 patients had received medications for hyperglycemia.

Discussion In this case series, we reported 8 patients who had unacceptable respiratory status despite antiviral and corticosteroid therapy, and they were treated with therapeutic plasmapheresis. Patients' respiratory status improved significantly after plasmapheresis and patients' chest CT scans showed a significant reduction in pulmonary involvement. At 2-week follow-up, most of them had no clinical issues and showed no clinically important symptoms related to COVID-19. This treatment modality was lifesaving for our patients who were in critical condition. It suppressed the cytokine storm and reduced the inflammatory status and helped the patients to defeat COVID-19.

The process that causes the death of patients does not seem to be viremia at all, but the activation of the cytokine cascade. We have come up with a 3-stage approach; in our view, the omission of any of these stages will lead to failure of treatment in critically ill patients.

The first stage is the reduction of virulence, in which we use different antivirals. We added interferon to the recommended treatment; we now have newer antivirals that we will use in the future.

The second stage is the reduction of cytokine production. We used corticosteroids despite the seemingly false initial ban (which was based on early advice and data on the disease); which also had good results. We now use tocilizumab.

The third stage is the elimination of cytokines produced that we performed in plasmapheresis patients. We have obtained good results from combining these 3 aspects and we advise physicians to use this approach to manage critically ill patients. What is important in this approach is the timing schedule of each of the stages and how to combine them.

In previous similar studies, Kawashima et al used therapeutic plasma exchange to treat patients with severe influenza virus infection. In these studies, after routine antiviral and corticosteroid treatments, patients still were in critical condition, therefore therapeutic plasma exchange was performed in them. This intervention significantly improved the patient's clinical condition. In another investigation, Liu et al performed a similar intervention on different subtypes of influenza virus, the avian influenza A (H7N9). They thought that hypercytokinemia played a major role in the pathogenesis of this virus, therefore, they performed plasma exchange and continuous venovenous hemofiltration to remove inflammatory mediators in critically ill patients who were infected with H7N9. This intervention reduced the level of cytokines and saved the lives of those patients. Both of these studies illustrate well the role of cytokine depletion and inflammation suppression in the treatment of patients with serious viral infections. The result of our study is in line with the results from the previous studies.

The pathogenesis of COVID-19 is not completely understood; however, recent studies have shown that host defense and the initiation of a cytokine cascade may play an important role in creating life-threatening clinical conditions, such as ARDS. From this perspective, therapeutic approaches that can help reduce or eliminate the over-production of inflammatory mediators and cytokines may be useful in patients with serious clinical condition. Therapeutic plasma exchange helps to alleviate
TABLE 1 Patients’ demographic information and clinical status before and after plasmapheresis

<table>
<thead>
<tr>
<th>Patient, no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Comorbidities</th>
<th>Corticosteroid therapy, d</th>
<th>Respiratory status before plasmapheresis</th>
<th>Plasmapheresis sessions, n</th>
<th>Respiratory status after plasmapheresis</th>
<th>Hospitalization length, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>70</td>
<td>Hypertension 6</td>
<td>Endotracheal intubation</td>
<td>3</td>
<td>Died after the third session</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>55</td>
<td>Diabetes 4</td>
<td>O2 saturation was 78% while receiving 10 l of O2/min with oxygen mask with reservoir bag</td>
<td>5</td>
<td>O2 saturation 94% on room air</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>64</td>
<td>Diabetes 5</td>
<td>O2 saturation was 78% while receiving 10 l of O2/min with oxygen mask with reservoir bag</td>
<td>4</td>
<td>O2 saturation 95% on room air</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>30</td>
<td>Without comorbidity 1</td>
<td>Endotracheal intubation on admission</td>
<td>4</td>
<td>Extubated after the second session and O2 sat 95% on room air at discharge</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>34</td>
<td>Without comorbidity 4</td>
<td>Endotracheal intubation on admission</td>
<td>5</td>
<td>Extubated 2 days after the fifth session, O2 saturation 95% on room air at discharge</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>54</td>
<td>Without comorbidity 5</td>
<td>O2 saturation was 79% while receiving 10 l of O2/min with oxygen mask with reservoir bag</td>
<td>4</td>
<td>O2 saturation 91% on room air</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>24</td>
<td>Without comorbidity 1</td>
<td>O2 saturation was 80% while receiving 10 l of O2/min with oxygen mask with reservoir bag</td>
<td>4</td>
<td>O2 saturation 96% on room air</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>52</td>
<td>Without comorbidity 5</td>
<td>O2 saturation was 77% while receiving 10 l of O2/min with oxygen mask with reservoir bag</td>
<td>4</td>
<td>O2 saturation 96% on room air</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: O2, oxygen

the inflammatory status of the patient and repair organ damage due to the overreacting of host defense by removing inflammatory mediators and suppressing cytokine storm.

Our first patient died after the third plasmapheresis session. We think it was due to his poor condition and late onset of plasmapheresis. According to our hypothesis, inflammatory mediators and cytokines were given the opportunity to cause severe damage to vital organs, and that damage was irreparable with plasmapheresis. The next 7 patients recovered and we consider this experience as a therapeutic option to treat similar patients.

We had several limitations in this case series. We had few cases without control groups. The next limitation is that it is unclear if these patients could improve without therapeutic plasma exchange or not, although the dramatic changes in clinical status and CT scan result represented encouraging findings. Patients received therapeutic plasma exchange on different days of hospitalization and corticosteroid treatment, hence it cannot be determined whether the plasma start time had any effect on the outcome or not.

We will continue to improve this experience by trying to remove the limitations and will publish the results. We hope, following this initial encouraging study, that other physicians would consider this approach in therapy of their patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available with the article at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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REFERENCES


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