



Efficacy of Plasmapheresis and Immunoglobulin Replacement Therapy (IVIg) on Patients with COVID-19

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Abstract

Since the rapidly evolving outbreak of COVID-19, several empirical therapeutic options have been recommended including the use of antivirals, steroids, and vaccines. According to recent observations about different modalities in treatment of patients infected with COVID-19, plasmapheresis and intravenous immunoglobulin (IVIg) have been reported to be an effective empirical therapeutic option to control the infection. In this review, we aimed to provide an overview on the possible application of plasmapheresis and intravenous immunoglobulin in patients with COVID-19.

Keywords COVID-19 · Coronavirus · Treatment · Plasmapheresis · Intravenous immunoglobulin

Introduction

In December 2019, a new member of the coronaviruses emerged in Wuhan, China. The World Health Organization (WHO) declared this novel coronavirus as a “Public Health Emergency of International Concern (PHEIC)” in January 31, 2020. The WHO officially named the 2019-nCoV as coronavirus disease 2019 (COVID-19) in Geneva, Switzerland. According to the WHO reports, the clinical spectrum of SARS-CoV-2 is wide and can be classified in 3 groups: patients with asymptomatic infection (mild type) with upper respiratory tract distress, patients with pulmonary infiltration (common type), and patients with severe signs that need intubation and intensive care (severe type).

To date, several empirical therapeutic options have been recommended, including generation of antivirals, steroids, and vaccines. However, the optimal and definite treatment strategy is not yet determined. According to the medical experiences in the treatment of patients infected with other

members of coronavirus family such as SARS-CoV and MERS-CoV, plasmapheresis and intravenous immunoglobulin (IVIg) have been reported to be an effective empirical therapeutic option to control the infection [1–7]. The aim of the present review was to evaluate the current evidence regarding the efficacy of plasmapheresis and IVIg in the management of patients with COVID-19.

SARS-CoV-2

Coronaviruses (CoVs) as a member of the Coronaviridae family comprised large, single, and positive-sense RNA categorized into 4 subgroups: alpha, beta, gamma, and delta CoVs [8, 9]. Among these 4 subgroups, 6 human CoVs (HCoVs) have been identified that can cause infection in human: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) [10]. In addition, SARS-CoV and MERS-CoV belong to the beta CoVs [11].

The first emergence of SARS-CoV was observed in 2003 in China, Guangdong Province, and later spread in 37 countries with a case fatality rate of 9% [12]. The novel coronavirus (2019-nCoV) that was first reported in Wuhan, China, also belongs to the beta CoVs based on viral genome assessment by the phylogenetic analysis [13, 14]. The genome sequence shared many identical sequences to SARS-CoV with almost 79.6% similarity. Also it has been revealed that COVID-19 is 96% identical at whole genome level to bat coronavirus [14].

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Plasmapheresis

Plasmapheresis involves separating the liquid part of the blood or plasma from the blood cells. There are fundamentally two different ways for plasmapheresis: centrifugation or membrane filtration. With centrifugation apheresis, the major blood components get separated into layers. The major advantage of this method is that there is no limit in the size of the molecules being removed. On the other hand, membrane filtration plasmapheresis is another option where its major disadvantage is the size of the molecules removed that has been limited by the size of the pore of the filter. This feature could be problematic as seen with the ultra-large von Willebrand factor multimers that can measure up to 12 million daltons [15]. Moreover, another potential disadvantage is the activation of the complement and leukocytes by the artificial membrane and the need for a central large-bore catheter to obtain the adequate blood flow [16].

The first reports of bloodletting began around 1000 B.C. in Egypt. Since antiquity, mankind believes in a bad component in sick patient's blood, called "humor." They believed that the removal of these humors that accumulate in blood makes patients feel better [15]. Nowadays, plasmapheresis is a great therapeutic way in such diseases such as myasthenia gravis, Guillain-Barre syndrome, and thrombotic microangiopathy. Moreover, plasmapheresis plays a major role in renal diseases. The pathologic factors that may be removed with plasmapheresis are including autoantibodies, complement products, lipoprotein, immune complexes, cryoglobulin, myeloma protein, ADAMTS-13, protein-bound toxins, cell platelets, and WBC [17].

Experiences with the Use of Plasmapheresis Against Coronavirus

It has been well-described that the "cytokine storm" plays an important role in the pathophysiology of the COVID-19 in critically ill patients [18]. Patients' condition may become deteriorated and require ICU admission along with mechanical ventilation support. Reports have shown that ICU patients have significant higher levels of cytokines and chemokine in their blood [19–23]. The first signs of the cytokine storm (define as decrease in blood oxygenation, declined lymphocyte count over time, serum enzymes, elevated creatinine levels, and high levels of CRP) and endothelial dysfunction are trigger points in the patients' medical condition [24]. Several case reports have shown favorable results of using plasmapheresis (PE) and immunoglobulin replacement therapy (IVIG) on prevention of worsening the condition and recovering the lymphocyte count [4–6, 25]. Based on these reports, the administration of plasmapheresis and IVIG should

be promptly administered to COVID-19 patients in order to have the highest efficacy in their treatment [7, 26, 27].

A report from the People's Hospital of Guizhou showed that a 50-year-old woman with laboratory-confirmed COVID-19 infection underwent antiviral therapy and inhaled interferon- α 2b followed by lopinavir and ritonavir. On the 13th day of admission, the patient's condition deteriorated, so PE treatment with IVIG was initiated. After four times of PE, the patient made a prompt recovery (DOI 17) and finally discharged from hospital with obvious improvements of chest radiographic evidence [26]. The initiation time of plasmapheresis in patients with COVID-19 is very important in the following stages of the infection, and we can prevent the urgent need of mechanical ventilations and intensive supporting care.

Risks and Benefits

The benefit of plasmapheresis is that it has a very successful precedent as a treatment option for a wide range of medical conditions, including disorders associated with brain and nervous system, such as acute Guillain-Barré syndrome [28, 29], blood disorders, such as thrombotic thrombocytopenia, some kidney disorders, such as Goodpasture syndrome, and hyperviscosity disorder, such as myeloma. There are not many reports about the risks of the plasmapheresis because frequently it has been reported as a safe treatment option in many cases. The adverse side effects of plasmapheresis include fall in arterial blood pressure, arrhythmias, sensation of cold with elevated temperature, and paresthesia. With continuous observation in healthcare faculties, these side effects could be closely monitored and ensure patients' safety [30].

IVIG (Convalescent Sera)

Immunoglobulin replacement therapy or intravenous immunoglobulin (IVIG) is a kind of a therapeutic choice for patients with antibody deficiencies. IVIG is a blood product, prepared from the serum of 1000 to 15,000 donors per batch. IVIG is used at a replacement dose of 200–400 mg/kg body weight, for 3 weeks. In contrast, we have high dose IVIG (hdIVIG), given frequently at 2 g/kg/month. hdIVIG is used as an immunomodulatory agent in various immune and inflammatory disorders [31]. As the world confronting a pandemic due to SARS-CoV-2, immunoglobulin replacement therapy (IVIG) could be an ideal option for prevention and treatment of COVID-19 disease. With the sufficient number of patients recovered from COVID-19 disease, they can donate their immunoglobulin-containing serum. IVIG has been used in a wide range of conditions including heart failure, mycobacterial infection, adult respiratory distress syndrome, and Alzheimer's disease. In the clinical specialties, neurology,

nephrology, hematology, immunology, rheumatology, and dermatology are using the largest amount of IVIG. Intravenous immunoglobulin (IVIG), in a simple explanation, consists of 4 separate components: [1] Actions mediated by $F(ab')_2$ with anti-proliferative properties, apoptosis modulation and immunomodulation of inflammatory responses. [2] Fc receptor (FcR), inhibition of phagocytosis, inhibition of ADCC, [3] Action mediated by complement binding within the Fc fragment, and [4] substances other than antibodies in IVIg preparations [32].

In the 1890s, before the introduction of the antimicrobial chemotherapy, serum therapy was one the treatment options for a wide range of diseases. At first, serum therapy was introduced for treatment of diphtheria, but nowadays, it has made significant progresses in curing diseases [33, 34]. Currently, immunoglobulin replacement therapy (IVIG) is used to stem the outbreak of the viral diseases such as influenza [35], poliomyelitis [36], mumps [37], and measles [38, 39]. In the threatening outbreak of measles in 193 in a boy's preparatory school, convalescent measles serum was used prophylactically on 66 uninfected boys; according to the experiments, it was expected that 25% of the group develop measles but only 3 cases of measles subsequently developed in that group [39]. Eight relevant studies on 1703 patients in 1918 world pandemic of influenza H5N1, complicated with pneumonia, showed that patients who received influenza-convalescent human blood product may have experienced a significant lower mortality rate [40]. In 2009, during the outbreak of the influenza H1N1, a prospective cohort study was conducted based on experiences from treatment of Spanish influenza and H5N1 influenza patients with immunoglobulin replacement therapy, by recruiting 93 patients with severe H1N1 infection that requires intensive care. The study showed that plasma treatment had significantly reduced mortality rate (20.0% vs 54.8%). This study showed that the convalescent plasma reduced the respiratory tract viral load, serum cytokine response, and mortality [41]. For further examples, we can indicate the use of IVIG for Lassa fever [42], Ebola virus [43], and Junin virus (Argentinian hemorrhagic fever) [44].

Experiences with the Use of Plasmapheresis Against Coronavirus

SARS1 in 2003, Middle East respiratory syndrome (MERS) in 2012, and SARS-CoV-2 (COVID-19) are the three viral outbreaks of coronaviruses in the twenty-first century. However, COVID-19 was declared as a world pandemic in 2019. The SARS1 epidemic was contained, although MERS became endemic in the Middle East and made a second major outbreak in South Korea. During the SARS epidemic, a study in the Prince of Wales Hospital, Hong Kong, was conducted

on 80 patients to evaluate the efficacy of convalescent plasma therapy in patient with severe acute respiratory syndrome (SARS); the result showed that the patients given convalescent sera before day 14 of illness showed better results than those who received the therapy after day 14 [1]. Another study in Taiwan showed that using IVIG on 3 infected healthcare workers with coronavirus (SARS) resulted in a significant reduction in viral load and anti-SARS-CoV IgM and IgG increased in a time-dependent manner [45]. According to the reports, China has used immunoglobulin replacement therapy on several COVID-19 patients during the outbreak of this novel coronavirus which showed promising results [46].

Risks of immunoglobulin replacement therapy fall into 2 categories, known and theoretical. Known complications are associated with other infectious diseases during transferring of blood substances or reaction to serum constituents such as serum sickness. The theoretical aspect of passive immunotherapy involves the phenomenon of antibody-dependent enhancement of infection (ADE) [47]. Previous studies have shown that the antibodies target one serotype of virus but only subneutralize another, leading to ADE [48–50]. ADE can lead to worsened symptoms in secondary viral infection, causing major concern for epidemiology. ADE has been observed in coronavirus for decades, and now it is a concern that it can occur in SARS-CoV-2 [48]. Another potential risk factor for immunoglobulin replacement therapy usage in patients with COVID-19 may be due to mitigating antibody response that could interfere with establishing efficient immune responses against viremia. So, still there are vulnerable individuals to subsequent reinfection. If this risk proved real, the individual should be vaccinated against COVID-19 when a vaccine becomes available [47].

COVID-19 immunoglobulin replacement therapy can be used for both prophylactic and treatment of the disease [4, 5, 7]. In the prophylactic way, the benefit of IVIG is that it can prevent infection in the individuals such as healthcare workers or patients that are at increased risk of disseminated infection [51]. In the therapeutic way, a controlled clinical trial should be conducted to infer the efficacy of this approach.

Conclusion

Since December 2019, many countries have been confronting to a new member of coronaviruses that emerged in Wuhan, China. According to the reports, confirmed cases of COVID-19 rise rapidly during the last 5 months, although there is no effective vaccine or therapeutic drug available for COVID-19. Significant progresses have been made through finding an effective vaccine, and a number of them showed promising results. Our clinical spectrum and pathophysiological changes of this virus have increased significantly; however, high rate and absence of effective therapies, as our experience in both

SARS1 epidemic in 2003 and MERS in 2012, led to using plasmapheresis and immunoglobulin replacement therapy (IVIG) as a main therapeutic option after anti-viral therapy in countries such as China and Iran [46, 52]. As reports demonstrated, the best results of plasmapheresis and IVIG therapy are highly dependent on timing. Clinical observation has shown that COVID-19 has 3 phases in symptomatic cases: starting phase with subsequent viremia, the accelerating phase that is the vital phase of the infection, and the recovery phase with progressive lymphocytopenia and elevated inflammatory markers [7, 53, 54]. Several studies have also shown that the administration of IVIG and PE before day 14 of the illness could be associated with better outcomes [1, 7]. The main reason for this observation may be partly due to the fact that viremia develops within the first week of infection. Subsequently, the primary immune response first appears in the blood by day 10–14 and followed by viral clearance. Moreover, the cytokine storm and hyperinflammatory shock more commonly occur in the third week, and deleterious effect of COVID-19 is believed to be caused by overactive immune system in normal tissues. Thus, in theory, convalescent plasma could be most effective if administered in the early stages of infection in order to minimize the clinical deterioration of these patients. In conclusion, plasmapheresis and IVIG are now the favorable options for prevention and treatment of COVID-19 cases that can be rapidly available and has low side effects and risks. With the ongoing clinical trials (NCT04321421, NCT04457349, NCT04374539, and NCT04343755) in regard to the efficacy of plasmapheresis and IVIG on COVID-19 patients' outcome, the results will shed light on our understanding of the potential role of this treatment modality in the management of COVID-19.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Not applicable.

Informed Consent Not applicable.

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