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Review Article

Convalescent Plasma Therapy for COVID-19

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Introduction

A novel flu-like coronavirus emerged from Wuhan, China in December 2019. It was named Severe Acute Respiratory Syndrome Coronavirus 2, (SARS-CoV-2), and causes Coronavirus Disease 2019, (COVID-19) [1]. SARS-CoV-2 rapidly spread, and on March 11th, 2020, the WHO declared COVID-19 a pandemic [2]. As of July 3rd there have been 10,719,946 confirmed cases of COVID-19 worldwide, including 517,337 deaths, reported to the World Health Organization [3]. Many therapies are being investigated for their anti-viral or immune modulation properties to treat COVID-19, with efficacy so far being demonstrated for dexamethasone [4] and remdesivir [5]. In recent pandemics, no standardized treatments were identified for SARS-CoV-1, Middle East Respiratory Syndrome or Ebola, due to the limited number of controlled clinical trials undertaken at the time, with none performed on SARS-CoV-1, and only 3 and 11 for Middle East Respiratory Syndrome and Ebola, respectively [6]. However, this has been addressed for COVID-19, and there are currently 1,358 clinical trials registered with ClinicalTrials.gov, of which 209 are investigating the use of convalescent plasma to treat COVD-19 [7].

Principles of Convalescent Plasma

Convalescent plasma is plasma, obtained from patients who have recovered from an infectious disease such as COVID-19, which contains antibodies specific to the pathogen, in this case SARS-CoV-2. This passive immunotherapy works by neutralizing pathogens, thereby decreasing the likelihood of cytokine storm occurring in the recipients. Convalescent plasma has been used as a therapeutic agent for over a hundred years. One of its earliest interventions for treating viral diseases was the Spanish H1N1 influenza A in 1918. Since then it has been used to treat Avian H5N1 influenza A epidemic (2003), Severe Acute Respiratory Syndrome (SARS, SARS-CoV-1) epidemic (2003), H1N1 influenza pandemic (2009-10), Middle East Respiratory Syndrome (MERS-CoV) epidemic (2012), Chikungunya, Ebola epidemic (2014-16) and Zika [2,3].

Is Convalescent Plasma Efficacious?

While it is important to await the findings for the clinical trials, there is some evidence that this approach will be successful. A meta-analysis of 32 papers evaluating the efficacy of convalescent plasma in SARS Coronavirus patients, (699 treated versus 568 untreated controls), demonstrated a reduced mortality rate in the plasma arm, compared with placebo or no treatment (odds ratio: 0.25%; 95% CI: 0.14-0.45). However, many studies included in the meta-analysis were of poor quality, lacked control groups, and demonstrated moderate or high risk of bias [8]. A meta-analysis of the use of convalescent plasma in Spanish flu also demonstrated a reduced mortality rate [9]. There is some evidence about the efficacy of convalescent plasma from several uncontrolled case series of convalescent plasma use in COVID-19 patients. A case-series of 5 critically ill COVID-19 patients, aged 36-65 years, received convalescent plasma, with a SARS-CoV-2 specific IgG binding titre greater than 1:1000 and a neutralization titre greater than 40, on days 10-22 following admission. The results were encouraging, with normalization of body temperature occurring within 3 days in 4 of the 5 patients. In addition, viral loads decreased and acute respiratory distress syndrome also resolved in 4 patients, both within 12 days of the transfusion, and 3 patients no longer required ventilation within 3 weeks [10]. Duan *et al.* 2020 also reported an improvement in 10 severely affected patients who received convalescent plasma [11]. Viremia disappeared within 7 days, due to significantly increased or maintained high levels of neutralizing antibody. In addition, lymphocyte counts increased and C-reactive protein values decreased, in comparison to the pre-transfusion levels. There were also varying levels of adsorption of lung lesions.

Zhang *et al.* 2020 reported the outcomes in 4 critically ill COVID-19 patients, who received various quantities of convalescent plasma, (300, 400 and 2,400ml) [12]. All patients became RT-PCR negative within 3-22 days of receiving the transfusion. However, the contribution from other therapeutic agents administered could not be discerned. A retrospective, observational study involving a small number of participants was less promising. Despite, all 6 patients testing negative for SARS-CoV-2 RNA within 3 days of receiving the transfusion, 5 of them subsequently died. However, the patients who received plasma survived significantly longer than the control arm. The median day of transfusion was 21.5, and it was postulated this was too late to minimise the hyperimmune response, as the 1 patient who received treatment on day 11 survived [13]. Kong *et al.* 2020 reported a case of a centenarian, who demonstrated improved clinical and laboratory findings following 2 transfusions of convalescent plasma, and was successfully treated by this approach [14]. In the study by Ahn *et al.* 2020, 2 COVID-19 patients who presented with severe pneumonia and acute respiratory distress syndrome demonstrated improved oxygenation, and decreased viremia and inflammatory markers, after the use of methylprednisolone and convalescent plasma [15].

A systematic review of five studies evaluating convalescent plasma in COVID-19 patients demonstrated a reduced mortality rate in critically ill patients. In the majority of cases, an increase in the neutralizing antibody titres was apparent, alongside disappearance of SARS-CoV-2 RNA, and an improvement in clinical symptoms. This study concluded that convalescent plasma was an effective means of reducing mortality in COVID-19 [16]. A Cochrane Rapid Review by Valk *et al.* 2020 included 32 patients, from seven case-series and one prospectively planned study [17]. Valk *et al.* 2020 reported a high level of bias, due to the small numbers of participants, study design, different disease severities and varying treatments of the patients [17]. They were unable to perform any statistical analysis and deemed very low-certainty evidence for efficacy, with the data available at present [17]. The first randomized clinical trial evaluating convalescent plasma was performed in Wuhan, China. It recruited 103 participants with severe or life-threatening COVID-19 and compared convalescent plasma in addition to standard treatment (n = 52) to standard treatment alone (control) (n = 51). However, no statistical significant benefit in mortality or clinical improvement 28 days after the plasma transfusion in all randomized patients was observed [18]. However, a possible benefit was seen in the severely ill subgroup, but not the critically-ill group, when the data was reanalysed according to disease severity. The lack of statistical significance was thought to arise from the early termination of the trial, due to enrolment difficulties as the virus was being contained. This resulted in only 103 of the expected 200 cases being recruited, which subsequently underpowered the trial [18].

Safety of Convalescent Plasma

So far the safety data for this treatment seems promising, despite concerns that antibody-mediated enhancement may exacerbate the condition via a proinflammatory effect, or complications may arise from transfusion-related lung injury and transfusion-related circulatory overload [19]. Other potential adverse events include breathing difficulties, transfusion transmitted infection, and hypersensitivity reactions, which manifest as rash, fever or chills. No severe adverse events were reported by Ahn *et al.* 2020 (n=2), Duan *et al.* 2020 (n=10), Olivares-Gazca *et al.* 2020 (n=10), Salazar *et al.* 2020 (n=25), Zhang *et al.* 2020 (n=4) or Zeng *et al.* 2020 (n=6) [11-13,15,20,21], and the meta-analysis also confirmed it was safe (Rajendran *et al.* 2020) [16], whereas Valk *et al.* 2020 reported very low-certainty evidence of adverse events [17]. In the trial by Li *et al.* 2020 [18], two of 52 recipients of convalescent plasma experienced adverse events within hours of receiving the transfusion. The chills and rash manifest in one of those patients suggested a transfusion reaction. The adverse events in both cases were managed by corticosteroids [18,22].

What do We Need to Know?

The controlled trials evaluating convalescent plasma will provide important information on the optimal dose and time to treat patients, donor selection, plasma collection and which patients are most likely to benefit. The meta-analysis on the use of convalescent plasma to treat Spanish flu by Luke *et al.* 2006 suggested that early treatment, (after <4 days of pneumonia complications), resulted in improved mortality rates than late treatment, (after ≥4 days of pneumonia complications), which was similar to the mortality rate among controls [9]. The study by Zeng *et al.* 2020 supports the use of convalescent plasma as an early intervention [13], and also by Li *et al.* 2020, particularly in less severely ill patients [18]. The concentration of donor neutralizing antibodies is likely to affect the efficacy, and these levels can be influenced by the prior treatment of the donor, such as steroids, antiviral drugs and intravenous immunoglobulin. It will also be interesting to explore convalescent plasma in combination with antiviral agents, such as remdisivir, due to their different mechanisms of action [22]. There is previous evidence that they may work well together [23]. The results of the many clinical trials investigating the use of convalescent plasma in COVID-19 are eagerly awaited, but the data from case-series and the use of this treatment in previous infectious diseases appears promising.

Keywords: *Convalescent plasma, Coronavirus disease 2019, COVID-19, Passive immunotherapy, SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2*

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