J Korean Med Sci. 2020 Apr 13;35(14):e150
https://doi.org/10.3346/jkms.2020.35.e150
eISSN 1598-6357·pISSN 1011-8934

JKMS

Editorial

Convalescent Plasma Therapy for Corona Virus Disease 2019: a Long Way to Go but Worth Trying

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▸ See the article "Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea" in volume 35, number 14, e149.

Received: Apr 5, 2020
Accepted: Apr 6, 2020

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Disclosure
The author has no potential conflicts of interest to disclose.

Convalescent Plasma as a Last Resort

As of 3 April, the number of patients with corona virus disease 2019 (COVID-19) in Korea has exceeded 10,000. The incidence of COVID-19 patients still shows no sign of diminishing. Now is the time to prepare for the protracted war ahead. Hence we need to find a specific treatment measure against COVID-19. Regrettably, however, no definite treatment has been available yet. Nevertheless, various treatments, including old and new antiviral agents, are currently being investigated.[1] As one of them, convalescent plasma administration has been carefully proposed.[2,3]

In this issue, Ahn et al.[4] have reported two cases of successful treatment of COVID-19 using convalescent plasma. At the same time as this report, five cases that were successfully treated in China have been published, too.[5] And it is anticipated that more attempts will be made in the future.

In fact, the idea of using convalescent plasma for the treatment of viral diseases is not new. It has already begun to be tried in the early 20th century.[6] It was a time when there was no effective antiviral agent, so it must have been devised with the feeling of catching a straw in danger of drowning. It's better than not trying, but it seems to have achieved a little in the early days. Since then, convalescent plasma therapy has been attempted several times. Most recently, plasma therapy was applied to severe acute respiratory syndrome (SARS), influenza, Ebola virus, and Middle East respiratory syndrome coronavirus (MERS-CoV), and, albeit not always successful, it seems to have managed to get 'not-bad' results.[6-11]

You'll Never Walk Alone

As the authors stated in this paper, there were several limitations in these treatment cases, although it was a happy ending.[4] In one case, plasma was administered 3 weeks after the onset. Given viral kinetics, it was already time for the titer to start falling.[12] It is also true that convalescent plasma treatment still lacks scientific evidence. In addition, proper

dosage and administration protocols have not been standardized yet. In both cases, plasma was administered when antiviral drugs and steroids were given. It is hard to tell that the successful treatment is not necessarily due to plasma, and it cannot be refuted even if it is interpreted as an effect of antiviral agent or steroid. Or it is possible that these three elements were combined to create a synergistic effect.

But I'm going to change the way of interpretation. Given the mechanism of convalescent plasma therapy, I think this combination is rather worth being recommended.

The targets of COVID-19 treatment should be largely divided into two categories. First, it is aimed at the virus itself. The first thing you can think of is destroying the body of the virus. However, destroying the virus itself is a concept of disinfection and is too dangerous for humans to apply. As a therapeutic agent, there are drugs that inhibit RNA-dependent RNA polymerase by inhibiting the replication of viruses (e.g., remdesivir), or drugs that inhibit protease (e.g., lopinavir/ritonavir).[1,13] Another target is angiotensin converting enzyme 2 (ACE2), a gatekeeper and receptor for viruses to enter human cells. By raising the intracellular pH, glycosylation of ACE2 can be prevented to block the entry of the virus (e.g., chloroquine),[13,14] or it can be prevented from binding to ACE2 in advance by sticking to the spike protein of the virus.[15,16] The latter, not the former, is the antibody.

Considering the above treatment mechanisms, it can be seen that it is difficult to succeed with only one mechanism to treat COVID-19. Blocking a virus with antibodies is not enough to win the battle. We must also suppress the replication of the virus, and prepare for a cytokine storm that occurs during treatment.[17] In conclusion, it makes no sense as to which of these treatment methods was a decisive factor in the successful treatment. Rather, it is necessary to combine all of these to engage in treatment.

Does It Hurt?

We need to examine another important problem in plasma treatment.

Is it safe?

Plasma therapy itself has important complications. Examples are transfusion-related acute lung injury (TRALI), circulatory overload, or anaphylaxis.[18] Fortunately, no adverse events have been reported. Nevertheless, these complications should always be a concern.

There is also the possibility of side effects that have been raised recently. It is the antibody-dependent enhancement of entry (ADE). Neutralizing antibodies, once bound to the spike protein of the virus, cause a conformational change of the spike and, consequently, could trigger the paradoxical result of better entry into human cells through the IgFc receptor.[19-21] This side effect has not yet been realized, but should be kept in mind in the future of plasma treatment and vaccine development.

https://doi.org/10.3346/jkms.2020.35.e150

We've Only Just Begun

Convalescent plasma therapy gives us a lot of hope, but there are challenges to overcome. In the implementation, thorough ethical verification is required, and donor selection criteria should be strictly enforced. And it needs further extensive research to see if it really works. To this end, I think that institutional support is required to approve every attempt as quickly as possible.

Again, it is time to focus all of our capabilities on treatment.

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