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Life-saving effect of convalescent plasma treatment in covid-19 disease: Clinical trial from eastern Anatolia

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ABSTRACT

Aim: Convalescent Plasma (CP) therapy is of interest as no vaccine or specific treatment is available for emerging viruses such as severe acute respiratory syndrome coronavirus 2 causing Covid-19. It was aimed to report the results of our patients who underwent CP in the treatment of Covid-19.

Methods: CP treatment was applied to 26 Covid-19 patients in intensive care unit who had quantitative reverse transcriptase–polymerase chain reaction positive Sars-Cov-2 infection. Plasma was collected at least 14 days after complete recovery from patients who had mild or moderate infection with Sars-Cov-2 infection. The collected CP (200cc) were applied to severe Covid-19 patients. Laboratory values of patients just before CP and after 7 days were compared.

Results: There were no statistically significant differences in leukocyte, neutrophil, lymphocyte, platelet, CRP, ferritin, LDH, ALT, AST, sO_2 and total bilirubin values just before and after 1 week of CP. A statistically significant difference was found between age and lymphocyte values of living and dying patients. The patients who died were determined to have older age (74,6 vs 61,85, p = 0,018) and more severe lymphopenia (0,47 vs 1,18, p = 0,001).

Conclusion: CP therapy has the potential to provide immediate and promising treatment options before specific vaccines and treatments are developed. In early stage Covid-19 patients who do not need mechanical ventilation, CP treatment may be a curative treatment option.

1. Introduction

A pneumonia associated with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China [1]. The SARS-CoV-2 infection spread rapidly all over the world. As of June 12, the total number of SARS-CoV-2 cases reported by the world health organization (WHO) reached 7.553.182 and 423.349 deaths [2].

There are currently no proven treatment for Coronavirus disease 2019 (Covid-19). There is no effective antiviral drug in the treatment of Covid-19 disease. It is an urgent need to seek an alternative strategy, especially in the treatment of serious patients. Convalescent Plasma (CP) therapy can be used for this disease. CP is the administration of antibodies collected from recently infected and recovered Covid-19 patients to Covid-19 patients for therapeutic purposes. CP was used during the 1918 flu epidemic and reduced mortality among plasma recipients [3]. CP treatment is a reliable treatment option for the prevention and treatment of infectious diseases for more than a hundred years [4]. However, the benefit of CP treatment to mortality in Ebola virus disease has not been showed [5]. Recently, CP was used as a effective and reliable treatment option in SARS-CoV-1 and Middle East respiratory syndrome (MERS) epidemics [6]. Therefore, it suggested that the use of CP transfusion may be beneficial in patients infected with SARS-CoV-2.

It is possible that CP provides clinical benefit when given early in the course of disease (ie, in patients who do not require mechanical intubation), but this remains uncertain [7].

There is a large global trial supported by the WHO, SOLIDARITY, to research available therapies for Covid-19, including remdesivir, chloroquine and hydroxychloroquine, lopinavir and ritonavir, and lopinavir + ritonavir + interferon-beta. There is widespread interest to CP from recovered Covid-19 patients as treatment. The United States Food and Drug Administration (U.S. FDA) has published guidelines for investigating CP for the treatment of COVID-19 [8].

CP treatment was used in our center for the first time in the world after China in the treatment of Covid-19 disease. The purpose of this study was to share our clinical experience with CP transfusion administered to severe Covid-19 patients.

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2. Materials and methods

2.1. Study design

CP treatment was applied to 26 Covid-19 patients in intensive care unit who had quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) positive Sars-Cov-2 infection. Plasma was collected at least 14 days after complete recovery from patients who had mild or moderate infection with Sars-Cov-2 infection. 500–600 cc plasma was collected from the donors with a therapeutic apheresis device for 60 − 90 min considering age and comorbidity. Donors were selected from those who could be blood donors between the ages of 18 − 60. All tests (Eliza, etc.) before donation to the donors were done before the procedure. Antibody titer was checked before donating to the donors. Plasma was collected from donors with antibody positivity. Before starting the procedure, PCR was confirmed to be negative for Covid-19 in both the swab and serum of the donor. Informed consent was obtained from both the donor and the patients. After the CPs were collected, they were prepared and frozen in 200 cc packages with a sterile combining set. The collected CPs were applied to severe Covid-19 patients. Laboratory values of patients just before CP and after 1 week were compared. This study was approved by the local ethical committee of Inonu University, Medical Faculty on 26 May 2020 under the number 2020/77.

2.2. Study population

PCR positive Covid-19 patients who received CP treatment were included in the study. Patients with no PCR positivity and strongly suspected Covid-19 disease were excluded from the study. In addition to supportive treatment, hydroxychloroquine and azithromycin were administered to all patients and then favipravir. Convalescant plasmas collected from Apheresis Unit in Inonu University Turgut Ozal Medical Center were sent to other cities including Mus, Siirt, Adiyaman, Kahramanmaras, Konya and Istanbul. Plasmas were administered totally 26 patients and clinical follow ups were recorded.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 25.0 software package. Shapiro-Wilk test was used to test the normality of distribution of the categorical variables. We used the Wilcoxon test to detect differences between parameters before and after CP. The relationship between disease severity and mortality was analyzed with Fisher's exact test. Mann-Whitney *U* test was used to compare clinical and laboratory parameters between the alive and dead patients. $p < 0,05$ was considered statistically significant.

3. Results

A total of twenty-six Covid-19 patients (8 females and 18 males) with a mean age of 67.4 ± 15.5 years were included in the study. Pneumonic infiltration was present in the chest computerized tomography of all patients. Twenty six patients were given only one session of CP. Laboratory values of patients just before CP and after 1 week were given in Table 1.

There were no statistically significant differences in leukocyte, neutrophil, lymphocyte, platelet, CRP, ferritin, LDH, ALT, AST, sO_2 and total bilirubin values just before and after 1 week of CP. The hemoglobin level in our patients treated with CP was statistically significantly lower than before CP. The reason for this was thought to be dilutional anemia due to hydration applied to patients.

No severe adverse reactions were observed after CP transfusion.

The time from admission to patients to CP administration was 13.87 ± 6.5 days. While 6 of 17 patients who needed mechanical ventilation were dead, none of 9 patients who did not need mechanical ventilation died.

Table 1
Laboratory values before and after CP.

Parameters	Before CP	After CP	p value
Leukocyte ($\times 10^3/\mu L$)	10,15 ± 4,21	8,86 ± 4,04	0,455
Neutrophil ($\times 10^3/\mu L$)	8,75 ± 4,32	7,23 ± 3,85	0,346
Lymphocyte ($\times 10^3/\mu L$)	0,87 ± 0,63	0,88 ± 0,67	0,601
Haemoglobin (g/dL)	12,84 ± 1,74	11,47 ± 2,03	0,001
Platelet ($\times 10^3/\mu L$)	244,39 ± 137,09	221,86 ± 131,41	0,761
Ferritin (ng/mL)	564,33 ± 522,19	579,04 ± 457,25	0,717
LDH (IU/L)	374 ± 217,05	496,6 ± 369,47	0,142
sO_2	84,67 ± 8,33	87,90 ± 8,08	0,167
ALT (U/L)	36,17 ± 26,88	82,17 ± 171,84	0,058
AST (U/L)	46,69 ± 31,61	91,30 ± 171,31	0,284
Total Bilirubin (mg/dL)	1,37 ± 2,33	1,42 ± 2,80	0,164
CRP (mg/dL)	13,13 ± 8,59	9,71 ± 7,35	0,808

Table 2
Parameters of alive and dead patients.

Parameters	Alive (n = 20)	Dead (n = 6)	p value
Leukocyte ($\times 10^3/\mu L$)	9,22 ± 2,77	11,37 ± 5,48	0,313
Neutrophil ($\times 10^3/\mu L$)	7,38 ± 3,08	10,53 ± 5,18	0,208
Lymphocyte ($\times 10^3/\mu L$)	1,18 ± 0,68	0,47 ± 0,22	0,001
Haemoglobin (g/dL)	13,11 ± 1,29	12,54 ± 2,18	0,661
Platelet ($\times 10^3/\mu L$)	290,08 ± 162,19	185 ± 62,73	0,148
Ferritin (ng/mL)	568,78 ± 544,26	557,66 ± 523,99	0,970
LDH (IU/L)	336,33 ± 195,41	430,5 ± 248,56	0,427
sO_2	83,35 ± 9,32	86,27 ± 7,12	0,674
ALT (U/L)	36,23 ± 27,59	36,1 ± 27,4	0,738
AST (U/L)	37,92 ± 23,48	58,1 ± 38,12	0,148
Total Bilirubin (mg/dL)	1,52 ± 2,52	1,18 ± 2,19	0,738
CRP (mg/dL)	12,69 ± 7,72	13,71 ± 10,01	1
Age (years)	61,85 ± 13,52	74,6 ± 11,62	0,018

Of the 26 Covid-19 patients included in the study, 20 were alive and 6 died. Laboratory values and clinical parameters of patients living and dying at the time of admission were compared (Table 2). A statistically significant difference was found between age and lymphocyte values of living and dying patients. The patients who died were determined to have older age (74,6 vs 61,85, $p = 0,018$) and more severe lymphopenia (0,47 vs 1,18, $p = 0,001$).

4. Discussion

There is no specific therapeutic agent for Covid-19 disease. Treatment of the disease and prevention of its spread are provided by travel restrictions, patient isolation and supportive medical care. Some of the treatment options used in the current treatment of Covid-19 are hydroxychloroquine, lopinavir / ritonavir, azithromycin, favipiravir and Interleukin-6 (IL-6) inhibitors. Remdesivir, a nucleoside analogue and a broad spectrum antiviral and CP therapy has been approved by the FDA for experimental use.

CP means of antibody transfer to provide passive immunity. The history of CP therapy is based on the 1890s used to protect against bacterial toxins [9]. Intravenous immunoglobulins collected from thousands of healthy donors are still used today to prevent viral infections in some patient populations. CP transfusion has been reported in the treatment of various infections over the past decades [10]. In the past two decades, CP therapy has been used with satisfactory efficacy and safety in the treatment of SARS-CoV-1, MERS-CoV and 2009 H1N1 outbreak [11,12]. Therefore, the use of passive antibody transfer is considered for treating Covid-19 patients. The FDA has approved the use of experimental CP therapy in clinical trials and critical Covid-19 patients without other treatment options, and has published a guideline for this purpose [13]. In order for CP treatment to be effective, it is a prerequisite to find suitable donors with a high level of neutralizing

antibodies [11].

Ahn et al. applied 200 mL CP therapy to two serious Covid-19 patients aged 67 and 71, whose anti-SARS-CoV-2 IgG antibody titer was measured by the Elisa test. CP treatment was started on the 7th day of admission to one patient and on the 22th day to the other patient. A decrease in viral load has been shown after CP treatment [14].

Duan et al. added 200 mL of CP containing high neutralizing antibody titers (> 1: 640) to the treatment of 10 critical patients with Covid-19 (age range 34–78) after an average of 16.5 days of admission to the hospital. CP treatment increased the neutralizing antibody titer, oxygen saturation and lymphocyte count in patients; however, it has been observed that it reduces CRP, SARS-CoV-2 viral load and lung lesions in radiological imaging. Compared to the CP treatment group and the control group (10 patients), there was no significant difference between the basic features of the patients, while the clinical results of the patient group given CP treatment were superior ($p < 0.001$) [11].

Shen et al. has applied 400 mL CP therapy including SARS-CoV-2 antibodies (titer> 1:40) to 5 critical patients (age range 30–70, two women) determined by Elisa test. After CP transfusion between the 10th and 22nd days of admission to the hospital, symptoms such as an increase in viral antibody titers, a decrease in SARS-Cov-2 viral loads and normalization of ARDS and fever decreased were observed [15].

Brown BL and McCullough J performed a meta-analysis to investigate the effect of CP therapy on Covid-19 disease [7]. They identified the reliability of CP treatment. CP therapy has been shown to reduce viral load. Its reliability was demonstrated in China, where it was used for the first time in this outbreak [16]. In the current outbreak, CP has been used in our clinic for the second time in the world after China.

Ling Li et al., added CP in addition to standard therapy in 103 Covid-19 patients. The trial was conducted in open, multicentric randomized 7 centers in China. CP and standard therapy were applied to 52 patients and standard therapy was performed to 51 patients. Improvement in CP treatment group was 51.9 %, improvement in standard treatment group was 43.1 %, and this difference was statistically nonsignificant (hazard ratio, 1.40, p 0.26). There was no significant difference in mortality rates between two groups [17].

Zhang et al. reported that 4 critical Covid-19 patients who received supportive therapy were cured with CP and stated that these results should be confirmed by randomized studies [18].

In our trial, twenty-six Covid-19 patients had no severe adverse reactions after CP transfusion. Accordingly to the literature, statistically significant difference was found between age and lymphocyte values of living and dying patients. The patients who died were determined to have older age and more severe lymphopenia.

5. Conclusion

CP has the potential to provide an urgent promising treatment option when evaluating existing drugs and developing new specific vaccines and treatments. CP looks to be effective for a better follow of Covid-19 when administered in severe and critically ill patients and may reduce the rate of intensive care unit hospitalization. We observed that all patients with early-stage Covid-19 who did not need mechanical ventilation improved with CP treatment. However, we observed that, despite CP treatment, 6 of 17 (35,29 %) patients who needed mechanical ventilation died. In early stage Covid-19 patients who do not need mechanical ventilation, CP treatment may be a curative treatment option.

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CRediT authorship contribution statement

Mehmet Ali Erkurt: Writing - original draft, Investigation, Methodology. **Ahmet Sarici:** Writing - review & editing, Project administration, Methodology. **İlhami Berber:** Conceptualization, Formal analysis, Data curation. **İrfan Kuku:** Supervision, Project administration, Software. **Emin Kaya:** Resources, Data curation. **Mustafa Özgül:** Investigation.

Declaration of Competing Interest

The authors have no conflict of interest to declare with regard to the submitted manuscript.

References

[1] Chen N, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.
[2] WHO. WHO coronavirus disease (COVID-19) dashboard 12 June 2020; Available from: 2020https://covid19.who.int/?gclid=EAIaIQobChMIz83VtZyC6gIVQuztCh0PrQ3WEAAYASAAEgIFB_D_BwE.
[3] Hung IF, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52(4):447–56.
[4] Chen L, et al. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020;20(4):398–400.
[5] Van Griensven J, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med 2016;374(1):33–42.
[6] Ko J-H, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018;23(7):617–22.
[7] Brown BL, McCullough J. Treatment for emerging viruses: convalescent plasma and COVID-19. Transfus Apher Sci 2020:102790.
[8] Food, U. and D. Administration, Investigational COVID-19 Convalescent Plasma-Emergency INDs. Accessed on April, 2020. 8.
[9] Francis F, Hall M, Gaines A. Early use of convalescent serum in influenza. Mil Surg 1920;47:177–9.
[10] Yeh K-M, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56(5):919–22.
[11] Duan K, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci 2020;117(17):9490–6.
[12] Soo Y, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10(7):676–8.
[13] FDA. Investigational COVID-19 convalescent plasma guidance for industry 26 May 2020; Available from: 2020https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma.
[14] Ahn JY, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci 2020;35(14).
[15] Shen C, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. Jama 2020;323(16):1582–9.
[16] Casadevall A, Pirofski L-A. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130(4):1545–8.
[17] Li L, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA 2020.
[18] Zhang B, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest 2020.