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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effect of convalescent plasma in the treatment of severe acute respiratory distress syndrome caused by COVID-19 infection

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SUMMARY

Introduction/Objective Convalescent plasma (CP) has been used in the past to treat several infectious diseases. It was hypothesized that CP could have a positive impact on severely ill patients with COVID-19 infection. The aim of the study was to present the results of CP application in patients with severe acute respiratory distress syndrome (ARDS) caused by COVID-19 infection.

Methods This is an observational study of critically ill patients who received CP according to the National Protocol for the Treatment of COVID-19 Infection at the University Clinical Center of Vojvodina in Novi Sad, Serbia, in 2020. Clinical outcomes were monitored before and after CP administration.

Results A total of 14 patients with severe life-threatening COVID-19 infection were included in the study. The patients age ranged 53–79 years. Most of them had two or more comorbidities, and more than half of them had blood type A Rh positive. Prior to CP administration, all patients received antibiotic therapy for severe pneumonia, corticosteroids, and anticoagulant therapy. Twelve out of 14 patients (85.7%) required endotracheal intubation and mechanical ventilation of the lungs, while two patients were on non-invasive mechanical ventilation. CP was administered 2–13 days after the confirmed diagnosis of COVID-19. The PaO_2/FiO_2 ratio before CP administration ranged 49.5–78.6. Twelve patients (85.7%) died during the course of the study.

Conclusion The use of CP in cases of severe ARDS caused by COVID-19 infection does not impact survival or lead to other forms of clinical improvement.

Keywords: COVID-19; acute respiratory distress syndrome; convalescent plasma

INTRODUCTION

Coronaviruses were identified about 60 years ago, and since then, there have been three major epidemics caused by these viruses. The first was the severe acute respiratory syndrome (SARS) epidemic in 2003, followed by the Middle East Respiratory Distress (MERS-CoV) in 2012. The third and most severe epidemic caused by coronaviruses is attributed to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a disease known as COVID-19. The early variants of the COVID-19 virus caused severe infection in 10–25% of the infected individuals, primarily leading to pneumonia, with a certain percentage complicated by acute respiratory distress syndrome (ARDS) and a mortality rate of 39–49% [1, 2].

Convalescent plasma (CP) has been used to treat several severe viral infections such as SARS, MERS, Ebola, and avian flu [3, 4]. Studies investigating the effect of CP therapy on these viruses have shown higher survival rates in patients receiving CP [5, 6, 7]. Based on this, it was assumed that CP could also be beneficial for COVID-19 infection. The use of CP for treating critically ill patients with severe COVID-19 infection was approved by the US Food and Drug Administration early in the pandemic, following the results of observational studies that demonstrated its safety and potential to improve outcomes [8, 9]. This therapy relies on providing neutralizing antibodies against the SARS-CoV-2 spike protein to patients with active infection [10]. Initially, the recommendation was to administer CP to critically ill patients with life-threatening conditions, such as dyspnea, high respiratory rate, low blood oxygen saturation, and low PaO_2/FiO_2 ratio [11]. However, later research on CP's application in these patients gave conflicting results, with some studies showing no significant impact on the disease course.

In our country, CP was recommended during the early stages of infection according to the National Protocol for the Treatment of COVID-19 Infection. This study presents our earliest experience with administering CP to patients with COVID-19. The goal of the study was to determine if providing CP to patients with severe ARDS caused by COVID-19 can alter the disease course, considering that all patients who

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received CP based on the National Protocol were in a severe ARDS condition.

METHODS

This study was conducted at the Clinic for Anesthesia, Intensive Care, and Pain Management, University Clinical Center of Vojvodina in Novi Sad, Serbia, between July 10, 2020, and August 20, 2020. The study included a group of 14 participants with confirmed COVID-19 infection who received convalescent plasma (CP) treatment.

Plasma donors

The criteria for plasma donors were as follows:
- age between 18 and 60 years
- body weight greater than 60 kg
- absence of comorbidities that are permanent contraindications for blood donation
- the donor had a confirmed diagnosis of COVID-19 and/or a positive result for SARS-CoV-2 test (nasopharyngeal swab)
- a negative result for SARS-CoV-2 test from the nasopharyngeal swab, and at least 14 days had passed since the resolution of all symptoms.

All donors were provided with information regarding the purpose of plasma donation, the safety of the procedure, and the potential occurrence of adverse reactions during the donation process, along with the methods of prevention and management. Written consent and agreement for the mentioned procedure were obtained from all donors. Each donor underwent a mandatory medical examination, and all of them had a normal physical examination.

Preparation of plasma

The process of preparing plasma for CP donors involved several steps and tests to ensure safety and compatibility. When donors first arrived, blood samples were taken to determine their ABO and Rh blood groups, and they underwent screening for irregular anti-erythrocyte antibodies. Serological tests were conducted for human immunodeficiency virus (HIV), hepatitis B virus antigen (HBs), hepatitis C virus (HCV), and syphilis. Additionally, nucleic acid testing (NAT) was performed for HBV, HCV, and HIV. Complete blood counts, complete biochemical analyses, total proteins, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin, cholesterol, triglycerides, blood glucose, creatinine, urea, serum iron, total IgG concentration, and protein electrophoresis were also evaluated. If the donor had a history of previous transfusions or if the donor was a female with a history of pregnancies, anti-HLA antibodies were also checked. During subsequent plasmapheresis procedures, samples were taken for serological tests for HIV, HBs, HCV, syphilis, and NAT. Screening for irregular anti-erythrocyte antibodies and anti-COVID-19 antibodies was also performed during each session. Every two months, complete blood counts and measurements of total proteins, albumins, and ALT were repeated, with additional biochemical analyses and protein electrophoresis performed as needed. In cases where ALT levels were elevated, AST and GGT levels were also measured, and donors were allowed to donate plasma as long as ALT levels did not exceed twice the upper normal limit. Total IgG concentration was determined every 5 donations. When the results were in accordance with the procedures for donor plasmapheresis, plasmapheresis was performed. The plasma collection process itself was carried out by an apheresis procedure, plasmapheresis, which implies the exfusion of the donor's blood, the separation and retention of a certain volume of plasma and the reinfusion of cellular components without compensating the removed volume. The procedure was performed on MSC+ 9000 devices (Haemonetics Corporation, Boston, Massachusetts, USA), blood component separators, using sets that are sterile and intended for single use, with the use of anticoagulants and preservatives. The volume of plasma collected from a single donor during a plasmapheresis procedure was approximately 600 mL, and the plasmapheresis process took around 40 minutes. The collected plasma volume could not exceed 16% of the estimated total blood volume, which was calculated based on the donor's sex, height, and body weight or alternatively as 10 mL/kg of body weight.

Donors could contribute plasma multiple times, and the usual interval between two procedures was 15 days. The frequency of plasma donations depended on the concentration of IgG. For IgG concentrations ranging 6–8 g/L, donations were made every two weeks; for concentrations 8–10 g/L, donations were made weekly, and for concentrations above 10 g/L, donations were more frequent, but with a minimum interval of four days. If IgG concentration was less than 6 g/L, plasma donation was postponed for at least three weeks. The number of CP donations was also assessed by observing the presence of anti-COVID-19 antibodies. When a decrease in serologically detected antibodies was observed, plasma donation was stopped. For CP donors with no anti-COVID-19 antibodies detected by serological tests, plasma donation was limited to three months after the first donation. After collecting the unit of plasma (600 mL), it was divided into two equal parts of 300 mL by transferring the plasma into a transfer bag for plasma, using a sterile connection device. The original unit of plasma and the transfer bag were issued together. The storage process for the plasma was the same as for fresh-frozen plasma, with a storage duration of up to 36 months at a temperature of -25°C or lower. If the plasma was stored at a temperature between 20°C and 60°C, it could be stored for a maximum of 48 hours.

Plasma recipients

Each patient was assessed for CP administration based on a scoring system formulated by the transfusion specialists at the Clinical Center of Vojvodina, following the National protocol for the treatment of COVID-19 infection. ABO blood group compatibility with the donor was determined

Table 1. Demographic and clinical characteristics of patients who received convalescent plasma

Patient	Sex (m/f)	Age (years)	BMI kg/m^2	Comorbidities	Blood type	COVID-19 therapy	Invasive mechanical ventilation (yes/no)
1	m	53	38.5	obesity, HTN, DM, smoking, AF	B-	AB + C + DN	yes
2	m	70	27.8	HTN, smoking, angina pectoris	A+	AB + C + DN	yes
3	m	72	26.3	HTN	0-	AB + C + DN	yes
4	f	62	45.6	obesity, HTN, DM, asthma	A+	AB + C + DN	yes
5	m	72	24.8	HTN	A+	AB + C + DN	yes
6	m	66	23.3	smoking	0-	AB + C + DN	yes
7	m	54	34.1	obesity, HTN	B+	AB + C + DN	yes
8	m	79	32.8	obesity	A+	AB + C + DN	yes
9	m	72	39.1	obesity, HTN	B+	AB + C + DN	yes
10	m	70	41.5	obesity, HTN	A+	AB + C + DN	no
11	f	69	26.9	HTN, hypotireoidism	B-	AB + C + DN	yes
12	f	74	25.7	HTN	A+	AB + C + DN	yes
13	f	76	26.2	DM	A+	AB + C + DN	no
14	m	76	29.4	HTN, DM	A+	AB + C + DN	yes

m – male; f – female; BMI – body mass index; HTN – arterial hypertension; DM – diabetes mellitus; AF – atrial fibrillation; AB – antibiotic; C – corticosteroid – DN – dantrolen natrium

Table 2. Disease course

Patient	Number of days from confirmed diagnosis to CP transfusion	Number of days from ICU admission to CP transfusion	PaO_2/FiO_2			The outcome (died/survived)	Day of death/discharge after CP transfusion
			1 day before	1 day after	3 days after		
1	4	2	54.3	61.2	62.6	died	7
2	3	1	68.4	67.2	70.1	died	6
3	4	2	66.4	54.6	51.4	died	6
4	2	2	49.5	46.2		died	1
5	3	3	68.2	29.2		died	2
6	6	4	69.2	64.2		died	1
7	3	1	78.6	81.2		died	1
8	13	11	58.4	58.4		died	2
9	11	9	63.5	61	62.3	died	7
10	6	3	78.2	78.2	84.1	survived	15
11	6	6	70.1	67.2		died	0
12	3	1	64.6	68.4	67.8	died	19
13	5	3	76.3	78.6	82.2	survived	5
14	4	2	57.3	51.2	49.8	died	3

CP – convalescent plasma; ICU – intensive care unit

for each patient eligible for CP. All patients received two units of CP, each containing 300 ml, totaling 600 ml, on the same day. Clinical parameters for the patients before and after CP administration were obtained through a review of their hospital medical records and included the following data: basic demographic information, the number of days from confirmed COVID-19 diagnosis to CP transfusion, duration of hospitalization in the intensive care unit, presence of comorbidities, details of therapeutic modalities such as antibiotic, corticosteroid, and anticoagulant therapy, and the need for invasive mechanical ventilation. Laboratory parameters were monitored before and after CP administration for all patients. These parameters included arterial blood gas analysis, hemoglobin levels, hematocrit levels, leukocyte counts, platelet counts, D-dimer levels, fibrinogen levels, C-reactive protein (CRP) levels, procalcitonin (PCT) levels, and the Sequential Organ Failure Assessment (SOFA) score for each patient one day before CP administration, one day after, and three days after for those who survived beyond three days following CP administration.

Statistical analysis

Statistical processing of the obtained data was performed using the IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA) software package. The paired-sample t-test was used for statistical processing. Results are presented as means ± standard deviations (SD). Statistical significance was established at the $p < 0.05$ level.

Ethical approval for the study was obtained from the Ethics Committee of the University Clinical Center of Vojvodina in Novi Sad (00-51, 25/02/2020).

RESULTS

There were a total of 14 patients with severe ARDS caused by COVID-19 infection included in the study. The age of the patients was between 53 and 79 years (mean 68.9 ± 7.8 years) (Table 1). The average body mass index was 31.6 ± 7.1 kg/m^2. The majority were male (71.4%).

Table 3. Comparison of laboratory results before and after convalescent plasma transfusion

Patient	Hemoglobin (g/l)			Hematocrit (%)			WBC ($\times 10^9$/L)			Neutrophils (%)			Lymphocytes (%)			Platelets ($\times 10^9$/L)		
1	114	111	112	35.9	35.9	36.1	7.8	9.6	11.2	88.6	90.3	88.2	7.3	6.4	7.1	187	224	233
2	151	163	143	47	50.1	45.8	8.5	13.3	12.1	86.4	90.9	87.2	8.6	5.2	7.6	265	281	290
3	124	115	110	39.2	37	35.3	15.7	13.9	10.1	85.4	91.2	90.1	11.7	6.2	6.9	181	125	119
4	83	79		31.2	31.2		8.3	2.1		84.5	62.2		11.2	32.4		392	518	
5	124	102		36	31		17.7	18.6		86.6	88.9		11.1	8.3		220	210	
6	107	102		30.2	28.8		11.8	13.8		90.5	92.7		7.7	6		215	176	
7	113	112		35.4	35.2		13.5	15.7		94	95.2		4.4	3.1		334	137	
8	132	129		37	34		18.7	14.6		85.1	88.1		10.8	8.6		232	212	
9	141	128	131	45.9	39.8	40.2	18.9	11.2	10.2	94.9	89.9	87.2	1.5	3.9	4.2	125	229	170
10	127	123	121	40.8	38.4	38.1	5.4	6.2	6.4	89.7	88.8	88	7	7.8	7.1	323	354	366
11	82	50		25.9	17.8		32.4	27.9		14.3	14.3		84.7	84.7		64	64	
12	135	117	121	41.7	35.8	36.8	4.3	6.6	7.1	86.1	90.7	87.2	9.8	5.9	8.9	168	158	167
13	124	123	122	40.1	39.9	39.5	5.3	4.9	5.6	89.9	90.7	84.2	4.8	5.8	8.4	214	198	202
14	117	90	104	34.8	27.9	29.8	20.6	13.75	10.1	84	88.4	86.1	8.4	6.5	7.2	498	406	399

WBC – white blood cells

Table 4. Comparison of inflammatory and thrombogenesis markers – and SOFA score before and after convalescent plasma transfusion

Patient	D-dimer (ng/mL)		Fibrinogen (g/L)			CRP (mg/L)			Procalcitonin (ng/mL)			SOFA score		
1	385	403	4.2	3.9	3.4	92.8	68	72.2	0.06	0.12	0.56	6	5	7
2	1427	1398	4.9	3.5	3.3	6	23.3	37.4	0.12	0.21	0.77	4	4	5
3	1247	1298	3.1	3	3.2	187.6	277.8	262.1	0.18	0.21	0.48	5	6	7
4	759		3.2	3.7		23.3	54.7		0.21	0.29		4	4	
5	198		5.8	4.1		118.5	109.2		0.18	0.78		4	4	
6	348		3.2			75.2	182.3		7.04	9.12		6	6	
7	1120		8	4.4		138.6	131.6		1.02	1.42		4	3	
8	854		4.6	4.2		123.4	142.3		0.015	0.33		5	5	
9	675	687	4.1	3.8	3.5	212.2	187.3	192.2	6.37	6.15	7.23	5	5	7
10	882	839	3.1	2.3	2.4	375.6	178.2	201.2	0.44	0.28	0.65	4	4	3
11	1023	1112	4.9	4.6		154.7	204.7		0.28	0.31		7	7	
12	1186	987	3.5	3.5	3.7	61.4	59.4	63.2	0.48	0.71	0.92	5	4	5
13	289	322	3.2	4.2	3.8	203.4	156.2	188.3	0.21	0.08	0.12	4	4	3
14	156	207	4.4	4.1	3.2	506	327	366	0.98	1.1	1.2	5	6	7

CRP – C-reactive protein; SOFA score – Sequential Organ Failure Assessment score

Most of them had two or more comorbidities (78.6%). The most prevalent comorbidity was arterial hypertension (78.6%), followed by obesity (42.8%) and diabetes mellitus (28.6%). More than half of them had blood type A Rh positive (57.1%). Before receiving CP, all patients were receiving antibiotic therapy for severe pneumonia, corticosteroids, and anticoagulant therapy. Twelve out of 14 patients (85.7%) were endotracheally intubated and on mechanical ventilation, while two patients were on non-invasive mechanical ventilation.

In Table 2, it can be seen that CP was administered 2–13 days after confirmed COVID-19 diagnosis (average 5.2 ± 3.2 days) and 3.6 ± 3 days after admission to the ICU. The PaO_2/FiO_2 ratio before CP administration ranged 49.5–78.6 (mean 66 ± 8.8), indicating that all patients had severe ARDS according to the Berlin definition [12]. Twelve patients (85.7%) died, all of whom were on invasive mechanical ventilation. The mean PaO_2/FiO_2 ratio the day after CP administration was 62 ± 14, and it did not significantly differ ($p = 0.199$), nor three days later (PaO_2/FiO_2 66.3 ± 12.6, $p = 0.955$).

Most patients experienced a decrease in hemoglobin ($p = 0.002$) and hematocrit ($p = 0.007$) values after CP administration (Table 3). The values of leukocytes (neutrophilic granulocytes and lymphocytes) and platelets did not show a consistent trend of change.

Table 4 shows the values of D-dimer, fibrinogen, CRP, PCT, and SOFA score. The average D-dimer before CP administration was 724.4 ± 469.1 ng/mL, fibrinogen 4.3 ± 1.6, CRP 162.8 ± 135.5, PCT 1.2 ± 2.3, while the average SOFA score was 4.8 ± 0.9. The only value that significantly changed three days after CP administration was PCT, which was significantly higher ($p = 0.007$).

DISCUSSION

The idea of using CP for the treatment of COVID-19 infection emerged at the beginning of the pandemic [13]. This form of passive immunization has been used in the past for treating several infectious diseases, with varying degrees of success. In this case series, 14 patients with severe ARDS due to COVID-19 infection received CP. All patients received two doses of CP within 24 hours, following the National Protocol for the Treatment of COVID-19 Infection. What is interesting is that, upon meeting the

criteria for obtaining CP, all patients were actually in severe ARDS (PaO_2/FiO_2 < 100 mmHg). Upon reviewing the literature, no other case series with severe ARDS and CP treatment were found, making this study unique in its presentation of CP administration in severe ARDS cases. The patients age ranged 53–79 years, and the most common comorbidities were arterial hypertension, obesity, and diabetes mellitus, consistent with existing literature data that these are the most common conditions that lead to more severe forms of the disease [14–17].

Transfusion of plasma can lead to adverse events such as allergic reactions, febrile reactions, transmission of infection, hemolytic reactions, transfusion-related acute lung injury, and transfusion-associated circulatory overload [17]. In this study, most patients tolerated the transfusion well. Statistically significant changes were the decrease in hemoglobin and hematocrit values after CP administration, as well as an increase in PCT levels.

CP has been the most intensively studied treatment against COVID-19, and nearly 50 randomized controlled trials have provided evidence to assess its correct place in the anti-COVID-19 therapeutic armamentarium [18]. The first report of CP administration in a COVID-19 patient was published in March 2020 by Chinese authors Shen et al. [19]. Five critically ill patients received two doses of CP from healthy donors who had recovered from the infection. Four patients showed reductions in inflammatory biomarkers, improved gas exchange, and resolution of lung lesions based on computed tomography scans. However, the analysis of this study revealed that the patients were not in severe ARDS, unlike the patients in our study. A study by Habtehyimer et al. [20] also showed that CP administration led to a decreasing of inflammatory cytokines. Another study by Duan et al. [21] showed that the administration of one dose of CP was associated with improved clinical outcomes. However, a large randomized trial (RECOVERY trial) involving over 16,000 patients demonstrated that CP administration did not affect the disease course compared to standard therapy [22]. The results of this study align with the conclusions drawn by Zhang et al. [23] that CP transfusion in the later stages of the disease does not affect survival. This conclusion was also supported by a study conducted by Iranian scientists [24]. On the other hand, Misset et al. [25] showed in their study that CP therapy within five days of starting invasive mechanical ventilation reduced 28-day mortality.

A multicenter randomized study evaluated the cost-effectiveness of CP in patients diagnosed with COVID-19 from the Canadian public healthcare payer's perspective [26]. When compared to standard care, CP was more costly and less effective at improving quality-adjusted survival.

As can be seen from the discussion, the results of the therapy of COVID-19 infection with CP are not uniform and are certainly still a subject of controversy. The results of this study suggest that CP therapy was considered a last resort at that time, used when all other measures available at the time did not give results. It's important to note that these patients were treated during the first wave of COVID-19 infection in the country, around mid-2020, when randomized studies confirming the justification for CP administration were not yet available.

The study has some limitations. It is a case series with a relatively small number of patients and lacks a control group. All included patients had severe ARDS, so conclusions cannot be drawn for mild or moderate forms of ARDS. Potential complications of plasma transfusion may have been masked by the patient's severe general condition.

CONCLUSION

Based on our study we can conclude that the administration of CP in cases of severe ARDS caused by COVID-19 infection does not impact survival or lead to other forms of clinical improvement.

Conflict of interest: None declared.

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Ефекат конвалесцентне плазме у лечењу синдрома акутног респираторног дистреса узрокованог инфекцијом ковидом 19

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САЖЕТАК

Увод/Циљ Конвалесцентна плазма (КП) у прошлости се користила за лечење неколико инфективних болести. У складу са тим дошло се до хипотезе да би примена КП могла позитивно утицати на болеснике тешко оболеле од инфекције ковидом 19.

Циљ студије био је да прикаже резултате примене КП код болесника са тешком формом синдрома акутног респираторног дистреса узрокованог инфекцијом ковидом 19.

Методе Ово је серија случајева критично оболелих болесника којима је ординирана КП према Националном протоколу за лечење инфекције ковидом 19, у Универзитетском клиничком центру Војводине у Новом Саду (Србија), у 2020. години. Клинички исходи су праћени пре и после примене КП.

Резултати У студију је укључено 14 болесника са тешком, животно угрожавајућом инфекцијом ковидом 19. Старост болесника била је између 53 и 79 година. Већина је имала две или више придружених болести. Више од половине њих је било са *A Rh* позитивном крвном групом. Сви су, пре примене КП, добијали антибиотску терапију због тешке пнеумоније, кортикостероиде и антикоагулантну терапију. Дванаест од 14 болесника (85,7%) било је ендотрахеално интубирано и на механичкој вентилацији плућа, док су два болесника била на неинвазивној механичкој вентилацији. КП је ординирана у периоду 2–13 дана после потврђене дијагнозе ковида 19. Однос PaO_2/FiO_2 пре примене КП износио је 49,5–78,6. Преминуло је 12 болесника (85,7%).

Закључак Примена КП у стању синдрома тешког акутног респираторног дистреса узрокованог инфекцијом ковидом 19 не утиче на преживљавање нити на други вид клиничког побољшања.

Кључне речи: ковид 19; синдром акутног респираторног дистреса; конвалесцентна плазма