


RESEARCH LETTER

Retrospective study shows that early administration of convalescent plasma in hospitalized COVID-19 patients may have a positive effect on disease progression

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KEYWORDS

convalescent plasma, COVID-19, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) which can occur with varying severity. Hospitalization rates and morbidity are particularly elevated in older adults and those with comorbidities.¹ Potential treatment options include convalescent plasma (CP), antiviral drugs, or cytokine modulators.²

In severe cases, an improvement in clinical symptoms, as well as specific parameters was shown after treatment with therapeutic antibodies from CP,³⁻⁶ whereas a dose-dependent improvement in condition was observed in patients with mild to moderate symptoms.^{7,8} Furthermore, an early start of therapy suggests a decelerated disease progression,⁸ while adverse events were reported very rarely after transfusion.^{3-6,8}

2 | METHODS

In this retrospective study, a total of 52 patients hospitalized between April 1, 2020 and February 28, 2021 and with SARS-CoV-2 infection confirmed by RT-PCR were included. Institutional Review Board approval was obtained from the ethics committee of Bad Oeynhausen (Reg. no. 2021-745).

All were treated with CP during their hospitalization. Twenty-eight patients with a severe disease course, characterized by more than 2 days

in intensive care (before CP), were excluded from the study. In addition, 10 patients were excluded because they did not receive plasma therapy until more than 10 days after the onset of the first symptoms, and 4 patients because no COVID-19-specific symptoms were detected.

At time of admission, data on symptom onset, previous illnesses, medication, vital signs, and laboratory parameters were collected (Table 1). Immediately before the first transfusion (<10 h) with CP and approximately 3 days after this first administration, vital signs, laboratory parameters, and symptoms were used for evaluation. For the comparison, only parameters were evaluated for which data were available for the individual patient at both observation times (Table 2). For evaluation of the parameters, the median was determined; outliers are considered by specifying the minima and maxima. Because supplemental oxygen was administered to some patients, oxygen saturation was not used for evaluation.

3 | RESULTS

In the present retrospective study, data were evaluated in a total of 10 patients at the following observation times: at time of admission (Table 1), before the start of therapy using CP and 3 days afterward (Table 2). The patients had a moderate COVID-19 course and were treated with a first transfusion of CP on average 8 days after the onset of symptoms.

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TABLE 1 Baseline characteristics, as well as vital signs and laboratory parameters, at the time of hospitalization

Baseline	Median (min-max)	n		
Age (years)	59.5 (41-82)	10		
Sex				
Female (%)	40	10		
Male (%)	60			
BMI (kg/m ²)	25.5 (23-53)	10		
Transfusion after onset of symptoms (days)	8 (2-10)	10		
	Median (min-max)	>norm	<norm	n
Vital signs on admission				
Body temperature (°C)	37.6 (37-39.2)	3	0	9
Pulse (beats/min)	80 (60-108)	1	0	9
Respiratory rate (breaths/min)	22 (12-32)	6	0	9
Laboratory parameters on admission				
GFR by MDRD (ml/min)	72 (27-122)	0	2	10
Lactate dehydrogenase (U/L)	272 (143-688)	4	-	9
CRP (mg/dl)	7.0 (0.9-30.1)	7	-	9
Leukocytes (10 ⁹ /L)	5.6 (3-15.6)	1	1	10
D-dimer (µg/L)	500 (193-1000)	4	-	9
IL-6 (ng/L)	31 (9-80)	4	-	4

The median age of the patients was 59.5 years; with 40% of participants were female. The median BMI of 25.5 kg/m² is age-specific in the population average. The median body temperature of patients on admission was 37.6°C, although three patients had fever (>38°C). The respiratory rate of 22 breaths/min was slightly increased, but two of the patients had a severely elevated rate of ≥30 breaths/min.

Decreased glomerular filtration rate (GFR by MDRD) of 27 and 34 ml/min was observed in two patients, whereas all others were within the reference range (60-140 ml/min). The median lactate dehydrogenase activity (LDH) with a value of 272 U/L was slightly elevated (norm: 0-248 U/L). One patient had a particularly high value of 688 U/L. The median C-reactive protein (CRP) of 7 mg/dl was significantly elevated (normal: 0-0.5 mg/dl).

Median values of leukocyte count and D-dimer showed no abnormalities on admission. However, elevated D-dimer levels (norm: 0-500 µg/L) of up to 1000 µg/L were observed in four patients. The examined patients showed strongly elevated concentrations of up to 80 ng/L for interleukin 6 (norm: 0-5.9 ng/L).

In addition, the parameters immediately before the start of therapy (<10 h before the first transfusion) and 3 days later were recorded (Table 2).

The body temperature and the pulse rate of patients decreased slightly after administration of CP. The median respiratory rate also showed a reduction from 23.5 to 20.5 breaths/min. Two patients showed a frequency of ≥30 breaths/min before administration, which decreased significantly after therapy.

The median of the GFR and leukocyte count increased slightly after therapy, with the median of both being within the normal range. The median LDH activity was slightly above the reference range

TABLE 2 Comparison of vital and laboratory parameters immediately before the first administration of convalescent plasma (<10 h) and on average 3 days later

	Before transfusion			∅ 3 days after transfusion			
	Median (min-max)	>norm	<norm	Median (min-max)	>norm	<norm	n
Vital signs							
Body temperature (°C)	37.70 (36.4-39.2)	4	0	36.75 (36.5-38.4)	1	0	8
Pulse (beats/min)	80.00 (63-95)	0	0	69.00 (42-94)	0	1	8
Respiratory rate (breaths/min)	23.50 (17-39)	7	0	20.50 (17-29)	5	0	8
Laboratory parameters							
GFR by MDRD (ml/min)	72.00 (31-126)	0	1	84.50 (31-124)	0	2	8
Lactate dehydrogenase (U/L)	251.0 (145-425)	6	0	259.0 (150-420)	6	0	9
CRP (mg/dl)	2.00 (0.08-28)	8	0	1.21 (0.49-13)	7	0	10
Leukocytes (10 ⁹ /L)	5.90 (3.7-9.6)	0	0	6.35 (3.3-9.6)	0	1	10
D-dimer (µg/L)	500 (193-1000)	2	0	500 (200-1100)	2	0	9
IL-6 (ng/L)	17.00 (7-49)	5	0	14.50 (<2-50)	4	0	5

Note: Shown are the medians of all parameters obtained, as well as minima, maxima, and number of values deviating from the normal range.

(0–248 U/L) before transfusion, and increased marginally after therapy. However, comparing individual patients, it can be seen that the activity decreased in six patients after therapy and increased in three patients. CRP concentration decreased slightly after CP administration, but was nevertheless strongly elevated.

The median D-dimer showed no changes. However, a total of six patients showed an increase in D-dimers after CP administration, with values predominantly within the normal range (0–500 µg/L). Interleukin-6 levels decreased slightly after therapy but remained elevated in most patients.

4 | DISCUSSION

In this retrospective study, patients with a moderate COVID-19 course after infection with SARS-CoV-2 were considered. Other studies have shown that early administration of high-titer CP can improve disease progression⁸ in patients with moderate COVID-19 and decrease mortality,^{9,10} whereas late administration is less effective in critically ill patients.¹¹ Recently, another study demonstrated that administration of CP in patients with hematologic cancer and COVID-19 was associated with significantly improved 30-day mortality.¹² In addition, several studies showed that administration of CP has a positive effect on mortality in immunodeficient or immunosuppressed patients, and these patients also show rapid clinical improvement.¹³ In the present study, a total of 10 patients were examined to determine the effect of treatment with CP on vital signs, various laboratory parameters, and disease progression.

Vital and laboratory parameters (Table 2) revealed a positive trend after start of therapy with CP. Both the acute-phase protein CRP and the direct inflammation marker IL-6 decreased within the observed period. This could indicate a possible regression of inflammation. Other laboratory parameters, such as leukocytes, GFR, and D-dimers, were within the normal range during the monitoring period. Consideration of individual patient D-dimer data reveals that after transfusion, values increased slightly in six patients, but predominantly remained within the normal range.

In the majority of patients, LDH activity is elevated compared to the normal range at both observation times. The median increases slightly after therapy. Single observation, however, shows that in six patients activity decreases after administration. In other studies, no significant change in LDH activity was detected after transfusion.¹⁴ It can be assumed that no further tissue is significantly destroyed during the therapy period, as documented several times for more severe COVID-19 diseases.^{15,16} The vital signs improve moderately after the start of therapy, evident in a decrease in respiratory rate and pulse. In addition, body temperature is reduced.

All patients showed improvement in general condition, resulting in discharge of all patients no later than 14 days after initiation of therapy. No patients showed side effects after the transfusion, confirming the results of other studies on the safety of plasma administration.^{5,6,8}

Since all patients were treated with other drugs during their hospital stay, the observations cannot be exclusively attributed to the efficiency

of CP therapy. Drugs such as dexamethasone and remdesivir were used, which have already been described to have a marginal effect on disease progression in COVID-19 patients.¹⁷ Another limitation is the lack of a control group and the relatively small patient population ($n = 10$). Nevertheless, our results suggest that early administration of CP may be beneficial in preventing severe courses. Furthermore, due to the low risks involved, no adverse effects are to be expected, so that administration in support of other therapies seems to be useful.

AUTHOR CONTRIBUTIONS

Investigation: Katharina von Bargen, Michelle Teune, and Christian Flottmann. *Formal Analysis:* Katharina von Bargen, Michelle Teune. *Conceptualization:* Ingvild Birschmann, Katharina von Bargen, and Michelle Teune. *Writing—original draft:* Ingvild Birschmann, Katharina von Bargen, and Michelle Teune. *Writing—review and editing:* Ingvild Birschmann, Katharina von Bargen, Michelle Teune, Christian Flottmann, Franziska Knüttgen, and Cornelius Knabbe. All authors have read and approved the final version of the manuscript. Ingvild Birschmann (Corresponding Author) had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST

Ingvild Birschmann received speaker's honoraria from Aspen Germany GmbH, Bristol-Myers Squibb/Pfizer, Siemens Healthcare, and CSL Behring and reimbursement for congress traveling and accommodation from aspen and performed contract research for Siemens Healthcare. Ingvild Birschmann is a member of the advisory board of LFB biomedicaments, Siemens Healthcare, and CSL Behring. The listed financial relationships had no influence on this study. All other authors have no competing interests.

TRANSPARENCY STATEMENT

Ingvild Birschmann affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Birschmann I, von Bargen K, Teune M, Flottmann C, Knüttgen F, Knabbe C. Retrospective study shows that early administration of convalescent plasma in hospitalized COVID-19 patients may have a positive effect on disease progression. *Health Sci Rep*. 2022;e714.
[doi:10.1002/hsr2.714](https://doi.org/10.1002/hsr2.714)