

## The novel use of convalescent plasma in patients with Covid-19 in Basra governorate: Case series review

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### ABSTRACT

**Background:** The idea of convalescent plasma usage is to give passive immunity to the patients, so their immune system has a good chance of combating the virus. This study will review 6 cases of eligible Covid-19 patients that had been treated with convalescent plasma therapy in Basra Covid-19 quarantine.

**Objectives:** to demonstrate efficacy and safety of convalescent plasma in the patient series that had been enrolled.

**Method:** this study has pioneered a new method to collect up to 3,000 mL of convalescent plasma in one session by an off-label use of Spectra Optia Apheresis systems/TerumoBCT /Exchange set. In this study 250 mL of the collected convalescent plasma had been given to each of the 6 patients, from one donor. Response in SpO<sub>2</sub>, dyspnea, and tachypnoea was observed. Any reaction to plasma also has been monitored.

**Result:** Our case series have demonstrated both safety and effectiveness of convalescent plasma. This study was successful in reaching our primary and secondary outcomes in all 6 patients (improvement in SpO<sub>2</sub> and symptoms). With negligible difference in time of post transfusion response.

**Conclusion:** convalescent plasma is apparently safe and effective. In this study 250 mL of convalescent plasma has been given to each of the 6 patients, from one donor, using Therapeutic Plasma Exchange (TPE) protocol by Spectra Optia Apheresis system/TerumoBCT.

**Keywords:** convalescent plasma, COVID-19, SARS CoV-2, apheresis, plasma exchange, plasma donation

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## INTRODUCTION

### **Covid-19 Pandemic**

SARS-CoV-2 or Covid-19 pandemic of severe acute respiratory syndrome coronavirus 2 has rapidly spread to all over the world and has been declared as a pandemic by the WHO on March 11, 2020 <sup>(1)</sup>. 118,319 cases were confirmed with 4,292 deaths over 114 countries around the world <sup>(2)</sup>. Many medications are currently being used to treat COVID-19 patients, such as Remdesivir, Chloroquine or Hydroxychloroquine, and Lopinavir with Ritonavir. However, according to the SOLIDARITY-WHO trial, no treatment that is both effective and safe for COVID-19 has been found yet <sup>(3)</sup>.

### **Convalescent plasma in the medical literature**

Convalescent plasma therapy has been used since 1918 in the era of Spanish flu till recent years in MERS, SARS CoV-1, Ebola, and H1N1 pandemics as an effective treatment capable of reducing mortality rates and as a prophylaxis agent as well <sup>(4)</sup>.

COVID-19 (convalescent plasma) therapy trials are currently being carried out in many countries. However, to the date of this study, only three publications in the medical literature have achieved success in clinical outcomes of COVID-19 patients from convalescent plasma (Shen et al., a study of five patients; Duan et al., a study of 10 patients, and Jin et al., a study of two patients). <sup>(5,6,7)</sup>

### **Convalescent plasma in the media**

Many countries have announced, through mainstream media, their success in using convalescent plasma in treating COVID-19 patients, including South Korea <sup>(7)</sup>, Israel (CBN NEWS 13/04/2020), and Turkey (AA news

agency 12/4/2020). Our institutions, Basra Health Directorate and the University of Basrah in Iraq, announced the success of convalescent plasma in the six patients on 10 April 2020, putting Iraq in position 3 in the convalescent plasma fight against the virus. Other countries have started convalescent plasma trials like the U.S. (by FDA announcement in March 25th 2020), the UK (The Guardian April 7th 2020), Iran (Iran NEWS 29/03/2020), Canada (Ipolitics April 7th 2020), Japan (Takeda Company March 10th 2020), Kuwait (SkyNewsArabia 10th April 2020), Emirates (GulfNews 12nd April 2020), and India (TV Venkateswaran, Jyoti Singh New Delhi, Updated on 10th April, 2020).

### **Convalescent plasma antibodies**

The idea of convalescent plasma usage is to give passive immunity to the patients so that their immune system has a good chance of combating the virus. As part of the immune system response to the virus, antibodies are formed in our body during the viral infection and recovery period. There are two types of antibodies against the virus: low affinity (binding capacity) antibodies and high affinity antibodies. The former are formed first followed by the latter. High affinity antibodies take about 2 weeks to form to peak when the B-cell lymphocytes undergo full activation and transform into plasma cells. These antibodies can bind to the virus particles and prevent it from infecting the cells. If the plasma containing the antibodies is transfused to an infected patient with the same virus, these antibodies then attack the virus in the host body <sup>(8,9)</sup>.

### Convalescent plasma production

The plasma can be collected from donors by sedimentation or separation of the whole blood. However, higher volumes of plasma can be collected using apheresis <sup>(10)</sup>.

### Apheresis

Apheresis systems are used to collect a blood component. This can be either for donation or therapeutic purposes. Plasma exchange is an example of therapeutic use. It is used to treat many medical diseases such as Thrombotic Thrombocytopenic Purpura, Guillain Barre Syndrome, Myasthenia Gravis, and ANCA vasculitis. The blood components are separated by centrifugation of the whole blood in polyvinyl tubes. The plasma is then separated and collected into a bag while other blood components are returned to the donor or the patient <sup>(11)</sup>.

Most used apheresis machines nowadays have built-in programming features that can calculate the amount of plasma that needs to be exchanged safely. It calculates the total plasma volume according to the patient's manually entered data (gender, weight, height, and haematocrit). It also measures the Plasma Removal Efficacy (PRE), which is a metric to analyze the performance of the apheresis machine:

$$PRE = \frac{Volrp}{Volp} \times 100 [(Vin - Vac) \times (1 - Hct) + Vac]$$

Volrp: Volume of plasma and anticoagulant (AC) removed, VIN: Volume of inlet blood processed VAC: Volume of AC used

In case of exchange, such as Spectra Optia machines, the plasma will be replaced by fresh frozen plasma or Saline Albumin (100 ml albumin with 360 ml 0.9 % NaCl) solutions of the same volume of removed plasma. A large quantity will be removed (i.e. 3,000 mL) with Spectra Optia. Whereas, in Trima Accel machines that are used for blood component donation, fewer amount of plasma is separated (i.e., 600 mL) without an exchange fluid. Both the methods use 14.4 mL of anticoagulant (AC) per 1 L of the whole blood processed and, every 1.15 L of the processed blood will produce 1 L plasma. Trima Accel is the global standard machine for plasma donation currently <sup>(12)</sup>.

Optia is a very safe device for exchanging plasma that is sterile and prevents any air bubbles or clots to pass through filters and sensors. This study uses therapeutic plasma exchange (TPE) for collecting convalescent plasma. TPE is used to treat many diseases following protocols adapted by the American Society for Apheresis (ASFA). ASFA adapts recommendations to use TPE to treat different diseases according to the reported randomized clinical trials (RCT). <sup>(13)</sup>

### Aim of the work

To review the safety and efficacy profile for patients with-SARS CoV-2 virus infection treated by the already FDA approved method of using convalescent plasma collected from recovered individuals using Apheresis.

## METHODS

This study was conducted at the infectious disease wards, Basra Teaching Hospital, the center of Covid-19 quarantine in Basra. Plasma donation using the Apheresis system was done at the Al-Sadr Teaching Hospital in Basra and was kept in the Central Blood Bank.

The procedures were approved by the Basra Health Directorate and were under the review and supervision of joint committee of medical specialists from the University of Basra and the Basra Health Directorate.

The procedures were accompanied by written and verbal consents.

### Donors Selection

This study followed the donor's criteria that was announced by FDA for using convalescent plasma for COVID-19 patients <sup>(14)</sup> and the regular blood banking instructions in Iraq, which are as follows:

1. The donor has been infected with Covid-19, and this is confirmed by positive PCR.
2. The donor can donate plasma after 14 days from recovery date, which is confirmed by negative PCR and being asymptomatic along these days.
3. The donor is free of blood-borne viruses HIV, HBV, and HCV.
4. The donor is 18-60 y.o.
5. The donor is not taking medications for chronic illnesses.
6. Blood group must be known.
7. The donor must be positive for Anti-Covid-19 IgG antibodies.

### Plasma Separation, Transportation, and Storage Methods: A Novel Method for Convalescent Plasma Collection

Currently, plasma collection for donation purposes by Apheresis is being done via the Trima Accel machine/TerumoBCT which collects up to 600 mL in each session with one IV access and no exchange fluid for the donor. Because of very few numbers of eligible donors and the increasing number of Covid-19 patients, this study pioneered a new method to collect up to 3,000 mL of convalescent plasma in one session by an off-label use of Spectra Optia Apheresis systems/TerumoBCT/Exchange set. To our knowledge, this study is the first of its kind to collect such large amounts of convalescent plasma safely from a single donor using this method.

Our eligible donor was a female physician, 57 years old, who had recovered from Covid-19 on 24 March 2020, was free of blood-borne viruses, she was positive for anti-Covid-19 IgG, and had not received any chronic medication. Her blood group was O+ve. A written consent was taken.

On 07/04/2020, the TPE protocol with Saline Albumin and 1 Total Plasma Volume (TPV) was used and, according to the safe limit of exchange calculated by the machine, 3,000 mL of plasma was collected and exchanged with Saline Albumine (0.9% NaCl 350 mL/Albumin 100 mL) of the same volume.

This study monitored the donor's vital signs before and after donation, as well as 3 days after donation. She showed good health with no complications.

Two peripheral 21-Gauge IV lines were used and the whole process lasted for 90 minutes.

The plasma bag was then disconnected from the disposable cassette using the T-seal mobile Tube Sealing Device/TerumoCBT. The longer

the tube connected to the plasma bag, the easier was the aliquotation process later on.

The bag was transferred in an ice-cold heat isolated safety box to the blood bank and aliquoted into 250 mL small units by using TSCD-II Sterile Tubing Welder machine and T-seal II Tube Sealing Device, both are products of TerumoBCT in a closed sterile procedure. The small units were labeled according to the FDA and the blood bank protocol and frozen by shock freeze (-36 °C) and were kept in deep freeze for later use.

This study was able to get 12 units of 250 ml of convalescent plasma for the treatment of Covid-19 patients as well as for research purposes.

### Patients Selection

Patients with the laboratory that tested positive for Covid-19, diagnosed using reverse transcriptase–polymerase chain reaction (RT-PCR) and Chest CT-Scan, were eligible to receive convalescent plasma treatment if they fulfilled the following criteria as per FDA instructions (14):

- Patient had hypoxia (SpO<sub>2</sub> is 93 or less with progression despite antiviral treatment).
- Patient had dyspnoea.
- Patient had tachypnea (RR is 30 or more).

The patients were selected by the treating physicians and our medical committee. Viral load measurement is not available in our facility.

Potential ABO compatibility with plasma was taken to minimize any chance of allergic reaction.

Six patients were selected according to the above criteria, and each patient was administered 250 mL of convalescent plasma

by IV infusion (over 1 hour) with close monitoring for any adverse effects.

Patients were labelled by their sex and gender: one letter for gender (M/F) and two digits for age. (Table 1)

All the patients were started on Hydroxychloroquine, Oseltamavir, Lopinavir/ritonavir once the Covid-19 diagnosis was confirmed; IV Methylprednisolone was started on the same day convalescent plasma was given to all patients. Case 1 was given Ceftriaxone, Case 6 Azithromycine, and Case 3 Azithromycine and Meropenim antibiotics.

All the subjects exhibited no comorbidity conditions except for Case 2 who presented with Heart Failure (HF), Chronic Kidney Disease (CKD), Hypertension (HT), and Diabetes Mellitus (DM), and Case 6 with HT. All of them were non-smokers.

Initial lab results (Table 2) showed that both the subjects (Case 2 and Case 6) had some features of Cytokine Release Syndrome (a severe, often fatal, hyper inflammatory response) that is characterized by significant rise in S.Ferritin, AST, and CRP. Cases 2 and 3 were in the Intensive Care Unit (ICU) while others were placed in the isolation wards.

### Outcomes

Primary outcomes: This study discovered changes of SpO<sub>2</sub> in our patients (with/without oxygen) since the day of admission till 72 hours after the administration of convalescent plasma that improved their respiratory system.

Secondary outcomes: improvement in the patients' symptoms (specifically shortness and breath).

Case serial No.	Gender/age	Admission date	CONVALESCENT PLASMA date	RN
Case 1	F/48	04/04/2020	08/04/2020	7500
Case 2	M/70	04/04/2020	08/04/2020	7476
Case 3	M/75	06/04/2020	08/04/2020	7514
Case 4	M/40	01/04/2020	08/04/2020	7801
Case 5	F/54	04/04/2020	09/04/2020	7829
Case 6	M/57	08/04/2020	09/04/2020	7568

**Table 1:** Patients’ labels with admission dates and convalescent plasma infusion dates. RN denotes Registration Number in the hospital.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Units
WBC	12.23	12.55	7.79	5.56	6.39	8.83	1000/ML
NEU%	92.1	81.2	72.9	68.2	75.9	82	%
LYM%	3.6	5.4	10.8	22.1	18.9	12	%
MON%	4.3	3	13.9	9.7	4.2	5.2	%
EOS%	0	10.2	2.3	0	0.9	0.7	%
BAS%	0	0.2	0.1	0	0.2	0.1	%
RBC	4.41	5.72	4.56	5.47	4	4.67	10 <sup>6</sup> /ML
Hb	8.2	15.9	13	12.8	11.1	13	g/dL
Hct%	28.7	45.9	38.7	39.4	33.8	38.1	%
Plt	668	180	205	181	367	283	1000/ML
ESR	120	43	11	23	120	96	
S.Ferritin	25.21	>2000	321.8	444.8	503.4	807.8	ng/mL
ALT	18.57	41.55	3.96	40.47	24.29	30.17	U/L
AST	22.3	67.66	17.79	45.07	45.53	52.74	U/L
S.Cr.	0.57	3.54	0.69	0.98	0.73	1.24	mg/dl
B.Urea	30.94	220.68	25.03	26.69	25.58	39.5	mg/dl
CRP	144	149	131	24	114	312	

**Table 2:** Initial lab results of patients: Abnormal results are in bold print.

### Data Collection

Data collection was done by reviewing the treating physicians’ rounding notes every 12 hours. This was done by two independent researchers. The rounding physicians, although aware of the study, were not a part of the study team.

### RESULTS

As shown in Table 3, there was improvement of primary outcome (SpO2) in all the six cases after the administration of convalescent plasma.

Case 1 (Figure 1) responded in 12 hours after the convalescent plasma administration and became less dyspnoeic. After 48 hrs, dyspnoea disappeared.

For Case 2 (Figure 2), SpO2 improved significantly after 48 hrs. His symptom (dyspnoea and confusion) gradually improved after the convalescent plasma infusion and was completely resolved after 60 hrs. However, he still required oxygen supplementation.

Case 3’s (Figure 3) SpO2 as well as general condition improved after 12 hrs, and he was shifted from the ICU to the medical ward. His dyspnoea and tachypnoea disappeared after 36 hrs after the convalescent plasma infusion.

Case 4 (Figure 4) responded to the convalescent plasma infusion after 24 hrs; he looked better and less dyspnoeic. After 36 hrs, he exhibited no fatigue and could ambulate without assistance. After 48 hrs, he exhibited no signs of dyspnoea.

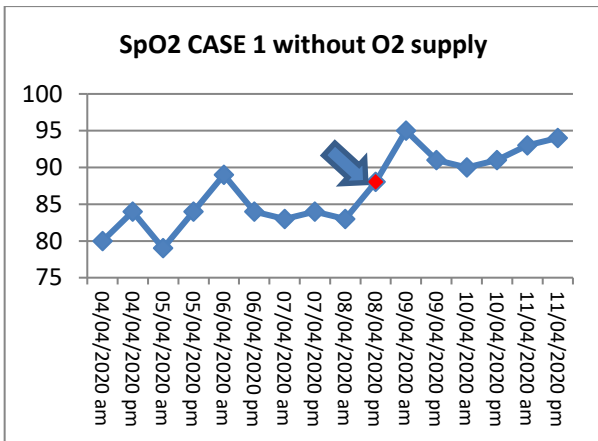
After 60 hrs, SpO2 rose significantly.

Case 5 (Figure 5) exhibited sudden decrease in SpO2 after five days of admission. After the convalescent plasma infusion, she responded well and presented no signs of dyspnoea and no wheezy chest after 24 hrs.

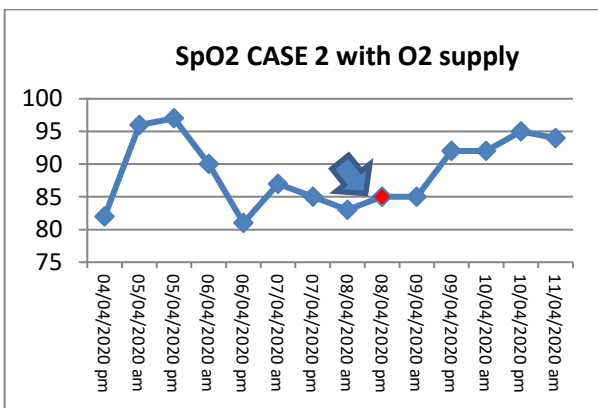
Case 6 (Figure 6) responded after 12 hrs when SpO2 rose; however, the issue of dyspnoea has resolved after 60 hrs.

#### FINANCIAL DISCLOSURE

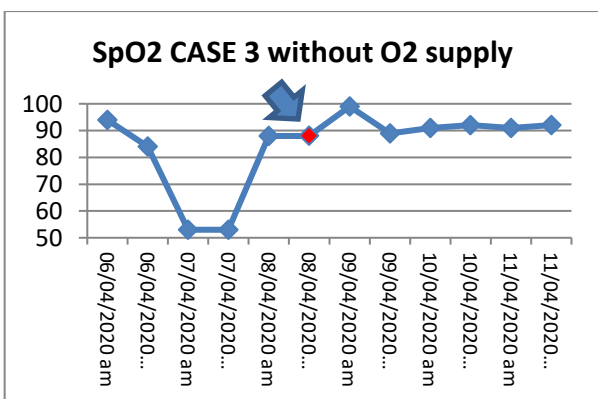
No one of the Authors of this paper has any financial interest in any device or material mentioned in this work.



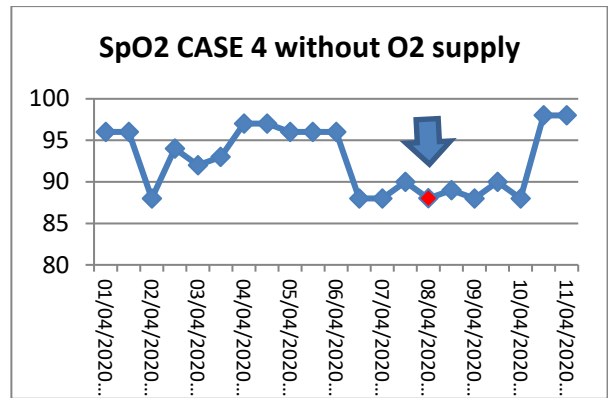
**Figure 1:** SpO2 follow-up for Case 1: Arrow points to Convalescent plasma infusion date



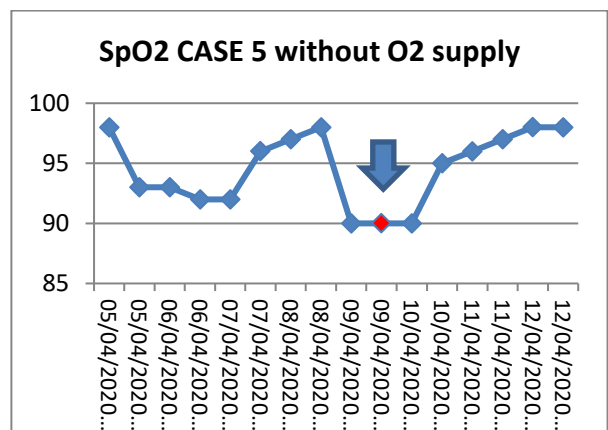
**Figure 2:** SpO2 follow-up for Case 2: Arrow points to Convalescent plasma infusion date



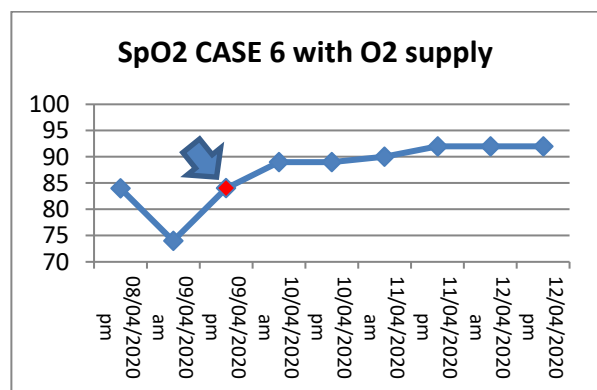
**Figure 3:** SpO2 follow-up for Case 2: the arrow points to the convalescent plasma infusion date



**Figure 4:** SpO2 follow-up for Case 4: the arrow points to the convalescent plasma infusion date



**Figure 5:** SpO2 follow-up for Case 5: the arrow points to the convalescent plasma infusion date



**Figure 6:** SpO2 follow-up for Case 6: the arrow points to the convalescent plasma infusion date

Date	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	SpO2	SpO2	SpO2	SpO2	SpO2	SpO2
01/04/2020 pm				96		
02/04/2020 am				96		
02/04/2020 pm				88		
03/04/2020 am				94		
03/04/2020 pm				92		
04/04/2020 am	80			93		
04/04/2020 pm	84	82		97		
05/04/2020 am	79	96		97	98	
05/04/2020 pm	84	97		96	93	
06/04/2020 am	90	90	94	96	93	
06/04/2020 pm	84	81	84	96	92	
07/04/2020 am	83	87	53	88	92	
07/04/2020 pm	84	85	53	88	96	
08/04/2020 am	83	<b>83</b>	88	90	97	
08/04/2020 pm	<b>88</b>	85	<b>84</b>	<b>88</b>	98	84
09/04/2020 am	95	85	99	89	90	74
09/04/2020 pm	91	92	89	88	<b>90</b>	<b>84</b>
10/04/2020 am	90	92	91	90	90	89
10/04/2020 pm	91	95	92	88	95	89
11/04/2020 am	93	94	91	98	96	90
11/04/2020 pm	94		92	98	97	92
12/04/2020 am					98	92
12/04/2020 pm					98	92

**Table 3:** SpO2 changes before and after the convalescent plasma infusion. Bold numbers represent the dates of convalescent plasma infusion for SpO<sub>2</sub> measurement. Case 2 and Case 6’s SpO<sub>2</sub> were measured using an oxygen mask; the rest were tested without an oxygen mask.

## DISCUSSION

In this study, 250 mL convalescent plasma was given to each of the six patients from one donor using the Therapeutic Plasma Exchange (TPE) protocol by Spectra Optia Apheresis system/TerumoBCT. This is a novel procedure for collecting large amounts of convalescent plasma for donation, and to our knowledge, this has not been done before. Our results have demonstrated both the safety and effectiveness of convalescent plasma. This study was successful in reaching our primary and secondary outcomes in all the six patients (improvement in SpO<sub>2</sub> and symptoms).

Four out of the 6 subjects responded significantly in 24 hours after the convalescent plasma infusion while for the rest, one in 48 hours, and one in 72 hours. (Table 3)

The latest response was seen in the youngest patient in the group, Case 4. He exhibited no chronic medical conditions. However,

convalescent plasma was administered to him after others during the hospital stay. The delay in the convalescent plasma infusion more likely led to a higher viral load since the virus had more time to reproduce. The poorest outcomes were seen in two patients, one who presented with HF, HT, DM, and CKD and the other with HT. Their SpO<sub>2</sub> improved, but they still depended on oxygen supply. This was possibly due to the presence of cardiovascular diseases or their late presentation to the hospital. They were admitted for more than 10 days after the onset of symptoms, as stated in their medical history.

There are only three published studies that have tested the convalescent plasma for Covid-19 treatment (5,6,7). They used different parameters to evaluate outcomes that are different from our study. However, they had similar results to ours. Chen et al. gave 200 mL/two doses of convalescent plasma to five critically ill patients and selected donors with a similar criteria to ours. Their donor criteria was as follows: age 18–60 years old, 10 days (instead of 14 days in our study) free of symptoms after recovery (which was confirmed by qRT-PCR negative test), and free of blood-borne viruses. Convalescent plasma was infused on 10–22 days post admission in their study, which is longer than our study (3–7 days) (5).

Duan et al. administered one dose or 200 mL of convalescent plasma to 10 critically ill patients. Convalescent plasma was administered after an average of 16.5 days since admission (6).

Jin Young et al. had given 500 mL of convalescent plasma to two critically ill patients; convalescent plasma was administered on day 7 and 22 of admission. They noted a clinical improvement in both patients after 24 hrs and later more improvement in the reduction of the viral load, CRP, and radiological imaging. The method of convalescent plasma collection adopted in the study by Jin et al. was by Spectra/Optia IDL set to collect 500 mL of plasma from each donor. (7).



All patients in our study and the previous three studies have shown to improve clinically within 72 hours and in SpO<sub>2</sub> records. The earlier convalescent plasma is given, the faster is the response (5,6). All the four studies showed no adverse side-effects of convalescent plasma. The three previously published studies have also shown improvement in other parameters such as increasing lymphocyte counts, PaO<sub>2</sub>/FiO<sub>2</sub>, CT scan imaging, AST, ALT, viral load, and CRP. Also, Duan et al. noticed an increase in anti-Covid-19 antibody titer after convalescent plasma administration in the patients' sera.

All the three previously published studies have had patients who required mechanical ventilation. Although none of our patients required mechanical ventilation, our patients did meet the severe illness criteria set by the FDA<sup>(14)</sup>. Also, in this study, a consideration was taken that if convalescent plasma infusion is given to Covid-19 patients late in the disease process (when there is multiorgan failure), then the response may not be optimal, if at all. This has been suggested in previous studies for Covid-19 as well as MERS and SARS (5,6,15). Also, due to the shortage of convalescent plasma, one should be judicious in giving it to the patients who may benefit from it the most. Our study, like the other three previously published studies, has its own limitations. The number of cases is small and the follow-up is rather short. To fully investigate the effectiveness of a treatment, a randomized controlled trial should ideally be conducted. Given the current disease pandemic, this would be nearly impossible and unethical. Given the already shown effect of convalescent plasma in previous viral illnesses and the potentially fatal complications of Covid-19, one cannot withhold such a treatment in the control group; IV steroids (in the form of methylprednisolone) were given concomitantly with convalescent plasma to all the patients in all the four studies (our study and the three previously published studies). One can argue that the favourable

outcomes seen with convalescent plasma can be attributed to the steroids' effect. However, some studies claim that convalescent plasma can be used as a rescue therapy for patients with ARDS with SARS viral illness when pulse methylprednisolone does not work (3,6). Some studies also suggest that the Covid-19 viral illness, if left untreated, may disappear after 7–10 days (7).

Some tests could not be performed in our study due to the lack of availability of the viral load before and after the convalescent plasma infusion by qRT-PCR and the anti-Covid-19 Ig titer in the collected convalescent plasma and recipients' sera. This study recommends these tests be performed only if available on a daily basis after the convalescent plasma infusion. Also, ordering blood tests and radiological imaging were left solely to the treating physician without any intervention by the research team.

Finally, any mortality reduction cannot be concluded from this study. However, improvement in the respiratory and general health condition in our study and previous studies encourage the use of convalescent plasma.

## CONCLUSIONS AND RECOMMENDATIONS

1. Collection of convalescent plasma in large quantities with a safe and fast procedure is possible using Spectra Optia Therapeutic Plasma Exchange protocol 1 TPV with Saline Albumin.
2. Convalescent plasma has improved the respiratory conditions in all the patients.
3. Four out of the six patients improved within 24 hours post the convalescent plasma infusion.
4. Sixty hours' response time is relatively a late response time possibly due to late convalescent plasma administration.
5. The patients presenting with cardiovascular diseases patients had the lowest response.

6. For better understanding the difference in the response, a viral load can be conducted before and after the convalescent plasma infusion and on a daily basis.
7. Convalescent plasma anti-Covid-19 antibodies titer can be calculated if the test is available to help determine the dose according to the viral load.
8. When more convalescent plasma is available, a second dose can be given to patients who lack good response to the first convalescent plasma dose after 24 hours

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