Original Article

Outcome of Critically Ill COVID-19 Patients After Getting Convalescent Plasma (CP) in ICU of DMCH

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Abstract:

There are no approved specific antiviral agents or vaccines against COVID-19 till now. In this study, 10 critically ill patients confirmed by real-time viral RNA test were enrolled prospectively. One dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:160 was transfused to the patients as an addition to maximal supportive care and antiviral agents. The aim of this study is to see the outcome of CP transfusion. It was possible to reduce oxygen support (step down) of 40%(04) patients, 10% (01) patient's parameters was unchanged and 50% (05) patients were need more oxygen support (step up) after getting CP which correlate with incremental response of lymphocyte counts and detrimental response of biochemical parameters of inflammation.70%(07) patients of total who received mechanical ventilation, after treatment with CP, 30%(03) patients were weaned from mechanical ventilation to high-flow nasal cannula, and 10%(01) patient discontinued high-flow nasal cannula to NRM.No severe adverse effects were observed. This study showed CP therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in critical COVID-19 cases. The optimal dose and time point, as well as the clinical benefit of CP therapy, needs further investigation in larger well-controlled trials.

Keywords: *Critically ill COVID 19, Convalescent plasma (CP), Oxygen therapy*

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Introduction:

The epidemic of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) originating in Wuhan, China, has rapidly spread worldwide 2019 (1–3). This epidemic spread rapidly worldwide within 3 months and was declared as a pandemic by WHO on March 11, 2020. There are no specific antiviral agents or vaccine against this virus(4-5). Although remdesivir has shown antiviral effect in one COVID-19 patient from the United States still randomized controlled trials of this drug are ongoing to determine its safety and efficacy (6). As there are no proven medications to fight against SARS COV 2 virus, it is an urgent need to look for an alternative therapy for COVID-19 treatment, especially among critically ill patients. Convalescent plasma was given as an empirical treatment during outbreaks of Ebola virus in 2014, and a protocol for treatment of Middle East respiratory syndrome coronavirus with convalescent plasma was established in 2015. This approach with other viral infections such as SARS-CoV, H5N1 avian influenza, and H1N1 influenza also suggested that transfusion of convalescent plasma was effective (7-10). As SARS, Middle East Respiratory Syndrome (MERS) and COVID-19 (15) have similar virological and clinical manifestations, CP therapy might be a good hypothetical treatment option for COVID-19 patients (11). Patients who have survived from COVID-19 with a high

neutralizing antibody titer may be a valuable donor source of CP. Risks and benefits of convalescent plasma as treatment in COVID-19 are still unknown.Hence the purpose of this study was to find out the outcome after giving convalescent plasma to critically ill covid-19 patients.

Method and materials:

Patient's selection:

From June 06, 2020 to July 17, 2020, 10 patients admitting in COVID ICU, Dhaka Medical College Hospitalswho were diagnosed as critically ill COVID-19 according to the WHO Interim Guidance (30) and COVID-19 of National guideline (31), confirmed by real-time RT-PCR assay, were included in this study. The enrollment criteria were :1) age ≥18 y; 2) respiratory distress, RR ≥30 beats/min; 3) oxygen saturation level less than 92 % in resting state; and 4) partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤300 mmHg. The exclusion criteria were as follows: 1) previous allergic history to plasma.2) cases with serious general conditions, such as severe organ dysfunction, who were not suitable for CP transfusion. Written informed consent is obtained from each patient or legal relatives.

Selection of Donors for CP Transfusion:

Donors were selected who recovered from COVID-19 and declared immune to corona virus. The recovery criteria were as follows: 1) normality of body temperature for more than 3 days, 2) resolution of respiratory tract symptoms, 3) two consecutively negative results of sputum SARS-CoV-2 by RT-PCR assay (2-days sampling interval) and4) Antibody titre at least or more than 1:160. The donor's blood was collected after 2 weeks of declared recovered but within 4 weeks of recovery. Written informed consent was obtained from each patient

Preparation of plasma from donors:

Apheresiswasperformed using a Baxter CS 300 cell separator (Baxter). A 200 ml ABO-compatible plasma sample was harvested from each donor depending on age and body weight, aliquots at 4 °C without any detergent or heat treatment. The CP was then treated with methylene blue and light treatment for 30 min in the medical plasma virus inactivation cabinet.

Real-Time RT-PCR Detection of SARS-CoV-2:

The neutralizing activity of plasma was determined by plaque reduction neutralization test using SARS-CoV-2 virus in the high biosafety level (BSL-3) laboratory of different institute of Bangladesh. Neutralization titer was defined as the highest serum dilution with 50% reduction in the number of plaques, as compared with the number of plaques in wells in the absence of novel coronavirus antibody as blank control. SARS-CoV-2 IgG antibody titer was tested by ELISA. SARS-CoV-2 RNA was detected by RT-PCR assay. Methylene blue residue was detected by the verified UV method.

Treatment:

All patients whowere admitted in ICUreceived antiviral therapy, antibiotic, antifungal, glucocorticoid, other supportive therapy and oxygen therapyby NRM, HFNC, and BiPAP or by MV at the appropriate situation. One dose of 200 mL of inactivated CP with neutralization activity of >1:160 was transfused into the critically ill COVID-19 patients and decided by treating consultantfollowing the WHO blood transfusion protocol.

Data Collection:

Data of thesepatients were collected from patient's records files that include demographic data, duration of illness, presenting symptoms. Bacterial coinfection was identified by a positive culture from respiratory, urinary, or blood culture after 48 h of hospital admission. Complications like acute renal failure, any cardiac events, ARDS, and nosocomial infection, were recorded. The applications of assisted mechanical ventilation, other different methods of oxygen delivery systems including HFNC, BiPAP and medication regimen were recorded. For the purposes of the study relevant data were recorded before giving CP transfusion and at the third day of CP transfusion.

Follow up for outcome assessment:

Follow up information were recorded by attending physicians daily. The blood test and biochemical tests were carried out every 1-2dyas interval. The aim of follow up was to assess the safety of CP transfusion through improvement of clinical symptoms, laboratory and radiological parameters within 3 days of CP transfusion. Clinical symptoms improvement was defined as temperature normalization, relief of dyspnea, oxygen saturation normalization, radiological improvement and normalization of biochemical marker of inflammation.

Result:

Total 10 patients were included in this study.

Table 1 *Information of patients who receive CP (n=10):*

Patient no		Sex	Age	Clinical classification	Days of admission from onset of symptoms	Days of getting CP	Symptoms	Comorbidity
01	Sazzad	M	61	Critical	10	12	Fever, Cough, SOB, Sore throat	DM
02	Mainul	M	34	Critical	5	8	Fever, Cough, SOB	
03	Shahidullah	M	63	Critical	8	10	Fever, Cough, SOB, Sore throat	DM, HTN
04	Jahir	M	59	Critical	7	8	Fever, Cough, SOB	DM, HTN
05	Mueed	M	58	Critical	5	6	Fever, Cough, SOB,	DM, HTN
06	Mostafa	M	69	Critical	10	11	Fever, SOB, Sore throat	DM
07	Hasina	F	57	Critical	7	10	Fever, SOB, Sore throat	DM, BA
08	Shudangshu	M	40	Critical	5	7	Fever, Cough, SOB	
09	Fulmoti	F	50	Critical	5	7	Fever, Cough, SOB, Chest pain	HTN
10	Hafiz	M	60	Critical	8	10	Fever, Cough, SOB	COPD

M=Male, F=Female, DM=Diabetes, HTN= Hypertension, BA= Bronchial asthma, COPD= Chronic obstructive pulmonary disease, SOB= Shortness of breath.

Among 10 patients 80% (8) are male and 20% (2) are female. All of them were critically ill COVID patients and 80% (8) had comorbid condition. All these patient ware admitted in COVID ICU in between 5^{th} to 10^{th} (mean 7^{th} day) of their symptoms onset and they got CP in between 6^{th} to 12^{th} (mean 8.9^{th} days).

Table II *Treatments getting other than CP*

Patient no	Antiviral	Antibiotic and antifungal	Corticosteroid	Heparin	Monoclonal antibody (Tociluzumab)	Oxygen therapy before CP	Oxygen therapy after 3d of CP
01	Sized	Remdesivir	Meropenem Moxifloxacin	MPS	UFH		MV MV but step up
02	Mainul	Favipiravir	Meropenem Moxifloxacin	MPS	LMWH		MV MV but step down
03	Shahidullah	Remdesivir	Ceftriaxone Clindamycin	MPS	LMWH		MV MV but step down
04	Jahir	Remdesivir	Meropenem Moxifloxacin	MPS	UFH	Yes	MV MV but step up
05	Mueed	Remdesivir	Meropenem Moxifloxacin	MPS	LMWH		MV MV but step down
06	Mostafa	Remdesivir	Meropenem Moxifloxacin	MPS	LMWH		MV MV but step up
07	Hasina	Remdesivir	Tazo-piper	DEXA	LMWH	Yes	MV MV but step up
08	Shudangshu	Remdesivir	Meropenem Moxifloxacin	DEXA	LMWH	NRM	NRM, No change
09	Fulmoti	Remdesivir	Meropenem Moxifloxacin	DEXA	LMWH	HFNC	NRM
10	Hafiz	Remdesivir	Cftazidime Clindamycin	DEXA	LMWH	BiPAP	MV

MPS= Methylprednisolone, DEXA= Dexamethasone, LMWH= Low molecular weight heparin , UFH= Unfractionated heparin, MV= Mechanical ventilation , NRM= Non rebreather mask, HFNC= High flow nasal cannula, BiPAP= Bi level positive airway pressure

Table III *Laboratory parameters before and after CP (n=10)*

Lymph-ocyte %	CRP		S. Ferritin		LDH		ALT		D-Dimer		APTT		PT					
	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP
01	2.3%	2%	6	320	1500	1460	638	2516	113	115	8.19	5	34	34	14	14	62	60
02	15%	20%	14	10	355	350	500	480	35	36	1.5	2	31	32	13	14	75	80
03	6%	10%	15	14	488	480	345	440	38	42	2.1	2.2	33	35	14	16	72	83
04	13%	10%	48	48	5236	2000	600	950	50	55	3.69	4.34	37.7	34.9	12	12.2	60	59
05	10%	16%	30	24	542	495	480	450	39	41	2.1	2.4	33	34	14	15	60	80
06	15%	10%	177	152	875	1663	430	1200	28	41	1	4.9	34	38	12	13.1	70	65
07	12%	10%	64	170	2411	1834	883	1133	56	55	0.83	1.11	31	31	12	12.4	64	68
08	20%	18%	32	38	2300	2010	470	510	39	40	2.0	2.3	34	36	14	16	67	62
09	15%	20%	40	33	1820	1530	420	405	41	39	1.5	2.0	35	35	13	14	70	81
10	23%	19%	34	39	920	1020	580	520	40	38	2.9	3.6	36	38	14	18	68	70

Table-IV *ICU events (n=10):*

Patient no and data	Oxygen delivery device		Need of FiO2		Need of PEEP		Need of oxygen flow		Oxygen saturation	
	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP	Before getting CP	After getting CP
1	MV	MV	80	90	12	14	50	50	92	90
2	MV	HFNC	70	50	10		50	40	92	98
3	MV	HFNC	80	50	14		50	50	92	96
4	MV	MV	100	100	10	14	60	60	94	94
5	MV	HFNC	80	50	12		50	35	90	98
6	MV	MV	100	100	14	16	50	50	88	86
7	MV	MV	80	90	10	12	50	50	90	90
8	NRM	NRM					15	15	88	88
9	HFNC	NRM	80	50			50	15	90	94
10	BiPAP	MV	80	100	10	12			88	82

Table shows that 40% (04) patients were weaned to oxygen supports, 10% (01) patient's parameters were unchanged and 50% (05) patients were need more oxygen support. 70% (07) patients of total who received mechanical ventilation, after treatment with CP, 30%(03) patients were weaned from mechanical ventilation to high-flow nasal cannula, and 10%(01) patient discontinued high-flow nasal cannula to NRM.

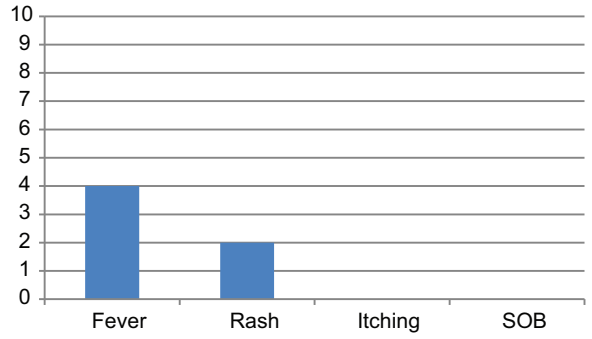

Figure 1 *Showing developments of complications after giving CP (n=10):*

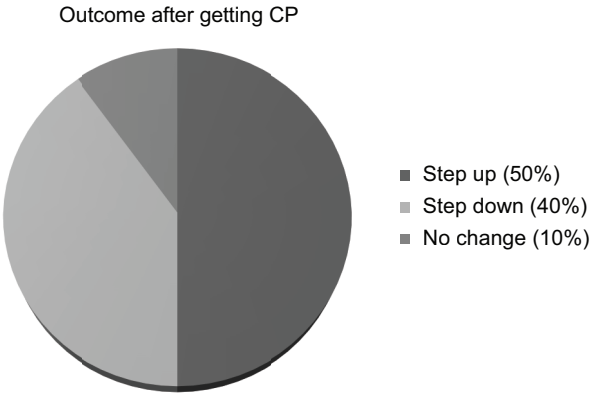

Figure 2 *Pie chart showing outcomes of patients after getting CP (n=10):*

Discussion:

10 criticallyill COVID-19 patients were treated with convalescent plasma. Assessmentwas done from day of treatment with convalescent plasma, and the clinical conditions of these patients were improved, as indicated by normalization of body temperature, improved PAO2/FIO2, chest imaging and biochemical marker of inflammation. Prior to CP treatment, seven patients received mechanical ventilation,one received high-flow nasal cannula oxygenation, one received BiPAP and one received oxygen therapy through NRM. Here data was taken before giving CP and at the third day of giving CP therapy.Lymphocytopenia, an important index for prognosis in COVID19, tended to be improved after CP transfusion, 40% (04)patients showing an increase of lymphocyte counts (Table. 3). Concerning other laboratory tests, we observed a tendency of decrement biochemical marker of inflammation as compared to the status before CP therapy. These included C-reactive protein (CRP), LDH, serum ferritin level. But liver function tests were not conclusive compared to other parameters (alanine aminotransferaseand aspartate aminotransferase (Table 3). An increase of SpO2, a measurement constantly performed in most patients in our study, was found, which could indicate recovering lung function.It was possible to reduce oxygen support (stepdown) of 40%(04) patients, 10% (01) patient's parameters was unchanged and 50% (05) patients were need more oxygen support (step up)after getting CP which correlate with incremental response of lymphocyte counts and detrimental response of biochemical parameters of inflammation.70%(07) patientsof total who received mechanical ventilation, after treatment with CP, 30%(03) patients were weaned from mechanical ventilation to high-flow nasal cannula, and 10%(01)patient discontinued high-flow nasal cannula to NRM. (Table 2).The results highlight the possibility that antibodies from convalescent plasma may have contributed to the clearance of the virus and also the improvement of symptoms. In the current study, all patients received antiviral agents (Favipiravir or Remdesivir) and Tociluzumab, during and following convalescent plasma treatment, which also may have contributed to the viral clearance. Regarding adverse effect 40% (04) patients showed fever and 10% (01) patients developed rashes. No other serious adverse reactions were recorded after CP transfusion.

Limitations:

This study has several limitations. First, this was a small number of patients that included no controls. Second, it is unclear if these patients would have improved without transfusion ofconvalescent plasma, though oxygen requirement and PAO2 / FIO2 represent encouraging findings. Third, all patients were treated with multiple other agents (including antiviral medications), and it is

not possible to determine whether the improvement observed could have been related to therapies other than convalescent plasma. Fourth, plasma transfusion was administered at 6th to 12th days after admission; whether a different timing of administration would have been associated with different outcomes cannot be determined. Fifth, whether this approach would reduce case-fatality rates is unknown.Sixth, we have no facility to follow up with viral load and HRCT scan of chest.

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