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HEALTH SCIENCES

Comparison of safety and efficacy of convalescent plasma with fresh frozen plasma in severe covid-19 patients

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Abstract: background: Role of Convalescent plasma (COPLA) to treat severe COVID-19 is under investigation. We compared efficacy and safety of COPLA with fresh frozen plasma (FFP) in severe COVID-19 patients. Methods: One group received COPLA with standard medical care (n = 14), and another group received random donor FFP, as control with standard medical care (n = 15) in severe COVID-19 disease. Results: The proportion of patients free of ventilation at day seven were 78.5% in COPLA group, and 93.3 % in control group were not significant (p= 0.258). However, improved respiratory rate, O2 saturation, SOFA score, and Ct value were observed in the COPLA group. No serious adverse events were noticed by plasma transfusion in both groups.

Key words: COVID-19, convalescent plasma, donor plasmapheresis, ARDS, immunoglobulins, antibodies.

INTRODUCTION

The SARS-CoV-2 pandemic outbreak involves more than 100 million people worldwide, with almost 1.5 million deaths and counting (Huang et al. 2020). The case-fatality rate of COVID-19 (Corona Virus disease-2019) has ranged from 1.2-13% (Huang et al. 2020, Chen et al. 2020). The current evidence-based strategy relies on providing supportive care in mild to moderate cases and providing mechanical ventilation and extracorporeal membrane oxygenation in severe cases. There is no targeted drug therapy available at present. Some studies have indicated benefits with intravenous Remdesivir and a combination of lopinavir and ritonavir for reducing severity and duration of illness, but not mortality (Cao et al. 2020, Grein et al. 2020, Shen et al. 2020). In the "RECOVERY trial" dexamethasone has shown reduced 28-day mortality among COVID-19 patients with respiratory failure requiring oxygen supplementation and mechanical ventilation (RECOVERY Collaborative Group et al. 2020). The plasma of convalescent patients who have recovered from SARS-CoV-2 infection may contain such neutralizing antibodies, which may accelerate virus clearance in the other COVID-19 infected patients (Chen et al. 2020). Providing passive antibody therapy through convalescent plasma in COVID-19 infection could be one of the approaches toward disease mitigation in the absence of definitive treatment (Zhang et al. 2020, Duan et al. 2020). We compared safety and efficacy of convalescent plasma with fresh frozen plasma (FFP) in severe COVID-19 patients.

MATERIALS AND METHODS

It was an open-labelled, phase II; pilot randomized controlled trial conducted to assess efficacy and safety of convalescent plasma at the Institute of Liver and Biliary Sciences and in collaboration with the Department of Internal Medicine, Lok Nayak Hospital (Maulana Azad Medical College), New Delhi. This trial was approved by institute ethics committee and was registered with ClinicalTrial.gov (identifier: NCT04346446). Total 29 patients were included in study instead of 20 patients in each group due to premature closure of trial in severe COVID-19 patients as per the ministry of health and family welfare guidelines to transfuse convalescent plasma in moderate patients only. We took Informed consent from all the patients before enrolment in the trial. Detailed inclusion and exclusion criteria of the trial are provided with Supplement Material – Table SI as trial protocol. Patients were enrolled for convalescent plasma transfusion and the standard treatment protocol in one group and fresh frozen plasma [FFP] and the standard treatment protocol in another group using block randomization. FFP transfused in the study was collected before the emergence of the virus in our country to avoid any chance of providing COVID-19 convalescent plasma in the control group. The primary outcome measure was the proportion of patients remaining free of mechanical ventilation in both groups on day seven. The secondary outcome measures included mortality at day seven and day 28, improvement in PaO2/FiO2, and the SOFA scores reduction at 48 hours and day 7, duration of hospital stay, duration of Intensive Care Unit stay, requirements of vasopressors, and days free of dialysis up to 28 days from randomization. COPLA was collected from COVID-19 recovered patients after 14 days of complete resolution of symptoms following the national guidelines for plasma donation (Drugs and Cosmetics Act, 1940). The determination of serum neutralization antibodies in donors was done by SARS-CoV-2 Surrogate Virus Neutralization Test Kit (Genscript, USA) and the minimum neutralization titre was 1:80 on ELISA method (Department of Health). The test was used to detect circulating neutralizing antibodies against SARS-CoV-2 which blocks the interaction between the receptor-binding domains of the viral spike glycoprotein (RBD) with the ACE2 cell surface receptor. The S1 RBD IgG antibody titres were determined in recipient samples at baselines and a day after transfusion in both treatment groups.

Clinical and laboratory monitoring was done as per trial protocol and ABO blood group compatible 250 ml plasma in two doses on consecutive days. Continuous variables were expressed as Mean (± SD) or median (range) and compared by Student's t-test or Mann- Whitney U test as appropriate. Categorical data were analyzed by Chi-Square test. To compare pre and post results, a paired t-test test was used. Cox-proportional hazard regression analysis was applied to find the predictor in survival analysis. The actuarial probability of survival was calculated by the Kaplan-Meier graph and compared by the log-rank test. The p-value < 0.05 was considered statistically significant. All statistical tests were performed using SPSS for Windows version 22 (SPSS IBM Corp. Ltd. Armonk, NY)

RESULTS

Total 29 patients were randomized, as shown in figure 1, were comparable in their baseline parameters. The baseline demographic details are provided in table I). The primary outcome shows no statistically significant difference in the proportion of patients free of ventilation on

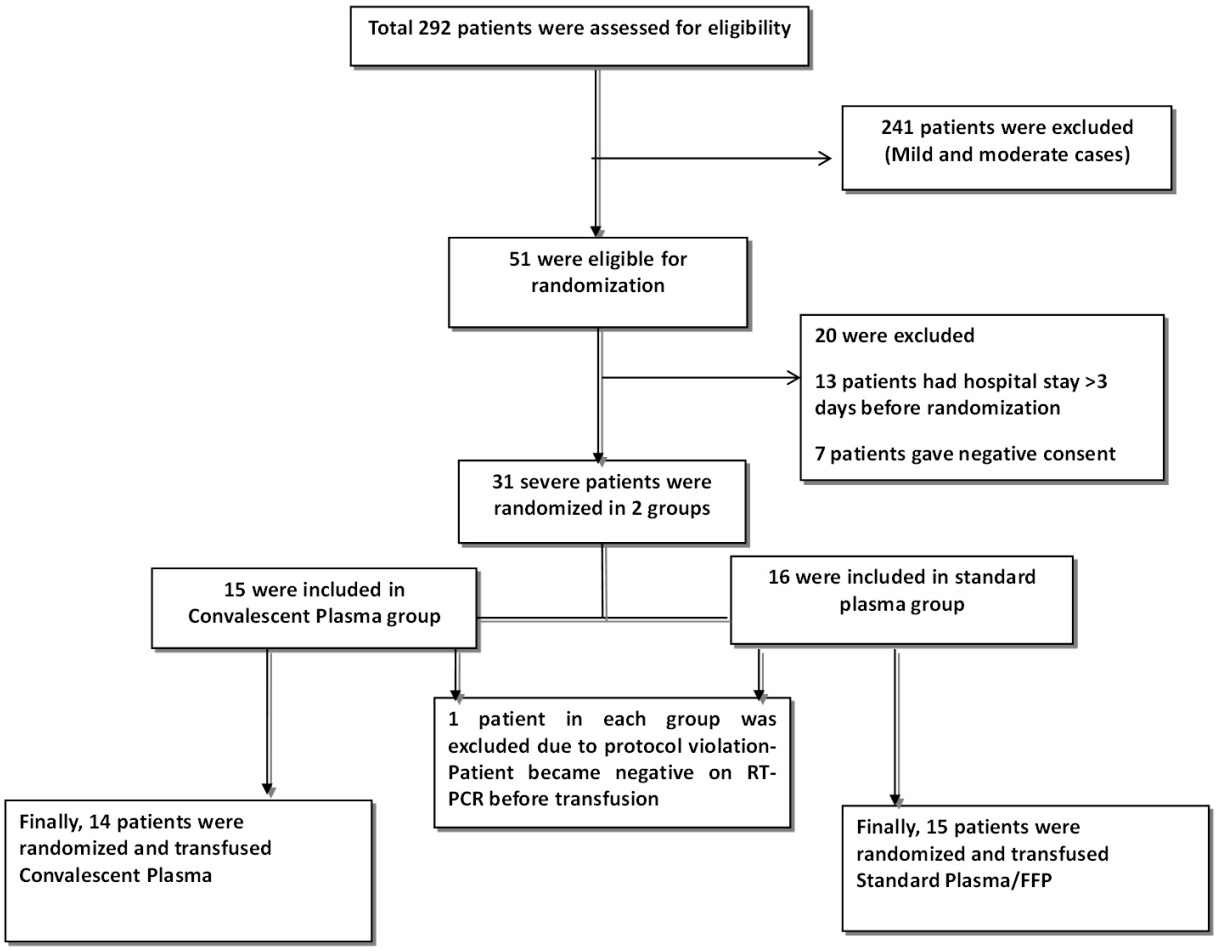

Figure 1. Patient selection and randomization.

day seven. The secondary outcome, including median reductions in respiratory rate per min, earlier improvement in O_2 saturation, and median reduction in SOFA score, favoured the use of convalescent plasma. No statistical improvement was noticed in ICU and Hospital stay in any treatment group, as shown in table II. On laboratory evaluation, the median increment in the Cycle threshold values on day seven showed a higher reduction in the viral load in the COPLA group, although the difference was insignificant (p=0.11), as shown in figure S1 of the supplementary material. The SARS CoV-2 S1 RBD IgG antibody titres of the 14 recipients ranged between 10 and 640 a day after the convalescent plasma transfusion and 0 to 640 after FFP transfusion, as shown in table I of the supplementary material. There was a significant time-dependent increase in the IgG antibody titres in 85.71% (12 out of 14) of the convalescent plasma recipients as compared to 20% (3 out of 15) FFP recipients (p= 0.001).On convalescent plasma transfusion, median post-transfusion IL-6, IL-10, and TNF-α levels were reduced while IL-1β level was increased at day 7. In the FFP group, the median post-transfusion levels of IL-1β and TNF-α were reduced while IL-6 and IL-10 increased, as shown in table II of the supplementary material. All these differences did not attain statistical significance post-transfusion. (Details of

Table I. Baseline characteristics of patients in the study.

Baseline parameters	Overall (n=29)	Convalescent Plasma group (n=14)	Fresh frozen Plasma group (n=15)	p-value
Mean Age (Years)	48.21 ± 9.79	48.14 ± 9.05	48.27 ± 10.75	0.96
Male (n, %)	22 (75.86)	11 (78.6)	11 (73.3)	1.0
Chest X-ray changes (n, %)	25 (86.20)	12 (85.7)	13 (86.67)	0.94
BMI	26.31 ± 2.29	26.28 ± 2.52	26.13 ± 2.22	0.78
Respiratory rate/min	34.9 ± 2.55	35.36 ± 2.65	34.47 ± 2.47	0.38
PaO2 (mmHg)	61.76 ± 4.96	62.71 ± 3.87	61.13 ± 5.74	0.58
O2 Saturation (%)	85.03 ± 4.03	85 ± 4.29	85.07 ± 3.92	0.53
FiO2 (mmHg)	0.38 ± 0.04	0.38 ± 0.03	0.38 ± 0.04	0.89
PaO2/FiO2 ratio	162.92 ± 13.77	164.92 ± 15.85	161.06 ± 11.77	0.43
Baseline Neutrophils (N) (per microliter)	3375 (2626, 6928)	3083 (2700, 7512)	3782 (2432,7520)	0.87
Baseline Lymphocytes (L) (per microliter)	968 (758, 1874)	935 (747, 1872)	1240 (760, 1950)	0.90
N / L ratio	3.8(3.37, 4.67)	3.67 (3.26, 4.46)	4(3.5, 5)	0.60
Platelet count (in lakh per microliter)	1.8 ± 1.20	2.05 ± 1.42	1.58 ± 0.95	0.49
Baseline Ct value	31.91 ± 3.44	30.83 ± 4.07	32.93 ± 2.46	0.12
SOFA Score	7.44 ± 1.86	7.71 ± 1.59	7.20 ± 2.11	0.32

laboratory findings, including cytokines, Ct value, and donor information of convalescent plasma, are provided in table SII). Both the treatment groups were compared for survival analysis using Cox-proportional hazard regression. In the COPLA group, three events of mortality were observed, while in the FFP group, one event was observed, the difference was statistically not significant (HR, 4.23 [95% CI, 0.43-41.6]; P = 0.22). One patient in each of the groups showed signs of mild urticaria during plasma transfusion.

DISCUSSION

Like our pilot trial, many other clinical trials show varying effects of COPLA transfusion in COVID-19, but the safety of convalescent plasma transfusion was on each trial card, including the findings reported by Joyner et al. on 20000 patients with only few transfusion reactions (Joyner et al. 2020). In this novel study, the purpose of using FFP in the control group was to supplement and balance the beneficial and adverse effects of plasma on coagulation abnormalities developing in severe COVID-19 patients to study the added benefits of transfusing SARS-CoV-2 antibodies present in COPLA in compare to FFP. Although no significant results were observed in the primary outcome of weaning of ventilation and mortality, early and significant improvement in O2 saturation, a reduction in respiratory rate,

Table II. Changes in clinical outcome parameters.

Variable	Convalescent plasma (n=14)	Normal plasma (n=15)	p-value
Median Reduction in Respiratory Rate/min at 48 hours	-6.5 (-10.25, -5)	-3 (-5,-1)	0.004
Median Reduction in Respiratory Rate/min at 7 days	-14.5 (-18.75, -13)	-10 (-14,-9)	0.008
Median Improvement in O2 Saturation at 48 hour	6.5 (5, 7.25)	2 (1, 2)	<0.001
Median Improvement in O2 Saturation at 7 days	10 (8.2, 11)	7.5(4.75, 9.25)	0.026
Mechanical Ventilation within 7 days (n) %	3 (21.4)	1 (6.7)	0.258
Median reduction in SOFA Score 48 hours	-2 (-2.25,-1)	-1 (-1, 0.0)	0.01
Median Reduction in SOFA Score 7 days	-5 (-6.5,-4.0)	-3 (-5.25,-2.75)	0.04
Median improvement in PaO2/FiO2 at 48 hour	41.94 (1.25, 55.58)	5.55 (-9.318, 11.11)	0.009
Median improvement in PaO2/FiO2 at 7 days	231.15(183.37, 245.20)	77.01 (56.93, 96.20)	<0.001
Median ICU stay	5 (4,7)	5 (4, 5.7)	0.72
Mean duration of Hospital stay (days)	12.07 ± 4.1	16.07 ± 5.6	0.08
Increase in S1 RBD IgG antibody titre post transfusion	12 (85.7%)	4(26.7%)	0.001
Median Improvement in Lymphocyte count at 7 days	896.5 (524.5, 1351.5)	105(-8, 523)	0.15
Transfusion reactions (n)	1 (7.1%)	1 (6.7%)	1
Median Improvement in Ct value at 7 days	7.7 (3.4, 9.2)	5.15 (3.3, 6.27)	0.11
Mortality till 7 days (n) %	2 (14.28%)	1 (6.7%)	0.60
Mortality till 28 days (n) %	3 (21.4%)	1 (6.7%)	0.25

and SOFA scoring were observed. We found a significant time-dependent increase in the S1 RBD IgG antibody titres and an early increase in the Ct values in patients who received COPLA compared to FFP, similar to Shen et al. specific effectiveness in terms of neutralizing antibodies in the COPLA (Shen et al. 2020). We could also find an increase in S1 RBD IgG antibody titres in FFP group patients, which reflects the natural immune response toward infection. In this pilot trial, early increment in Ct values demonstrated a speedy reduction in the viral load, a laboratory marker for assessing the effectiveness of therapy similar to previous studies done on it (Ng et al. 2018, Wu & McGoogan 2019). Although, few observational studies favored outcome with COPLA transfusion (Shen et al. 2020, Zhang et al. 2020, Duan et al. 2020).

Further, Libster et al. found that early transfusion of high-titer convalescent plasma in COVID-19 infection can reduce the disease's progression (Libster et al. 2021). We did not find statistically significant improvement in severe and critically ill COVID-19 patients in terms of need of ventilation and mortality after 28 days of monitoring, similar to the findings observed by Li et al., PLACID trial, and PlasmAr Study Group (Li et al. 2020, Agarwal et al. 2020, and Simonovich et al. 2020). Libster et al. found that early transfusion of high-titer convalescent plasma in COVID-19 infection can reduce the disease's progression (Libster et al. 2021). The

appearance of the anti-inflammatory marker IL-10 and reduction in levels of pro-inflammatory markers (IL-1, IL-6, and TNF- TNF-α) has been well correlated with the disappearance of clinical symptoms. Further, the decrease in the level of pro-inflammatory markers (IL-6 and TNF-α) and increase in anti-inflammatory marker IL-10 after COPLA transfusion shows it may limit immune-mediated damage in the COPLA group, while in FFP group, we found only a decrease in TNF-α level with the beneficial effect of FFP on endothelium lining and coagulation system (de Brito et al. 2016, Velazquez-Salinas et al. 2019, Straat et al. 2015).

COPLA therapy is safe and may be beneficial for COVID-19 patients (in terms of clinical and laboratory parameters). More extensive clinical trials are needed to be conducted with Convalescent plasma in different drugs combination and at different timing (early and delayed) in patients to explore the role and efficacy of COPLA transfusion.

CONCLUSION

COPLA therapy is safe and may be beneficial for COVID-19 patients (in terms of clinical and laboratory parameters), and more extensive clinical trials are needed to draw more robust conclusions.

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SUPPLEMENTARY MATERIAL

Figure S1. Reduction in viral load after transfusion (ct value).
Table SI. Convalescent Plasma Donation Details (n=14).

Table SII. Median baseline and post transfusion cytokine level.

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