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CONVALESCENT PLASMA: ITS EFFECTIVENESS IN TREATING MODERATE AND SEVERE CASES OF COVID 19 IN A TERTIARY CARE CENTRE IN UTTARAKHAND

Transfusion Medicine

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ABSTRACT

Introduction: Convalescent plasma, is the component of blood which contains antibodies and is obtained from people that have recovered from COVID- 19. These antibodies have antiviral properties and may be useful in COVID 19 patients In our study we intend to study the benefits of plasma by observing various clinical parameters on patients before and after therapy. If a significant improvement is seen we can suggest its use in the treatment of COVID-19. Since the current pandemic has taken a toll on millions of lives so far, it is important that we come up with newer treatment methods and also study the importance and relevance of already suggested treatment modalities to improve patient care. **Aim :** To study the effectiveness of COVID - 19 convalescent plasma in the treatment of COVID-19 by comparing 28 day mortality and various lab parameters and clinical improvement of patients that received plasma therapy vs those that did not. **Material Method:** This is a clinical case control study from September 2020 to May 2021 conducted in Blood Bank, Government Doon Medical College and Hospital, Dehradun. 100 patients suffering with moderate and severe COVID 19 disease were taken in the study who were transfused with convalescent plasma and 100 control patients were taken who were only given best supportive treatment. Various clinical and serological parameters were studied in the two groups to see its effectiveness on the patients status. Serological parameters included in the study are C- reactive protein, IL-6 and serum Ferritin. **Results:** On performing chi square test, no significant difference between plasma and control groups in the clinical outcome after 28 days both for moderate cases (P=0.261) and severe cases (P=0.191) was found. The overall difference in mortality in the two groups was also not statistically significant (p=0.415). The mean biochemical lab parameters showed an overall downward trend in both the groups but difference in the improvement was not statistically significant except in case of interleukin 6 that improved significantly in patients that received plasma therapy (p=0.01) **Summary:** Convalescent Plasma therapy did not show any additional benefit in clinical outcome, reduction in 28 day mortality and lab parameters s except for IL-6.

KEYWORDS

COVID – 19, convalescent plasma, C- Reactive Protein, Serum Ferritin, Interleukin 6 (IL-6)

INTRODUCTION

In the past Convalescent plasma (CP) has been used in the treatment of many bacterial and viral diseases effectively such as influenza A H1N1 [1] , Spanish flu, and even more recently Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and Ebola virus [2-4]. Convalescent plasma (CP) contains receptor binding domain specific antibodies which have potent antiviral activity [5,6]and is well-tolerated by the patients with few adverse effects which can be easily managed [7].

Studies have shown that virus-neutralizing antibodies in the form of convalescent plasma may accelerate the process of disease resolution and may be helpful in the treatment of COVID-19 [8,9]. The US FDA and Indian Central Drugs Standard Control Organization had approved the use of convalescent plasma therapy (CPT) for COVID-19 [10]. In India, use of convalescent plasma therapy was approved by the Ministry of Health and Family Welfare (MoHFW) I during COVID -19 pandemic in patients with moderate to severe COVID-19 patients who were not improving despite the use of steroids [11].

AIM

To study the effectiveness of COVID - 19 convalescent plasma by comparing the 28 day clinical outcome, mortality and serological lab parameters such as C- reactive protein (CRP), Interleukin 6 and serum Ferritin in patients that received plasma therapy vs patients that received best supportive medical care only for the treatment of COVID 19.

MATERIALS AND METHODS

The is a clinical case control study from September 2020 to May 2021 and conducted in Blood Bank, Government Doon Medical College and Hospital, Dehradun. We took a convenience sample of 100 patients that tested positive for COVID 19 and admitted to Government Doon Hospital that were transfused with convalescent plasma therapy in course of their treatment of COVID- 19 were enrolled in the study (CPT group) and 100 control patients of COVID-19 were taken who were not transfused with convalescent plasma but were given best supportive medical treatment which was according to the standard treatment guidelines by Ministry of Health and Family Welfare version 3 prevailing at that time [11].

A prior informed consent was taken before plasma therapy from each patient. Clinical assessment of the patients was done on the basis of WHO 10 point ordinal scale of clinical progression [Table 1]. This scale was used to assess patients at the time of admission and outcome at 28 days.

Post transfusion various serological parameters like C- reactive protein (CRP) , IL 6 and serum Ferritin of the patients were assessed on day 1, day 3 and day 14 and were compared with the serological parameters in control group.

Quantitative measurement of high-sensitivity C-reactive protein was done by particle enhanced immunoturbidometric assay. Electrochemiluminescence immunoassay (ECLIA) sandwich method was used for the quantitative determination of Serum Ferritin and automated ELISA for IL-6.

28 day treatment outcome, serological lab parameters and mortality in CPT and control group were compared using chi-square test. p-Value <0.05 was considered statistically significant.

Inclusion Criteria

Moderate to severe COVID 19 positive patients of age more than 18 years that were transfused with convalescent plasma for COVID-19 treatment in Government Doon Hospital.

Exclusion Critera:

In our study we excluded Mild cases of COVID-19, patients below the

age of 18 years, patients that were transfused convalescent plasma for treatment outside our hospital or patients that were given plasma transfusion for any other reason

Table 1: WHO 10 – point ordinal scale of clinical progression

Uninfected	No clinical/ virological evidence of disease	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised (moderate disease)	Hospitalised, no oxygen therapy	4
	Oxygen by mask / nasal prongs	5
Hospitalised (severe disease)	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO2/ FiO2150 or SpO2/FiO2200	7 (ventilator)
	mechanical ventilation pO2/ FiO2< 150 (SpO2/FiO2>200) or vasopressors	8 (ventilator)
	Mechanical ventilation pO2/ FiO2< 150 and vasopressors, dialysis or ECMO	9 (ventilator)
Dead	Death	10

DONOR SELECTION CRITERIA:

Convalescent Plasma donors were selected as per the criteria defined by Drugs and Cosmetics (second Amendment) Rules, 2020 in order to be selected for donation (12) .

For the purpose of the present study, qualitative immunoassay of anti SARS-COV2 IgG was done and results were based on the sample signal-to-cut- off (S/CO) ratio, with values <1.0 and ≥1.0 corresponding to Negative and Positive results. The volume of plasma donated by donor was 400 ml. The first 200 ml (one unit) plasma was infused over one to one and half hours. If the patient did not show any improvement after 24 h, based on the decision of the responsible physician, another unit of plasma was administered.

RESULTS:

The mean (SD) age of patients in test group was 54.3 (15.9) years and mean age of patients in the control group was 52.3(13.6) years . Maximum number of patients in both the groups were between 50- 60 years i.e. 38% and 42% respectively [Table 2]. Out of 100 patients in the study 68% were males and 32% were females in test group and in control group 63% were males and 37% were females.

In the test group that received plasma therapy along with best supportive treatment out of 100, 36 patients were moderately ill (WHO score 5) at the time of admission and 64 patients were severely ill (WHO score≥ 6) [Table 3].

Table 2: Distribution of cases according to Age

S. NO.	Decade	No. of Patients (CPT group)	No. of Patients (Control group)
1.	21 -30	10 (10%)	7 (7%)
3.	31- 40	9 (9%)	11 (11%)
4.	41-50	18 (18%)	16 (16%)
5.	51-60	27 (27%)	42 (42%)
6.	>60	36 (36%)	24 (24%)
7.	Total Cases	100	100

Table 3: Distribution of Cases according to Severity

S.No.	Severity of Disease	No. of Patients (CPT group)	No. of Patients (Control group)
1.	Moderate (WHO score 5)	36 (36%)	41(41%)
2.	Severe (WHO score6)	64(64%)	59(59%)

At the end of 28 days, following plasma therapy and best supportive treatment 29 out of 36 (81%) moderate cases improved and became ambulatory whereas 26 out of 41(63.4%) moderate cases in control group became ambulatory. However, there was no significant statistical difference in the improvement between the two groups (p=0.09). 11 out of 64 (17%) severe cases became ambulatory in CPT group and 9 out 59 (15%) severe cases in control group became ambulatory with no statistical difference between the two groups (p=0.772).

Overall, there was no significant difference between CPT and control groups in the outcome after 28 days both for moderate cases (P=0.261) and severe cases (P=0.191) [Table 4].

The overall mortality in severely ill patients of CPT group was 5 out of 64 (8%) vs control group was 7 out of 59 (12%). This difference is also not statistically significant (p=0.415).

The mean serological lab parameters such as mean CRP, mean Serum Ferritin and mean IL-6 level showed an overall downward trend in patients post plasma therapy. Similar downward trend was also seen in patients that received best supportive treatment and the difference in the improvement of lab values was not statistically significant except in case of interleukin 6 that improved significantly in patients that received plasma therapy (p=0.01) by day 14 [Table 5].

Table 4: 28 day Outcome of Patients that received Plasma therapy vs Patients that received best supportive treatment only

Severity (N=100)	Ambulatory		Moderate		Severe		Death		P value
	CPT	Control	CPT	Control	CPT	Control	CPT	Control	
Moderate	29 /36	26/41	5/36	14/41	2 /36	1/41	00	00	P=0.261 Chi square test
Severe	11/64	09/59	39/64	29/59	9/64	14/59	05/64	07/59	P=0.191 Chi square test
Total	40/100	35/100	44/100	43/100	11/100	15/100	05/100	07/100	

Table 5: Comparison Of Mean Serological Lab Parameters In Patients That Received Plasma Therapy Vs And Best Supportive Treatment:

LAB PARAMETERS (mean)	Day 1 (CPT)	Day 1 (control)	P value	Day 3 (CPT)	Day 3 (control)	P value	Day 14 (CPT)	Day 14 (control)	P value
CRP (mg/ L)	87.17 ± 57.9	114.7 ±166	0.27	35.8± 30.7	43.54 ± 58	0.41	12.9± 18.0	16.38 ±25.9	0.18
S. FERRITIN (ng/ml)	1143.2± 620	1154 ± 681	0.92	794 ± 430	925.2 ± 535.9	0.17	631 ± 419	744.98 ± 430	0.44
IL-6 (N= 0-44 pg/ml)	34.64 ± 43	47.82 ± 66	0.24	13.20 ± 13	21.46 ± 26	0.05	5.89 ± 7.3	12.3 ± 16.3	0.01*

*P<0.05 is significant.

REFERENCE RANGE: CRP = <5.0 mg/L; Serum Ferritin (male)= 30-400 ng/ml (Female) 13-150 ng/ml; IL-6=0-7pg/ml; as per

DISCUSSION

This study was done to study the effectiveness of convalescent Plasma in patients with moderate to severe COVID-19 disease by comparing the 28 day clinical outcome, mortality and lab parameters in patients that received CP and best supportive treatment with control group that received best supportive treatment only.

In our study we found no significant difference in the clinical outcome after 28 days and mortality between CPT group and control groups. Our findings were similar to study conducted by Ling li et al. who also found no significant difference in clinical parameters or 28 day mortality (15.7% vs 24%; p = 0.3; OR = 0.59, 95% CI: 0.22–1.59) in CP group versus control group [13].

Study conducted by Agrawal al. on patients with moderately severe COVID 19 also found no significant difference in the two groups in terms of duration of respiratory support, proportion of patient requiring invasive ventilation and vasopressor support. Mortality in CP group vs control group was 14.5% vs 13.5% respectively (odd ratios was 1.06). However, the study did not include any life threatening COVID-19 patients [14]. Budhiraja et al, also found that there was no significant difference in mortality between CP and non CP group (22.4% vs 18.5%; p = 0.125) [15].

In another study by Altuntas et al., there was a significant reduction in duration of stay in ICU in CP versus control group (9 days vs 12 days; p = 0.001) with reduction in rate of mechanical ventilation and a significant reduction in vasopressor requirement (24.7% vs 34.3%; p =

0.001) . But the there was no statistically significant difference in the fatality rate between the CP and control groups (24.7% vs 27.7%, p = 0.150) [16].

Klassen et al. compared findings from various studies and found that CP showed a 51% reduction in mortality rate as compared to patients that standard treatments only (19% vs. 29% mortality; 95% CI: 0.37, 0.64, p < 0.001) [17]. Study by Salazar et al. showed a significant reduction in mortality in COVID-19 patients with severe disease (2.7% vs 8.9%; p = 0.04) [18].

Another study by Abolghasemi et al., conducted on moderately ill COVID-19 patients, demonstrated that significantly more number of patients were discharged from hospital within a period of 5 days versus control (28.1% vs 8.9%; p = 0.010). But there was no significant difference in mortality in CP group versus in control group (p = 0.09) [19].

Our study showed slight improvement in serological parameters in plasma group vs non plasma group but this difference was not statistically significant except in case of interleukin 6 (p=0.01). Similar to our study, significant reduction in CRP was noted in a study by Alsharidah et al, CRP in moderate as well as severe groups(p = 0.001) [20]. Study by Kurnianda et al also showed significant improvements in CRP values (p = 0.0041) after CP transfusion, while other serological parameters such as IL-6 and procalcitonin also showed an improvement but was not statistically significant [21].

CONCLUSION

From our retrospective study CP administration in patients with moderate and severe COVID-19 was not associated with significantly improved clinical outcomes and reduction in mortality rates. In addition, administration of CP in both moderate and severe cases was associated with improvement in serial serological lab parameter, however this improvement was not statistically significant except in case of IL-6 which showed significant improvement.

Limitations of the study

During the study duration, patients also received several treatments depending on the prevailing hospital guidelines at that time and we did not observe any interaction between these drugs and effect of CCP in our patients. We also did not determine the titre of SARS-CoV-2 IgG antibodies in CCP donors, due to a lack of these tests at that time in our hospital.

REFERENCES

1. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011 Feb 15;52(4):447-56. doi: 10.1093/cid/ciq106. Epub 2011 Jan 19. PMID: 21248066; PMCID: PMC7531589.
2. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. N Engl J Med. 2016 Jan 7;374(1):33-42. doi: 10.1056/NEJMoa1511812. PMID: 26735992; PMCID: PMC5856332.
3. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med. 2006 Oct 17;145(8):599-609. doi: 10.7326/0003-4819-145-8-200610170-00139. Epub 2006 Aug 29. PMID: 16940336.
4. Marson P, Cozza A, De Silvestro G. The true historical origin of convalescent plasma therapy. Transfus Apher Sci. 2020 Oct;59(5):102847. doi: 10.1016/j.transci.2020.102847. Epub 2020 Jun 12. PMID: 32565057; PMCID: PMC7289739.
5. Zeng QL, Yu ZJ, Gou JJ, Li GM, Ma SH, Zhang GF, et al. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in Patients With Coronavirus Disease 2019. J Infect Dis. 2020 Jun 16;222(1):38-43. doi: 10.1093/infdis/jiaa228. PMID: 32348485; PMCID: PMC7197534.
6. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020 Apr;20(4):398-400. doi: 10.1016/S1473-3099(20)30141-9. Epub 2020 Feb 27. PMID: 32113510; PMCID: PMC7128218.
7. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin Proc. 2020 Sep;95(9):1888-1897. doi: 10.1016/j.mayocp.2020.06.028. Epub 2020 Jul 19. PMID: 32861333; PMCID: PMC7368917.
8. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected: interim guidance. (2020).
9. Nie J, Li Q, Wu J, Zhao C, Hao H, Liu H, et al. Establishment and validation of a pseudovirus neutralization assay for SARS-CoV-2. Emerg Microbes Infect. 2020 Dec;9(1):680-686. doi: 10.1080/22221751.2020.1743767. PMID: 32207377; PMCID: PMC7144318.
10. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ. 2020 Mar 26;368:m1256. doi: 10.1136/bmj.m1256. PMID: 32217555.
11. Ministry of Health & family Welfare. Clinical Management Protocol: COVID-19 version 3, dated 13/6/20 www.mohfw.gov.in/pdf/ClinicalManagementProtocolfornormalCOVID19.pdf.
12. Final G.S.R. 166(E)_Amendment in Part X B & Part XII B pertains to Blood center and Blood components, Drugs and Cosmetics Act 1940 and Rules 1945, amended 11th March 2020 (accessed 2020 March 18, Cited 2020 July 23), available from, https://cdsco.gov.in/opencms/opencms/en/Notifications/Gazette-Notifications.
13. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA. 2020 Aug 4;324(5):460-470. doi: 10.1001/jama.2020.10044. Erratum in: JAMA. 2020 Aug 4;324(5):519. PMID: 32492084; PMCID: PMC7270883.
14. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020 Oct 22;371:m3939. doi: 10.1136/bmj.m3939. Erratum in: BMJ. 2020 Nov 3;371:m4232. PMID: 33093056; PMCID: PMC7578662.
15. Budhiraja S, Dewan A, Aggarwal R, Singh O, Juneja D, Pathak S, et al. Effectiveness of convalescent plasma in Indian patients with COVID-19. Blood Cells Mol Dis. 2021 May;88:102548. doi: 10.1016/j.bcmd.2021.102548. Epub 2021 Feb 18. PMID: 33621948; PMCID: PMC7891064.
16. Altuntas F, Ata N, Yigenoglu TN, Bascı S, Dal MS, Korkmaz S et al. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci. 2021 Feb;60(1):102955. doi: 10.1016/j.transci.2020.102955. Epub 2020 Sep 19. PMID: 33011076; PMCID: PMC7501849.
17. Klassen SA, Senefeld J, Johnson PW, Carter RE, Wiggins CC, Shoham S et al. The Effect of Convalescent Plasma Therapy on COVID-19 Patient Mortality: Systematic Review and Meta-analysis. medRxiv [Preprint]. 2021 Feb 2:2020.07.29.20162917. doi: 10.1101/2020.07.29.20162917. Update in: Mayo Clin Proc. 2021 May;96(5):1262-1275. PMID: 33140056; PMCID: PMC7605561.
18. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. Am J Pathol. 2020 Nov;190(11):2290-2303. doi: 10.1016/j.ajpath.2020.08.001. Epub 2020 Aug 11. PMID: 32795424; PMCID: PMC7417901.
19. Abolghasemi H, Eshghi P, Cheraghali AM, Imani Fooladi AA, Bolouki Moghaddam F et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study. Transfus Apher Sci. 2020 Oct;59(5):102875. doi: 10.1016/j.transci.2020.102875. Epub 2020 Jul 15. PMID: 32694043; PMCID: PMC7362821.
20. Alsharidah S, Ayed M, Ameen RM, Alhuraish F, Rouheldeen NA, Alshammari FR, et al. COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: A multicenter interventional study. Int J Infect Dis. 2021 Feb;103:439-446. doi: 10.1016/j.ijid.2020.11.198. Epub 2020 Dec 4. PMID: 33285283; PMCID: PMC7717772.
21. Kurnianda J, Hardianti MS, Triyono T, Thobari JA, Trisnawati I, Wisudarti CFR et al. Efficacy and safety of convalescent plasma therapy in patients with moderate-to-severe COVID-19: A non-randomized comparative study with historical control in a referral hospital in Indonesia. J Infect Public Health. 2022 Jan;15(1):100-108. doi: 10.1016/j.jiph.2021.10.028. Epub 2021 Nov 10. PMID: 34794908; PMCID: PMC8579701.