Original Research Article

Convalescent Plasma Safe, Effective and Supportive Tool During Covid-19 Pandemic- 6 Months Retrospective Study at a Tertiary Care Hospital

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Abstract

Background: Convalescent Plasma (CP) is one of the promising & effective modality of massive immunization during pandemic, as currently no licensed vaccines or therapeutics are available. Systematic extraction of Single Donor Plasma (SDP) from post-Covid recovered patients by one of the useful method by Apheresis technique. Our study is to determine the role and efficacy of CP in Covid-19 infection. A total of 92 donors from Post-Covid recovered patients and their CP were extracted and collected by means of apheresis technique. 52 donors were between age group of 20 -35 yrs, 32 donors between 30 – 50yrs, 8 donors between 50-65 yrs. A total of 201 patients received CP, out of which 184 showed signs of recovery 16 reported deaths as these were severely critical & CP was ineffective in these cases. Our study has 50 control groups who did not received any convalescent therapy. In case of moderate to Severe Covid Patients, Plasma transfusion improves clinical condition and decreases mortality rates {p-value-0.001}. CP seems to be a safe and probably effective treatment for critically-ill patients with COVID-19.CP use should be encouraged to be made within the scope of clinical trials in cooperation with national and international health authorities.

Keywords: Convalescent Plasma (CP), Apheresis, SARS COV2.

Introduction

Covid-19 infection caused by novel Corona Virus SARS-COV2 was first identified at Wuhan China, which produces pneumonia like symptoms predominantly affects lungs has reportedly higher mortality rate than the seasonal flu [1-2], Subsequently WHO declared pandemic on 11 March 2020 [3]. As if now more than 50 million confirmed cases of Covid19 are in the world wide. The mortality increase with associated co-morbid conditions like COPD, DM, HTN, old age, H/o smoking also increased mortality. Although there were clinical trials regarding the development of therapeutics and vaccines, but there are currently no licensed vaccine for Covid19. Passive antibody therapy features a history going back to 1890's and was the sole method of treating some infectious conditions before the event of antimicrobial therapy in 1940s. Passive antibody therapy involves administering antibodies against a particular agent to susceptible individuals in order to protect or treat an infectious disease associated with this agent. On the contrary active vaccines require stimulation of an immune response takes time to develop. Therefore, passive antibodies administration is the only way to immunize people immediately. Anti SARS CoV-2 antibody-containing plasmas, obtained from the recovered individuals who had confirmed COVID-19, began to be collected using apheresis devices and stored in blood banks in some countries in order to administer to the patients with COVID-19 for reducing the necessity of intensive care and the mortality rates. Therefore, during this review, we aim to point out some important issues associated with convalescent plasma (CP) and its use in COVID-19. CP could also be an adjunctive treatment choice to the anti-viral therapy. The protective effect of CP may continue for weeks and months. After the assessment of the donor, 200-600 mL plasma is often collected with apheresis devices. The donation interval may vary between countries. Even though limited published studies are not prospective or randomized, until the development of vaccines or therapeutics,

CP seems to be a safe and effective treatment for critically ill patients with COVID-19. It could also be used for prophylactic purposes but the potency and effectiveness of this approach should be tested in randomized prospective clinical trials.

This innovative study was undertaken for-

1. Systematic extraction of SDP (single donor plasma) from Post Covid recovered Patients by Apheresis technique.
2. Usage of CP in Covid-19 infection.
3. To determine safety & efficacy of CP in management of Covid-19 of moderate to severe category.

Materials and Methods

This study is retrospective study of 6 months duration between MAY 2020 to OCT 2020 at Chirayu Medical College & Hospitals, Bhopal INDIA. All the donors registered under the Apheresis Centre of Blood Bank under the Dept. of Pathology were taken for recruitment and predonation evaluation were made under following criteria.

Donor Inclusion criteria

1. Summary of diagnostic test of RTPCR during hospital stay with discharge summary were mandatory.
2. Complete resolution of Covid symptoms at least 28 days prior to donation.
3. Healthy donors of post Covid both male & female between age group 25-65yrs, wt>60kgs for males &>50 kgs for females.
4. Any antibody titer if available are measured & noted.

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5. Donor consent with no h/o of fever in the last 10 days.

Donor Exclusion criteria

Pregnant woman, H/o any Co morbid conditions like DM, HTN, COPD were rejected for donation.After successful completion of predonor evaluation they were subjected to apheresis machine at the blood bank centre. CP were extracted from each donor up to 400ml, the collected plasma volume (excluding the anticoagulant) should not exceed 600ml for each apheresis

Procedure of plasma collection- by aphaeresis technique

Before the procedure

Before convalescent plasma therapy, the health care team prepares the donor for the procedure. A health care team member inserts a sterile single-use needle connected to a triple tube (intravenous, or IV, line) into the cubital vein in one of the arms of the donors and the tube is connected to the aphaeresis device. There is a continuous flow of ACDA (Acid Citrate Dextrose Anticoagulant) in the triple tube.

During the procedure

Blood gets extracted from the vein of the donor and flows from the triple tube and reaches the centrifuge chamber of the aphaeresis device. First 50ml of blood reaching the chamber, plasma gets separated from the blood and plasma is collected in a separate bag and remaining amount of blood is pumped back through the device into the donor. Multiple rounds of extraction takes place thereby minimizing the loss of blood from the donor and maximizing the extraction of plasma. It takes about one to two hours to complete the procedure. During the procedure the donor may feel little tingling and numbness because of the anticoagulants, to overcome this we provide chewable calcium tablets for chelation. At the end of each procedure nearly 400ml of plasma were extracted from each donor to make two units of 200ml each.

After the procedure

Donors were given refreshments and closely monitored, observed for an hour after donating the convalescent plasma. Necessary advices were given such as taking ample amount of fluids; avoid driving and heavy exercising for next 24hours.

Storage and usage

CP can be stored by freezing or can be supplied within 6hr without freezing. Freezing should be started within first 6 hr of completion of aphaeresis procedure. The dose of CP in all clinical trials, one unit of plasma (200ml) has been planned for treatment. The same were used in our study.

Patient or recipient selection-

Following criteria were used

1. Lab confirmed Covid-19 by diagnostic RTPCR.
2. Severely affected Covid-19 of moderate to severe category clinically, pathologically & by Radiological Parameters.
3. Falling saturation with multiorgan dysfunction.
4. All the cases admitted in ICU for critical care management.
5. Critically deranged pathological and biochemical parameters.

Control groups /patients who did not receive plasma therapy

In our study, the control groups who did not receive CP were about 50(all under moderate to severe category.

Statistics

As our study involves donors, recipients (tests) and control groups from various age groups 18-60yrs.Test and control groups from mild, moderate and severe covid category. Hence the relevant Statistical designs in our study used are population based age-gender distribution, Chi-square test, and p value for statistical significance.

Results

Donor distribution based on age and sex

A total of 92 donors (Graph-1) and their CP were extracted and collected by means of Aphaeresis Technique. Out of which 80 were males & 12 were females. (Graph-2)

- 52 donors were between age group 20 -35 yrs.
- 32 donors between 30 – 50yrs.
- 8 donors between 50-65 yrs.

Outcome of study in test groups

A total of 201 patients (Table 2) received CP out of which 161 were males & 40 were females, 124 patients were from (ICU, SICU, and MICU) critically ill patients under intensive treatment 19 patients were from Covid ward of moderate category, few patients required multiple doses of CP, and each unit of CP consists of 200ml.

Characteristics of outcome in test groups

Out of all total number of patients received CP, 184 patients showed signs of recovery & their radiological & pathological parameters improved and subsequently discharged 1 patient developed mild reaction to TRALI, 16 deaths reported as these were severely critical & CP was ineffective in these cases (**Table-3**).

Outcome of study in control groups

In our study, the control groups who did not received CP were about 50(all under moderate to severe category) out of which 20 got recovered and 30 died due to covid complications.

Comparison with other studies

Hence with all these available data the recovery rate of plasma therapy is significantly high nearly 90% & mortality of those received CP drastically reduced to 8%. Hospital stay of these patients who received convalescent therapy has drastically reduced then those who not received CP; hence our study is in concordance with the study conducted by Wuhan & Korea (**Table 3**). CP seems to be effective & one of the adjuvant and supportive role in the management of Covid-19 during pandemic when definite treatment is not available.CP is more beneficial than its adverse effects as it activates complement system which is useful for denaturation and neutralization of virus by promoting Ag-Ab reaction and also promoting cytotoxic mediated lysis by T-cell activation which is a scientific reason. Hence CP has net beneficiary effect in management of Covid-19 patients.

Statistical Analysis

The statistical methods used in this study were Chi- Square and p value**.** P value (<.001) showing highly significant for our research study.

Table 1:Cases and control

	Case	Control	Total
Recovered	a(184)	b(20)	204
Death	c (16)	b(30)	46
Total	200	50	250(N)

Chi- Square

$$X^2 = \frac{(ad-bc)^2 \times N}{(ad+bc)(b+a)(c+a)(a+c)}$$

$X^2 = 62.5$

***P value <0.001*Showing highly statistically significant Result**

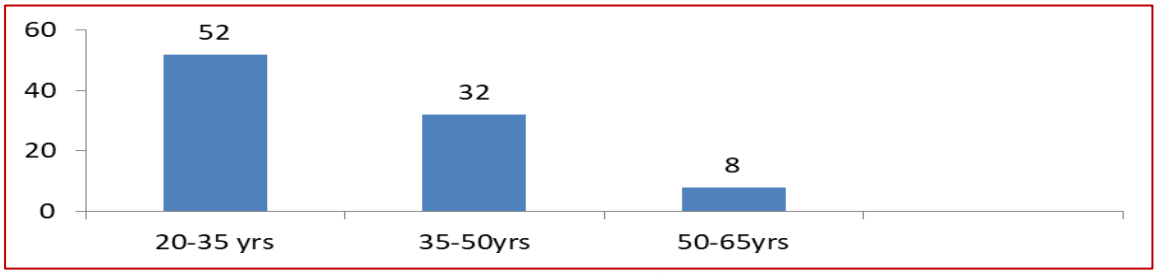

Fig 1: Age distribution of donors

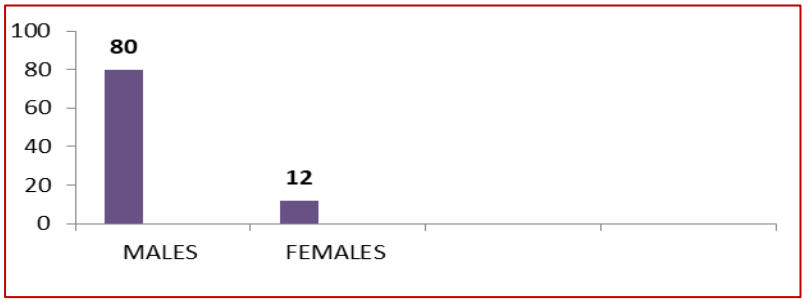

Fig 2: Gender distribution of donors

Table 2: No of patients received convalescent therapy (n- 201)

Covid -Category	No of patients
Moderate	51
Moderate to severe	110
Severe	40
Total	**201**

Table 3:Response to convalescent therapy

	No of patients (test group)	Controls groups	P Value
Recovered	184 (91.50%	20 (40%)	
Deceased/Death	16 (8%)	30 (60%)	
Reaction	01 (0.50%)	-	
Total	**201**	**50**	**<0.001**

Table 4: COVID-19- Recent trials and locations with key findings

No. of Patients in Trial/ Locations	Dose of CP &Titers	Key Findings
Shenzhen, China [14] 5 patients,	400ml in two consecutive doses of 200 ml each • ELISA anti-SARS CoV-2 antibody titre less than 1:1000 • Neutralising antibody titres> 40	Clinical status improved, SOFA score decreased, ARDS resolved, viral antibodies not detectable, increase in PAO2/FIO2 (range 172-276 before and 284-366 after), all were on other medications including steroids and antiviral, no significant adverse effects reported
Wuhan, China [15] 10 patients,	200ml-500ml Neutralising anti-SARS CoV-2 antibody titres> 1:640	Clinical status improved, increased oxyhemoglobin saturation, absorption of lung lesions in radiographic examination noted, significant adverse effects, other therapy included steroids, antimicrobials and antiviral.
Korea [18] 2 patients,	500 ml in total; infused 250ml twice in 24 hrs Antibody titre Not stated	1 patient was successfully extubated and discharged from hospital while other also showed immediate improvement.
Beijing, China [32] 245 patients,	Not stated Antibody titre Not stated	91 patients benefitted, plasma therapy said to be safe and effective
Chirayu Medical College, Hospital Research Center Bhopal, (M.P.), India 201 patients	200ml of CP Few with multiple doses	184 showed signs of recovery, CP therapy to be safe and effective, NO significant adverse effects

Discussion

Convalescent Plasma (CP) therapy includes administration of immunoglobulin's containing plasma of a recently recovered individual from a selected infection (SARS-2) to a person who is susceptible or, infected (has manifested symptoms) for specific disease (such as COVID-19) for the aim of prophylaxis and treatment [10]. In our research study 201 patients receive plasma therapy, nearly 134 patients improved their pathological and radiological parameters after CP and were discharged eventually.50 patients received multiple dosages along with steroids and Remdesivir, their oxygen saturation were gradually improved and transferred from ICU to general wards and subsequently discharged after complete recovery. Hence our study is comparable with other research studies and meta-analysis conducted at Wuhan city of China and Korea having good concordance with them. The details of these studies are discussed further in the discussion part below.

Mechanism of Action

Immunized plasma acts by binding to a given pathogen including virus (SARS-2) directly and causing its denaturation & neutralization, eventually eradicating the latter from the peripheral blood stream while other antibody mediated pathways including compliment system, antibody dependent cell-mediated cytotoxicity and phagocytosis might also contribute towards the therapeutic effects achieved [11].

In the absence of any proven drugs or, therapy, convalescent plasma (CP) has been used previously in outbreaks of Machupo virus, Junin virus, Lassa fever and few others to name. In recent times, Convalescent plasma therapy has been used effectively in treating SARS, MERS and Ebola virus outbreaks. Some studies also suggest convalescent plasma therapy to be effective in treating H5N1, Avian influenza, and H1N1 influenza. The use of pooled plasma or extracted immunoglobulin's from recovered patients of West Nile encephalitis has demonstrated a protective effect in infected mice and clinical benefit in patients as well. [12-15]

Relavant study design conducted during pandemic

In a Chinese study on 5 critically ill patients with confirmed COVID-19 infection as verified by laboratory diagnostics using reverse polymerize chain reaction (RTPCR) including 1 male and 1 female patients in an age range of 50-70 years wherein the patients were kept on corticosteroid methylprednisolone and anti-viral drugs (Lopinavir/Ritonavir) with Interferon alpha 2b; clinical status improved in these (**Table 4**).

Meta analytical study design

In another meta-analysis study on 10 patients with 7 confirmed COVID-19 cases and 3 patients wherein viral load was not detectable but those who presented with the symptoms were treated with transfusion of 200 ml of immune plasma with neutralizing antibody titers of 1:640 in addition to the anti-viral drugs and methylprednisolone, post-transfusion results showed complete resolution of symptoms in all the treated patients while 7 confirmed cases of COVID-19 tested negative after the plasma therapy who previously tested positive with a concomitant increase in their oxyhemoglobin saturation curve and absorption of lesion as seen on radiographic examination. Amongst these, 9 patients received Arbidol monotherapy or, combination therapy with Remdesivir, Ribavirin or, Peramivir while one patient received Ribavirin monotherapy. Six of them, also, received intravenous methylprednisolone. In the same study, a comparison data was recorded with 10 other patients who weren't kept on plasma therapy together with corticosteroid methylprednisolone and anti-viral drugs wherein it was observed that 3 patients died while 6 others were in stable condition and one case within the control group revealed resolution of the symptoms, thus, revealing a higher mortality rate of around 30% in patients who did not receive plasma therapy [17].

Similar study across the world during pandemic

In a similar study in Korea, (**Table 4**) 2 patients who presented clinical symptoms of COVID-19 infection confirmed by reverse transcriptase polymerase chain reaction (RTPCR) were treated in through convalescent plasma in combination with anti-viral drugs (Lopinavir/Ritonavir, 400 mg/BD) and Hydroxychloroquine, 400 mg OD. In the said study, neutralizing antibody titers were not determined and 250 ml of plasma was infused twice in a day along with intravenous methylprednisolone (1 mg/kg/day). In patient 1, the value of cycle threshold (Ct) changed from 24.98 on day 10 to 33.96 on day 20 after plasma infusion while SARS-CoV-2 was negative after day 26 and the patient was successfully weaned from mechanical ventilation while in patient 2, leucocytosis and lymphopenia were immediately recovered after convalescent plasma infusion while on day 9, the density of bilateral infiltration on chest X-ray showed resolution with increased PaO2/FiO2 up to the levels of 230. The level of C-reactive protein (CRP) and Interleukin 6 (IL-6), also, recovered to the normal range. SARS-CoV-2 was quantified by reverse transcriptase polymerise chain reaction(RTPCR) and was found to be negative after day 20 while the value of cycle threshold (Ct) changed from 20.51 on day 5 to 36.33 on day 9 after plasma infusion. The patient was successfully extubated and discharged from the hospital on day 24 [18]. In a study conducted by Duan K, Liu B, Li C. Effectiveness of convalescent plasmatherapy in severe COVID-19 patients 17 showed promising results [15]. Despite this uncertainty, the efficiency of plasma transfusion can't be denied since there are reports wherein it has shown considerable reduction in the death rate as well as length of hospitalization. The mortality rate for Covid-19 infection in the age group of 50-59yrs as estimated by researchers at Imperial College, London has been kept at 0.6 while the same rate as per WHO reports in this age range can be as high as 21% looking globally [30]·In an analysis study with COVID-19 patients, the mortality rate was found to be as high as 30% without plasma therapy [13]. It can thus be concluded that the use of convalescent plasma therapy in COVID-19 patients is safe and effective, if transfusion guidelines are strictly followed [16]· Plasma therapy has been proven to be effective in several outbreaks in corona infections and even, has shown good results in COVID-19 cases in the Chinese and Korean studies, though to increase its acceptability and to prove its efficacy; further controlled clinical trials are highly recommended. Even 69 and 73 years old critically ill patients have shown promising recovery with marked improvement in their clinical status leading to RT-PCR test negativity for SARS-COV-19 once the plasma therapy was initiated [30]·

Significance of all the trials

The findings of the various trials done so far, thus signify that convalescent plasma therapy has an ability to decrease the mortality rate and improve clinical condition in cases of SARS-CoV-19 infections and may be used as a promising therapy in future. Convalescent plasma contains neutralizing antibodies which have the power to suppress the virus. In animal research, it has been found that passively transferred antibodies i.e. immune plasma into individual shows maintenance of high level of antibody titers until the host immune reaction is increased for the clearance of the prevailing infection. In-vitro study suggests neutralizing antibodies add in the acceleration of virus clearance [31]· Despite limitations of the present research add this aspect and no well-established clinical trials; this data that's available in the literature suggests that the convalescent plasma recovered from patients who have survived COVID-19 infection could be beneficial in the treatment of active COVID-19 patients. In the early onset of disease, if convalescent plasma containing high antibody titers is provided, it would be more beneficial with minimal adverse effects.

Conclusion

In case of critically ill patients, plasma transfusions improved clinical condition and decreased the mortality rates, though further studies and controlled clinical trials are always mandated to work out its

efficiency and exact role in treatment of Novel Corona Virus. In conclusion, SARS-CoV-2 continues to spread worldwide. The precise treatment of COVID-19 disease is currently unknown. Even though limited published studies aren't prospective or randomized, until the development of vaccines or therapeutics, CP seems to be a safe and probably effective treatment for critically ill patients with COVID-19. Atleast preliminary results of multicentre randomized controlled clinical trials should be awaited. Meanwhile, during this pandemic, scientists should be encouraged to collaborate on common research protocols, instead of conducting independent researches. International multicenter randomized controlled trials are needed. CP use should be encouraged to be made within the scope of clinical trials in cooperation with national and international health authorities.

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