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Original article

Convalescent Plasma Therapy in the management of COVID-19 patients-The newer dimensions



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ABSTRACT

Background. – COVID 19 infection caused by novel coronavirus with no specific established treatment. Convalescent Plasma Therapy has been authorized as an off-label therapeutic procedure. We assessed the outcome of convalescent plasma (CP) units versus standard treatment on the complete recovery, improvement and 28 days' mortality of COVID 19 patients.

Materials and methods. – The present was multi-centric case controlled observational prospective study. The study was conducted for a period of four and half months from July 15 2020 to 30 November 2020 after taking approval from the Expert Committee, Health & Family Welfare Department, Government of Odisha. Plasma therapy was applied on two groups of 1189 serious COVID patients (959 number of pre-critical and 230 number of critical patients) not responding to oxygen therapy. It was compared with non-transfused control group of 1243 patients (996 number of pre-critical and 247 number of critical patients).

Results. – Discharge was better in (55.5%) transfused than (43%) in non-transfused pre-critical patients and the mortality was lower (44.3%) in transfused, (48.9%) than non-transfused critical patients respectively. Complete recovery was highest in those who were transfused with CP with neutralizing titer more than 1:160 (52.5%), 18–30 years' age group (64%), females (53%), 'O' Rh D positive blood group (51.5%). There was no adverse reaction due to CP transfusion.

Conclusions. – CP is effective in improving the recovery rate with earlier discharge and decrease in the 28 days' mortality than in the control non-transfused group. CP with neutralizing antibody titer more than 1:160 has the best outcome with complete recovery and decrease in the mortality. It is more effective in treating pre-critical patients when transfused early, in female patients, in younger age group and in blood group 'O' Rh D positive.

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1. Introduction

COVID-19 is the infectious disease caused by the most recently discovered coronavirus. The novel coronavirus disease (COVID-19), which began in Wuhan, China, in December 2019, has been declared to be a pandemic by the World Health Organization (WHO) [1]. Passive antibody transfer, including convalescent plasma or serum,

has previously been used to treat infectious diseases that involve the respiratory system [2,3].

In this context, the coronavirus disease 2019 (COVID-19) pandemic has revived interest in the use of convalescent plasma for the treatment of hospitalized patients with COVID-19 as currently there is no known medicine or treatment that can prevent or cure COVID-19. However, individuals who have completely recovered from COVID-19 may have certain antibodies in their plasma (the liquid part of their blood), known as "convalescent plasma", that can be used to treat individuals with serious or life-threatening COVID-19 infections.

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Basing on this, Government of India, on 13.6.2020, and National Blood Transfusion Council (NBTC), on 01.7.2020, have issued circulars to use convalescent plasma from recovered COVID-19 patients for the treatment of moderate to severe COVID-19 patients not responding to oxygen therapy as off label treatment [4,5]. Basing on the above circulars, Government of Odisha decided to establish Plasma Bank in the State of Odisha, India. Plasma therapy was started in our center, Department of Transfusion Medicine in Sriram Chandra Bhanja (SCB) Medical college & Hospital, Cuttack, Odisha after the approval from the State Ethical Research Committee. It was decided to transfuse Plasma units prepared from the recovered COVID 19 patients to the COVID patients admitted at various COVID Hospitals under the Govt of Odisha free of any cost.

The objective of the present study was to analyze outcome of convalescent plasma (CP) units versus standard treatment on the complete recovery, improvement and 28 days' mortality of COVID 19 patients. The analysis was further carried on to find out the effect of Convalescent Plasma (CP) with IgG antibodies with neutralizing antibody titer of three groups, with titer less than 1:80, between 1:80 to 1:160 and more than 1:160 on moderate to serious COVID 19 patients with respect to the duration of onset of therapy, number of transfusions, blood groups, gender and age group as off label therapy on the complete recovery, improvement and also on the 28-day mortality. COVID 19 patients were divided into two groups, pre-critical–those who were not responding to oxygen therapy and the second group–Critical, with those who were already on ventilator.

2. Materials and methods

2.1. Study designs

The present multi-centric case controlled observational prospective study was conducted for a period of four and half months from July 15 2020 to 30 November 2020 after taking approval from the Expert Committee, Health & Family Welfare Department, Government of Odisha. The study was conducted on 1189 patients who received CP and compared with non-transfused control group of 1243 patients which included 996 number of pre-critical and 247 number of critical patients. The controlled group was in the same age group, gender, clinical condition who did not give consent to be infused with CP. Plasma units prepared in the Plasma Bank in the Department of Transfusion Medicine, SCB Medical College & Hospital, Cuttack, Odisha, India were transfused to COVID 19 patients admitted in 29 dedicated/designated COVID Hospitals. The data on outcome of the therapy was collected by the State registry set-up in the Nodal Center, incidentally the center of working of the authors.

2.2. Donor selection criteria

Two thousand five hundred and forty two number of Plasma units were collected from Plasma Donors (who had a positive RTPCR report of COVID-19 infections and had completely recovered 28 days back and had given consent for Donation). The Donors were from the 18–60-year age group, were above 55 kilograms, nulliparous ladies and the selection was done adhering to the rules and stipulations as per the Drugs and Cosmetics Rule [6], seronegative for Transfusion Transmitted Infections (TTIs) like Syphilis and Malaria by rapid kit test, Hepatitis B, C, HIV, by Enzyme linked Immunosorbent assay (ELISA) and Nucleic Acid Amplification Test (NAT). Screening of TTIs like Hepatitis B, Hepatitis C and HIV (Human Immunodeficiency virus) were done by ELISA. All ELISA seronegative samples were again subjected to NAT testing for the screening of the Hepatitis B, Hepatitis C and HIV viruses as a double screening process to issue safe Convalescent Plasma as per the

SOP implemented by the Health and Family Welfare Department, Government of Odisha, India. All the Plasma Donors were screened for IgG antibody and those with positive IgG antibody (cut-off being 1.4 IgG Index) estimated by Electro-chemiluminescence immunoassay (ECLIA) technology (Abbott Architect i2000SR) were allowed to donate. The samples of all Plasma Donors were screened for the presence of anti-SARS COV2 IgG antibody in our State's reference laboratory, Regional Medical Research Centre (RMRC), Bhubaneswar, which is the regional branch of the Indian Council of Medical Research. The quality of testing was at par with the National reference laboratory in Indian Council of Medical Research (ICMR), New Delhi, India.

Donors with positive IgG antibody were divided into three groups -neutralizing antibody titer with less than 1:80, between 1: 80 to 1:160 and more than 1:160. The Convalescent Plasma was collected by Plasmapheresis procedure (Trima Acele machine) maximum up to 500 ml and was divided into two aliquots each with 200 to 250 ml of Plasma. The Plasma units were stored at -30°C in the Deep Freezer and were administered after thawing at 37°C . Since the plasma was collected by Plasmapheresis procedure which is a sterile process and collects only plasma without any contamination, the CP collected were safe to be transfused to the patients.

2.3. Inclusion criteria for the patients who were Transfused

- hospitalized, confirmed COVID-19 patients;
- age > 18 years;
- had given written informed consent. Written consent was taken from the patient if conscious and from the relatives if patient was unconscious/illiterate;
- moderate to Severe symptoms having any of the two:
 - $\text{PaO}_2/\text{FiO}_2$ (arterial PO_2 divided by fraction of inspired Oxygen) < 300,
 - respiratory rate: > 24/min and SaO_2 < 93% on room air.

2.4. Exclusion criteria for the patients

The patients excluded were as following:

- pregnant women;
- breastfeeding women;
- patients with known hypersensitivity to blood products;
- patients in receipt of Pooled Immunoglobulin in last 30 days;
- critically ill patients:
 - With P/F ratio < 200 [moderate–severe Acute Respiratory Distress Syndrome (ARDS)],
 - In Shock (Requiring Vasopressor to maintain a Mean Arterial Pressure (MAP) > = 65 mmHg or MAP below 65);
- clinical status precluding infusion of blood products.

Total 1189 number of patients (196 number of females and 813 number of males) were in the age group 18 age to 85 years who received CP and 1243 number in the non-transfused control group (205 number of females and 1038 number of males) were in the age group of 18–82 years.

The patients who were administered with Plasma and in controlled group were divided into two groups:

- pre-critical–those who were not responding to oxygen;
- critical–those who were already on ventilator/having any organ failure.

2.5. Outcome

It was assessed both in the transfused and non-transfused control groups. The primary outcome was the decrease in progression of disease or any other causes affecting the mortality in 28 days. If the severity of the disease increased with 28-day mortality, the outcome was considered to be bad and if the disease progression or mortality could be prevented, then the outcome was good.

The assessment of the secondary outcome was done on the weaning of the ventilator/decrease in the requirement of oxygen/off the oxygen therapy/decrease in the stay of the patient in the hospital/increase in the survival of the patients, resolution of symptoms like fever, cough, breathlessness. Few patients who responded to the plasma therapy, but required the transfusion of the second Plasma unit after 24 hours from a separate Donor to recover completely were also included in the study. The outcome was also assessed on the basis of early (less than 7 days of hospitalization) or late (more than 7 days of hospitalization) plasma transfusion.

2.6. Statistical analysis

We first set the research question that whether there is any effect of CP on the improvement and 28 days' mortality of the COVID patients in comparison to the control non-transfused group? Then, we sought to answer three specific research questions in relation to the effect of CP. Firstly, which of the groups of CP, among the ones containing IgG with neutralizing antibody titre less than 1:80, between 1:80 to 1:160 and more than 1:160, is most effective in the decrease in the mortality of the disease and prevention of progression of the symptoms with recovery? And secondly, whether CP is more effective in patients receiving transfusion in moderate to serious stage, pre-critical patients, who are only with oxygen therapy or in critical patients who are on ventilators & with other organ abnormalities? Thirdly, whether CP is more effective in patients receiving the same within 7 days of onset of disease or after 7 days of onset? To analyse more closely on the effect of CP, we also correlated the complete recovery and 28-day mortality effect of the therapy with the gender, age group (18–30, 31–50, 51–70 and > 70 years) and Blood Groups. Finally, as a post hoc addition, we repeated our main analysis with 95% confidence intervals.

2.7. Patient and public involvement

No patient/public was involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patient/public was asked to advise on interpretation or writing of results.

3. Results

3.1. Effect of Convalescent Plasma over standard treatment of non-transfused control group

The complete recovery with discharge from the hospital was (55.5%) in transfused cases in 10–15 days, (43%) in non-transfused pre-critical patients in 20–25 days respectively. The recovery was better in the transfused critical cases (23%) than in controlled critical group (20.6%). There was decrease in the mortality (44.3%) in transfused patients than (48.9%) in non-transfused critical patients.

3.2. Effect of Convalescent Plasma Therapy in reference to the neutralizing antibody titer and on the stage of the disease

There was complete recovery & discharge from the hospital in case of 585 patients (49.2%), marked improvement in 348 cases (29.3%) but no improvement/death was seen in 256 cases (21.5%)

out of 1189 number of patients getting plasma therapy. Out of 108 number of Plasma units with neutralizing antibody titer less than 1:80, 408 units with neutralizing antibody titer between 1:80 to 1:160 and 673 units with neutralizing antibody titer with more than 1:160 transfused to patients, there was total improvement with discharge from the hospitals of 47 patients (43.5%), 187 cases (45.8%) and 351 cases (52.2%) respectively and death of 29 (26.9%), 85 (20.8%) and 142 cases (21.1%) respectively (Fig. 1). There was discharge of 532 cases (55.5%) out of 959 pre-critical cases followed by 53 cases (23%) in critical patients and death of 154 cases (16.1%) and 102 cases (44.2%) in both pre-critical and critical patients respectively who succumbed due to other associated co-morbidities (Fig. 2).

3.3. Effect of Convalescent Plasma Therapy in reference to the days of transfusion after onset of the disease and number of transfusions

One thousand and thirty nine number of patients who received Plasma Therapy early, that is, within first 7 days of hospitalization and 150 numbers of late Plasma therapy, after 7 days of hospitalization, discharge was seen in 49% of cases in both the groups, but mortality was higher (28%) in late transfusion cases compared to 20.6% in early transfusion (Fig. 3). Out of 766 patients who had received Plasma transfusion only once, 369 (48%) patients completely have recovered. Out of 423 patients who had to be transfused with the second Plasma unit after 24 hours, 216 (51%) completely have recovered and were discharged (Fig. 4).

3.4. Effect of Convalescent Plasma Therapy in reference to the gender and age groups of the patients

Out of 993 males and 196 females, 481 (48.4%) and 104 (53%) completely recovered respectively and have been discharged (Fig. 5). The recovery percentage was highest in 18–30 years' age group (64%), followed by 51–70 years (50.47%), 31–50 years (49.8%) followed by more than 70 years' age group (36.6%) (Fig. 6).

3.5. Effect of Convalescent Plasma Therapy in reference to the Blood Groups of the patients

Two hundred and twenty two (51.5%) patients of 'O' Rh D positive, 131 (50.8%) of 'A' Rh D positive, 38 (50.6%) of 'AB' Rh D positive, 1 (50%) of 'AB' Rh D negative, 183 (45.9%) of 'B' Rh D positive, 03 (42.9%) of 'A' Rh D negative, 02 (22.2%) of 'O' Rh D negative and 01 (12.5%) of 'B' Rh D negative patients completely recovered (Fig. 7).

3.6. Outcome analysis

So the maximum successful outcome with reduction in the stay of hospitalization and as well in mortality within 28 days in patients receiving plasma therapy were seen with neutralizing antibody titer more than 1:160, pre-critical patients, with early Plasma transfusion, second transfusion after 24 hours, younger age group, females and 'O' Rh D positive patients where patients were discharged after 2–5 days of Plasma therapy. We lost the long term follow up of the patients as the recovered persons did not come for further follow-up after being discharged from multiple COVID hospitals.

3.7. Adverse reactions

No adverse reactions to Plasma therapy were reported.

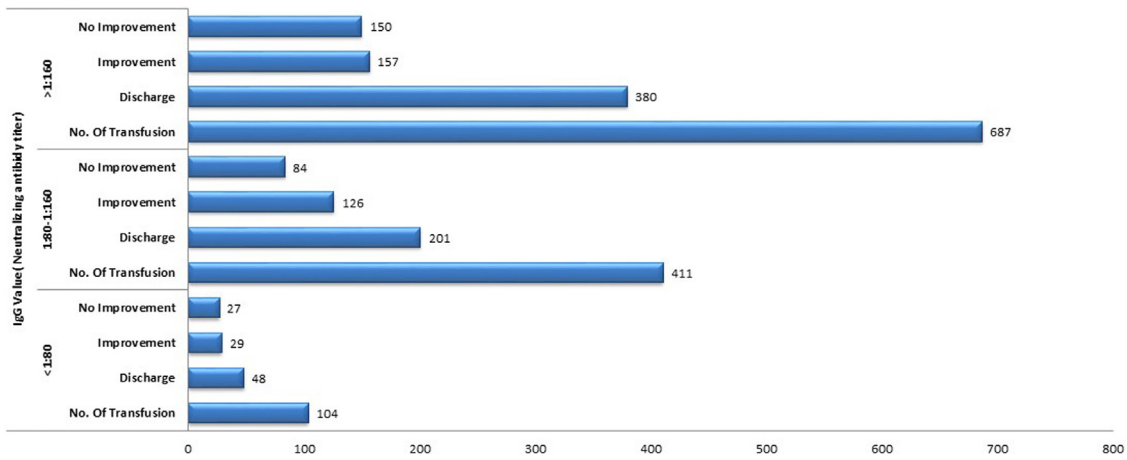


Fig. 1. Transfusion based on the neutralizing Antibody titer in the CP and patients' outcome.

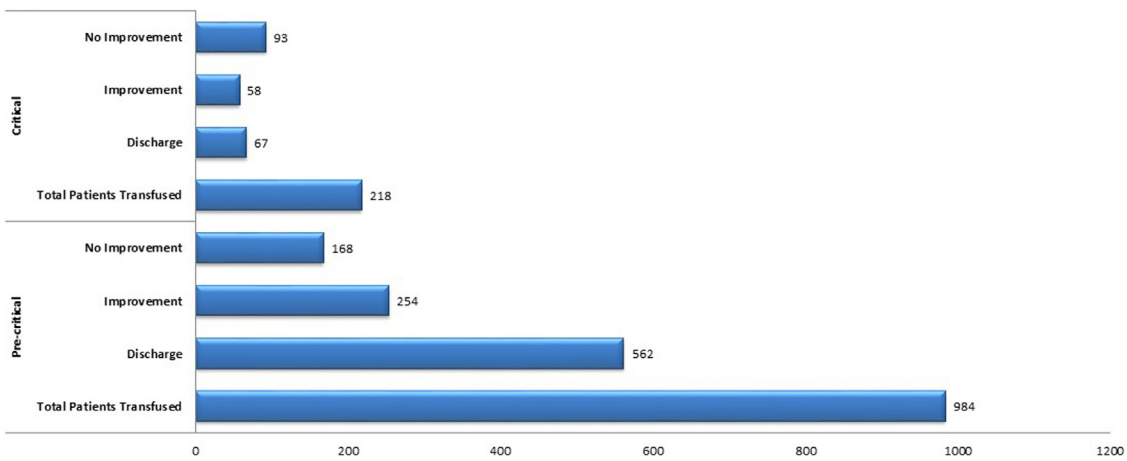


Fig. 2. The outcome of patients in pre-critical and critical patients.

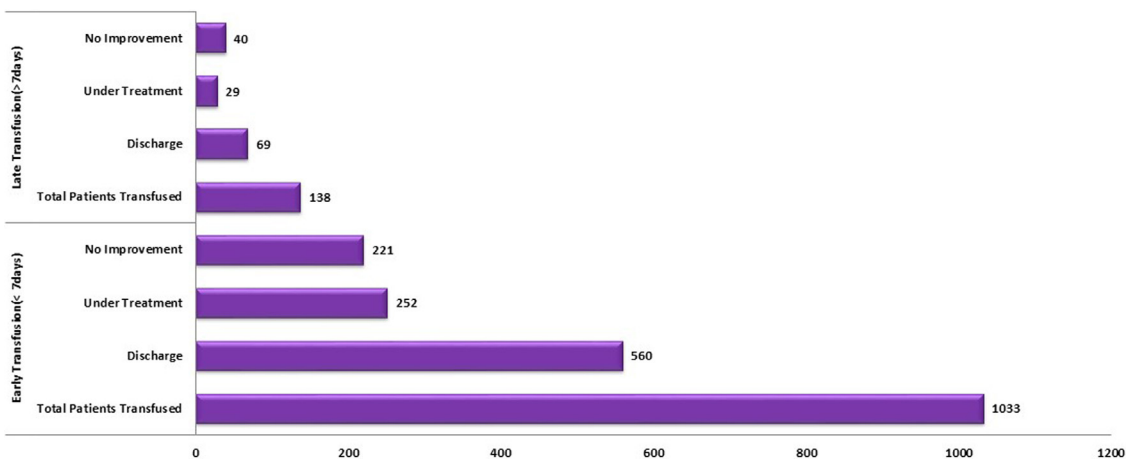


Fig. 3. The outcome in patients according to the days of administration of plasma.

4. Discussion

CP has been used as an investigational treatment for COVID-19 since the early days of the pandemic. Numerous observational studies report safety and signals of possible efficacy of CP in hospitalized patients with COVID-19 [7–14]. We studied the effect of CP on the progression of the disease and the mortality of COVID patients in comparison to the standard non-transfused controlled group. We

got favourable result of better recovery rate in the transfused pre-critical cases with earlier discharge from the hospital. The mortality was reduced in the critical cases who received CP than the patients in standard care. Our results are consistent with previous studies [13,14].

Convalescent plasma therapy remains a solid option to treat COVID patients, though this option falls into a portfolio of many other therapeutic approaches [15]. The treatment schedule is

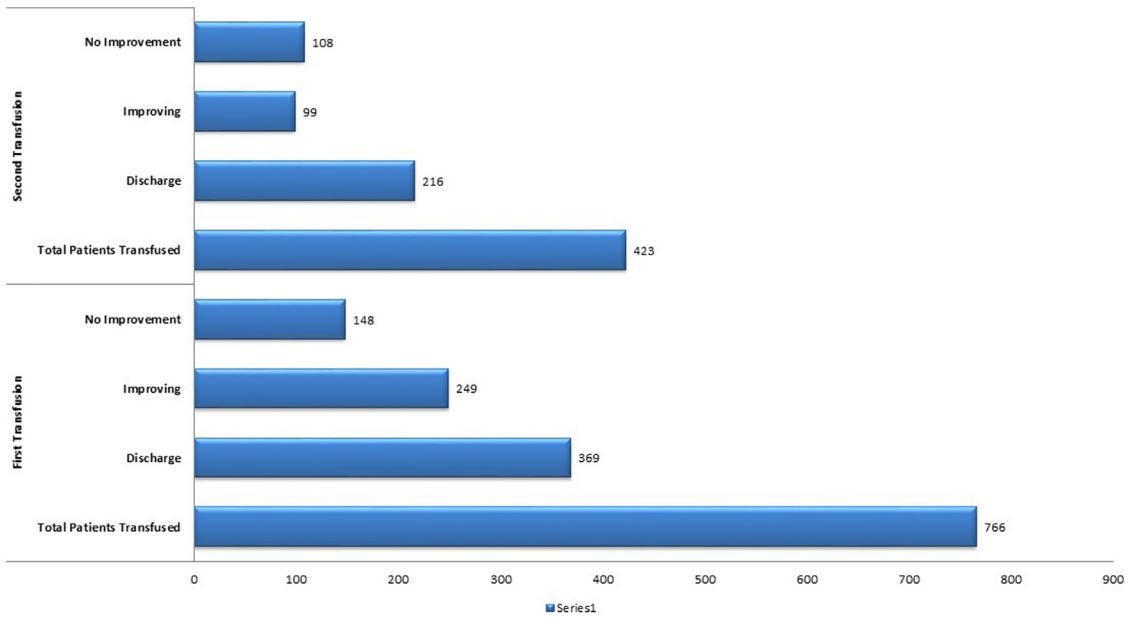


Fig. 4. Outcome of first and second transfusions.

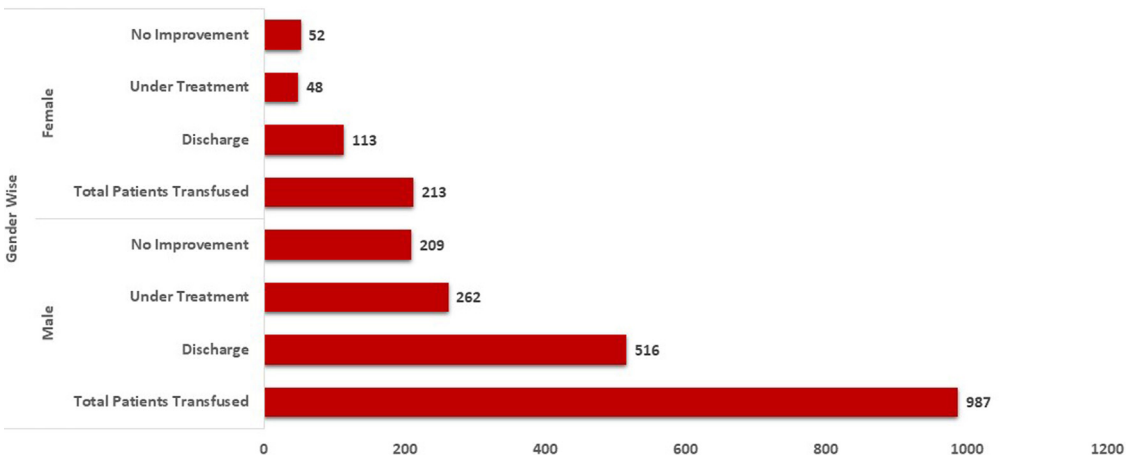


Fig. 5. Gender wise number of Plasma transfusions and number of patients discharged.

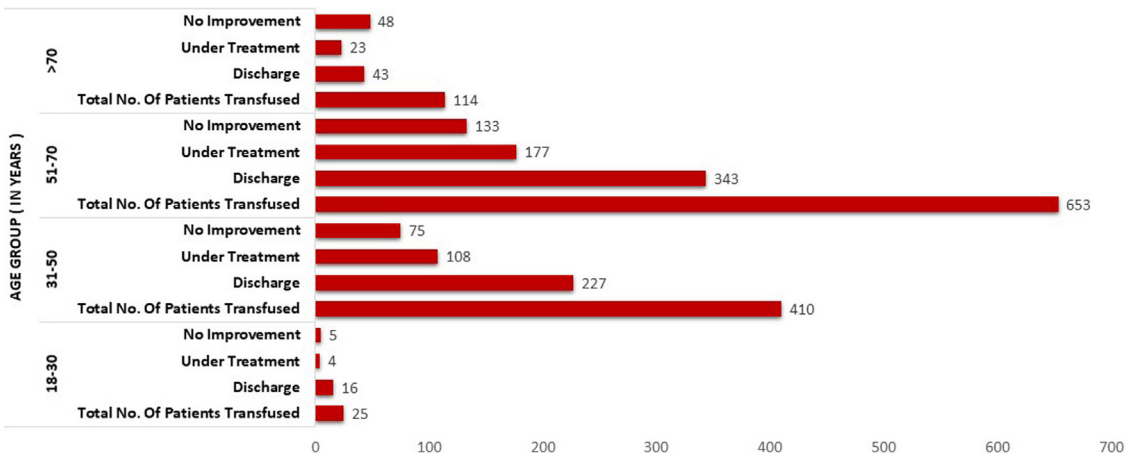


Fig. 6. Age wise number of Plasma transfusions and number of patients discharged.

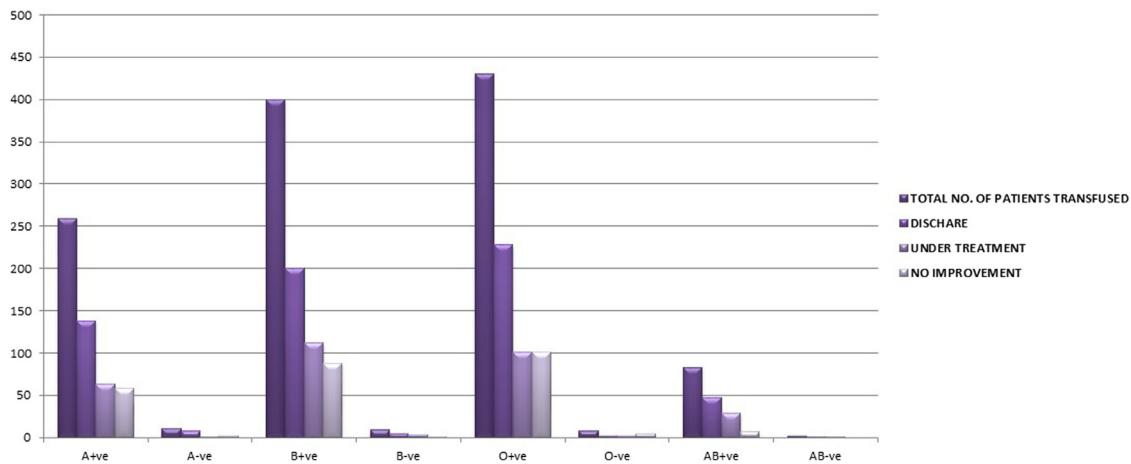


Fig. 7. Blood group wise number of Plasma transfusions and number of patients discharged.

likely to be refined to sort out the target populations and the most appropriate time frame, and also when to collect plasma from convalescent donors [16]. Another study examined efficacy in 39 patients compared to retrospectively matched controls whose results showed that patients receiving convalescent plasma therapy had improved survival and supplementary oxygen requirements at day 14 post-transfusion compared to non-transfused controls [17]. In a smaller study by Hegerova et al., 20 COVID-19 patients who received convalescent plasma had improved laboratory and respiratory parameters compared to matched controls, and in both matched control studies, non-intubated patients benefited more from transfusion than intubated patients [13].

Plasma donation at our centre was purely voluntary and without any incentives/pressure given to the donors or any harassment to the relatives of the COVID patients to arrange for a Plasma donor. Due to this ethical practice, persisting efforts from our end and support from the State Government, we got one of the highest number of Plasma donations in the country, as a single medical institute. An important related issue here is that Plasma Donation process in the State was driven, controlled, regulated and monitored at the Government level. State Government sponsored the entire Plasma Therapy procedure as the Therapy was administered in all COVID-Institutions run by the Government. The Government made Plasma Therapy issues a subject of Government Information Education Communication (IEC) campaign and motivation levels were such that it was seen more from Altruistic and ethical angles than anything else. As the Government made food, transport and accommodation logistics free for the donors, donors came forward to readily take part in donation exercise. With publicity given to the donors in media and certificates handed over to them by State Government proclaiming Plasma donors as Plasma Warriors, the morale of the Plasma donors was high. No financial incentive was required for donors.

In our present study, though we had collected plasma from donors with positive IgG antibodies and more than 43.5% discharge rate was noticed with the Plasma therapy, the maximum number of discharge (52.2%) was found with units transfused having neutralizing antibody titer of more than 1:160. On 17th November, 2020, Indian Council of Medical research has circulated the decision matrix of required concentration of neutralizing antibodies to be 1:80 [18].

Written consent was taken from the patient if conscious and from the relatives if patient was unconscious/illiterate. Role of Plasma Therapy was so widely discussed in various media that general awareness regarding Plasma Therapy was high. No problem whatsoever was encountered in getting written consent from

patients/relatives. In fact, treating physicians had to convince many non-serious COVID patients and their relatives that Plasma was not required in their cases. In the present study, we got a result of 45.8% complete recovery after plasma therapy. In this study, maximum number of patients were male (813) from 51–70-year age group, but the recovery was better in females and in the younger age group of both genders.

The blood group most commonly affected which received Plasma therapy being 'O' Rh D positive and outcome was also best in the same 'O' Rh D positive blood group. We have evaluated the efficacy of CP transfusion in detail in both ABO and Rh blood group phenotypes. This facilitated to know the rate of efficacy of CP on both the major blood group systems. Till now there is no report and or publication in the English medical literature regarding the effectiveness of CP in correlation to blood group. Females had a better outcome than males and 31–50 years' age group had the best outcome of Plasma Therapy. The younger age group was responding to the therapy better. The outcome was also assessed based on the pre-critical stage of the patients who were moderate to serious cases not responding to the oxygen therapy even after the administration of Steroid or new anti-viral therapy like Remdesivir/Favipiravir versus critical cases who were on mechanical ventilation or with any organ failure. The outcome was measured in terms of the weaning of the ventilator/decrease in the requirement of Oxygen/off the oxygen therapy/decrease in the stay of the patient in the hospital/increase in the survival of the patients. The discharge was better after second transfusion (51%) than first transfusion (48%). The recipient whose oxygen requirement slightly reduced with the first dose, but, still on higher side with P/F ratio between 200–300, when received the second Plasma unit after 24 hours showed much improvement and were off oxygen support with early discharge from the hospital.

Our centre participates in the hemovigilance programme and submits hemovigilance report every month to National Institute of Biological (NIB), Noida, India which is the authorized national centre for receiving the hemovigilance reports. In our case, there was no reporting of any adverse reactions with Plasma transfusion from the COVID hospitals. The daily reporting format regarding the progress of the recipient was received in our registry from all COVID centres which included the reporting of any adverse reactions. The reason may be that the storage & transport of the Plasma in proper cold chain and immediate administration to the patient. No adverse reaction was noted in our study with the Plasma Transfusion.

The concept of administrating CP to various infectious diseases is not new. Recently, it was used to treat Ebola patients and eventually led to identifying specific antibodies with high neutralizing activity against the virus and for production of monoclonal synthetic anti-

bodies to treat Ebola [19]. Shen et al, have found that administered CP (Convalescent Plasma) with high levels of neutralizing antibodies suggested improved outcome and reported no adverse events in patients with COVID-19 [20,21]. Similar result was seen in patients receiving Plasma therapy with high neutralizing antibody titer in the present study.

A randomized controlled study recently published showed some improvement in 50 severe and critically ill patients. Beneficial effect was limited to patients with moderate to severe disease rather than with critical disease [22]. In our study, we also found more beneficial effects of plasma therapy in pre-critical, moderate to severe cases than in the critical cases. Prior studies demonstrated that CP is more effective when administered early during the disease course or as prophylaxis closely after exposure to the infectious agent [23].

Similar effect was seen in the present study where the number of recovered patients was highest when transfused within seven days of hospitalization with increase in the oxygen requirement. Recently, ICMR has also circulated the decision matrix for the plasma therapy that the potential recipients should be in the early stage of COVID-19 disease, with symptoms preferably within 3–7 days, but not later than 10 days [17]. A previous large study of 80 patients in Hong Kong infected with SARS demonstrated that patients who were treated before day 14 had improved outcome as defined by discharge from hospital before day 22, supporting early administration of CP for optimal effect [23].

5. Conclusions

In conclusion, our results support the beneficial effect of CP than the standard care in the management of COVID patients in terms of better recovery, earlier discharge with reduction in the mortality rate. The best outcome of Convalescent Plasma can be found with presence of desired amount of IgG antibody with neutralizing antibody titer of > 1:160 for treatment of COVID-19 patients and in moderate to serious patients rather than in critical patients. Younger age group, females, Blood Group 'O' Rh D positive, early Plasma Transfusion have better outcome of CP therapy.

Further randomized controlled studies are required to establish the role of CP in COVID 19. Nevertheless, in the absence of any specific treatment, vaccine and limited resources in many settings, we propose to consider wider use of CP for patients with moderate and severe COVID-19 disease.

5.1. Strengths of this study

- Large number of participants in trial and control groups;
- study involving wider spectrum of parameters;
- as the study was a Government study, with CP being issued without any cost or asking for a replacement Plasma Donor to the recipient's relatives, the day to day positive feedback on the effectiveness of CP in reducing the mortality and early recovery to Government of Odisha was giving a favourable impact and enhancement of CP transfusion.

5.2. Limitations of this study

Long term follow-up the patients after the discharge from the hospitals couldn't be done as recovered patients did not turn up.

5.3. What is already known on this topic

CP has certain role in the management of critical COVID patients than conventional therapy. Convalescent Plasma has role in the treatment of COVID patients which has neutralising antibody titer of 1:640 or more than that in a previous study by Yasmin Maor in

treating moderate to severe pneumonia in COVID 19 patients. It is said to be more effective when transfused early.

5.4. What this study adds

CP helps in improved recovery rate with earlier discharge from hospitalisation and reduced mortality rate in severe COVID patients not responding to oxygen therapy. In comparison to other studies, this study involves the effect of CP on a large number of patients (1189) and 1243 patients in the control group involving so many parameters/factors on the outcome of the therapy. We have found most favourable outcome in reducing the 28 days' mortality and progression of disease with CP having neutralising antibody titre of more than 1:160, though it has also been effective in treating COVID patients with titre in between 1:80 to 1:160 also. CP is better acting in resolution of symptoms and early recovery with discharge from the hospital in pre- critical patients, when transfused early within 7 days of onset of symptoms. Few other published literature have correlated transfusion within and after 14 days, but none has established relation to the Blood groups. In the present study, we have found that CP acts best in Blood Group O' Rh D positive, in 18–31 years' age group, and in females.

Disclosure of interests

The authors declare that they have no competing interest.

Ethics approval statements

The study protocol was approved at the stage of conception and initiation by Expert Committee, Health & family welfare Department, Govt. of Odisha, India.

Contributorship statement

Dr CBK Mohanty has given concept of this paper along helped in the data compilation. Dr Roma Rattan had done the IgG antibody testing for the COVID 19 infections, helped data compilation and write up. Dr Smita Mahapatara has compiled all data and written the manuscript.

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