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Outcome of Indoor Covid Cases with Moderate to Severe Disease; Convalescent Plasma Transfusion vs Conventional Therapy

Lubna Meraj, Muhammad Usman, Nadia Shams, Muhammad Umar, Sidra Tahir, Nasim Akhtar, Muhammad Khalid Mehmood Randhawa, Asif Majid, Ashar Alamgir

ABSTRACT

Objectives: Global COVID-19 epidemic has been therapeutic challenge. Convalescent plasma is observed to improve clinical outcomes. This research aims to study whether convalescent plasma therapy reduces the mortality and duration of hospitalization in moderate to severe Covid.

Study Design and Setting: This interventional study was conducted after ethical approval at RIUT COVID-19 center from1st June-30th Nov 2020.

Methodology: Hundred Covid patients included; Total 100 hospitalized adult SARS Cov-2 PCR positive with moderate to severe disease who agreed for convalescent plasma transfusion were included. Fifty in plasma transfusion group and fifty in conventional therapy group. T*hose with* contraindications for plasma transfusion, delayed presentation, indoor stay <5 days were excluded. Convalescent plasma was obtained from donors with prior documented SARS CoV-2 infection meeting donor eligibility criteria. 50 cases received convalescent plasma and50 received conventional therapy. Hospital stay and outcome documented.

Results: Amongst 100 Covid cases; 44 females and 56 males; mean age 57.88+11.95 years, 74% had moderate covid and 26% severe. Fifty cases received conventional therapy for Covid and 50 received plasma transfusion. Both groups comparable for gender, age, smoking, obesity, and disease severity. Invasive ventilation administered in 25% and was associated with mortality (p=0.004). Mortality observed in 29 cases; 20(69%) in plasma transfusion group Vs. 09(31%) in conventional therapy group (p=0.015). The hospital stay was comparable between two groups The relative risk ratio was 2.22 with 95% CI (1.12-4.39).

Conclusions: There was no therapeutic benefit in Covid patients treated with convalescent plasma as compared to conventional treatment.

Keywords: SARS COV-2, Convalescent plasma transfusion, COVID PCR, Donor Eligibility Criteria.

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INTRODUCTION:

The Corona virus (SARS-Cov-2) was first detected in 2019 in Wuhan province of China.[1] The novel corona virus leads to various degrees of severity of symptoms from mild fever, myalgia to severe respiratory distress. Several medications and therapeutic modalities are under trials for safety and efficacy. To date 153 million cases reported worldwide with 3.2 million deaths. These figures are on persistent rise despite of ongoing vaccination process worldwide. The World Health Organization estimates that serious illness may occur in as many as 13.8% of cases and 6.1% are critical.[2] When

fulminant, patients may develop sepsis, acute respiratory distress syndrome (ARDS), and/or multiple organ failure which are not unique to coronavirus.[3]

The convalescent plasma is retrieved from the recovered cases of a particular disease and has been used since more than a century for management of several infectious diseases including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic.[4] The convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been studied for management of patients with COVID-19. Studies have demonstrated significant safety profile and efficacy of convalescent plasma. The benefit was particularly observed in patients less than 80 years age and by administration of plasma with high titers of antibodies.[5] However, long term data denies the difference in reduction of mortality based on titers of antibodies in plasma[6] or the administration of plasma versus placebo.[7]

The SARS-Cov-2 has been a therapeutic challenge for the health care system. The infectiousness and lethality of the virus demands extensive and fruitful efforts to control the spread of epidemic as well as definitive cure for illness. The therapeutic aims are not only to target the virus, but also the management of complex phenomena of cytokine storm, inflammation, endothelial dysfunction, coagulopathy and multi-organ failure. These are short-term observations of the COVID, however since the time to emergence of COVID is rising, certain long-term complications including interstitial lung disease, cardiovascular and cerebrovascular events are claiming more lives.

There has been limited and contradictory regional data addressing convalescent plasma in COVID patients.[8] Current study may provide a reference data and enable us to determine and compare the safety, efficacy and prospects of convalescent plasma in our patients.

METHODOLOGY:

This interventional study was conducted at Rawalpindi Institute of Urology that is serving as COVID-19 infection isolation and management center. Study was conducted from 1st June 2020 to 30th November 2020. Ethical approval was obtained from ethical review board of RMU (ref# 55/IREF/RMU/2020). Covid was a novel disease, with the approved therapy of convalescent plasma that was also new and not time tested regarding the Covid therapy. There were certain limitations to sample size calculation with varying prevalence of cases during pandemic. Hence, during the selected time frame for the study, all the patients meeting the inclusion and exclusion criteria were selected by consecutive sampling.

Hundred indoor adult SARS COV-2 (PCR positive) cases of both genders were included by consecutive sampling. Moderate to severe Covid cases meeting plasma transfusion therapy criteria were selected. Mild disease, contraindications for plasma transfusion, who changed decision regarding plasma transfusion or left against medical advice were **excluded**. Fifty cases were included each in plasma transfusion and conventional therapy group. Patients were clinically classified as mild, moderate, severe, and critical according to National Institute of Health, Pakistan guidelines.[9]

The selected patients were randomly allocated into two equal groups according to computer generated random numbers table. Fifty cases were included in plasma transfusion group and conventional therapy group each. Written consent was obtained from the patients or their first degree relative.

Operational Definitions

Moderate COVID disease is defined as

- evidence of lower respiratory disease during clinical assessment or imaging
- SpO_2 =94% on room air at sea level.

Severe COVID disease is defined as one or more of the following:

- Shortness of breath (dyspnea).
- Respiratory frequency = 30/min.
- Blood oxygen saturation = 93%.
- Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300.
- Lung infiltrates > 50% within 24 to 48 hours.

Life-threatening COVID disease is defined as one or more of the following:

- respiratory failure.
- septic shock.
- multiple organ dysfunction or failure.

Demographic details and history were obtained including symptoms and co-morbid conditions. Clinical evaluation and laboratory investigations were conducted (i.e., blood complete picture, d-dimers, C reactive protein, LDH, creatinine, ALT, ECG, Chest x-ray, CT-scan chest, arterial blood gases).

Donor Eligibility Criteria: COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:

- Evidence of COVID-19 documented by a laboratory test either by a diagnostic test (e.g., nasopharyngeal swab) at the time of illness OR positive serological test for SARS-CoV-2 antibodies after recovery
- Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

The convalescent plasma was obtained from donors with prior documented SARS CoV-2 infection meeting the donor

eligibility criteria. There were several difficulties regarding plasma acquirement like arranging and screening donors for anemia, calcium, Hepatitis-Bs Ag, anti HCV, HIV. Several donors were not included due to inability to fulfill the screening criteria. The donor plasma which did not contain the antibodies or had less antibody titer were excluded. Plasma extraction itself was a cumbersome process. Plasma was replaced with normal saline; hence the donor didn't get dizziness and dehydration due to loss of volume. Then plasma was either transferred or stored in blood bank in BBH or handed over to attendant for recipient treatment in RIUT.

Apart from the donor issues, few eligible recipients had contraindications for plasma transfusion i.e., multi-organ failure, cytokine release syndrome and renal failure. Patients were provided recommendation and eligibility for plasma transfusion therapy in addition to conventional therapy. Those who agreed for plasma transfusion were included. The selected cases received plasma from donor in addition to conventional therapy with all the pre-requisites for plasma transfusion. Patients were managed and monitored till the recovery and discharge or death.

Record keeping: A health care provider who is participating maintained the records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patients. Record included the unique identification number (e.g., the ISBT donation identification number).

All the details were entered on specially designed proforma and data was analyzed by SPSS version 22. Quantitative variables (age, duration of hospital stay) presented as mean and standard deviation. Qualitative variables (gender, Covid severity, modes of ventilation, outcome, co-morbids) presented as frequencies and percentages. Chi-square test applied to study association of qualitative variables with modes of therapy and outcome, fisher's exact test for qualitative variables having less than five values and student-t test for quantitative variables. P-value<0.05 considered as statistically significant. Data presented as tables, bar graphs and pie charts.

RESULTS:

Amongst 100 cases of moderate to severe covid, there were 44 females and 56 males. The mean age was 57.88 +11.95 years with the range of 28-83 years. Obesity (BMI>30 kg/m^2) was found in 33(33%). Smoking was reported by 9(9%) patients. Regarding the severity of Covid, 74(74%) cases had moderate disease and 26(26%) had severe disease.

Fifty cases received the conventional therapy for covid and 50 cases received plasma in additional to conventional therapy. Both the groups had equal number of male and female cases ($p > 0.05$). The mean age in conventional therapy group was 55 +12.9 years Vs. 60.7+10.26 years in plasma group (table 1; p=0.081). Both groups were comparable in terms of obesity (p=0.351) and smoking (p=0.193).

The mean level of antibodies was 17.12 (range 1.82-78.79). During plasma transfusion, 45(45%) cases had no immediate adverse reaction during or after plasma transfusion. Fever with shivering was seen in 2(4%), skin rash in 1(2%) and tachycardia in 2(4%) cases.

Patients received multiple modes of oxygenation and ventilation. 17(17%) were managed by oxygen via nasal canula alone. High flow oxygen was given in 11(11%) cases. 42(42%) cases were managed by non-invasive ventilation and 25(25%) by invasive ventilation. Only 05(5%) were the cases that didn't required any oxygen therapy. Regarding 25 cases that received invasive ventilation, 18(72%) belonged to plasma transfusion group and 07(28%) conventional therapy group with a significant difference (p=0.004).

Among 74 cases with moderate covid, 39(52.7%) were from plasma transfusion group and 35(47.3%) were from conventional therapy group. There were 26(26%) cases having severe covid, 11(42.3%) were from plasma transfusion group and 15(57.7%) were from conventional therapy group. There was no statistical difference in severity of disease between two groups (p=0.362).

The main outcome of the study showed that 71(71%) cases were successfully treated and discharged from hospital. Among these 71 recovered cases, 30(42.3%) were from plasma transfusion group and 41(57.7%) were from conventional therapy group. Mortality was observed in 29 out of 100 cases (i.e., 29%). 20(69%) of the deaths were from plasma transfusion group and 09(31%) deaths were from conventional therapy group (p=0.015).

In terms of duration of hospital stay, there was no difference in mean hospital stay between two groups (p=0.133). The mean hospital stay was 13 days in conventional therapy group and 15 days in plasma transfusion group. There was no association of mortality with gender, age, duration of hospital stays. However, mortality was found to have significant association with severity of Covid, obesity and invasive ventilation ($p<0.05$; Fig 1, 2 & Table 2).

The Relative risk ratio was calculated through Medcalc.[10] The relative risk (RR) or risk ratio is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. Together with risk difference and odds ratio, relative risk measures the association between the exposure and the outcome.[11] In this study the exposed group was that of plasma therapy and conventional group was the unexposed group. The outcome was measured in terms of mortality and survival. The relative risk ratio was calculated by Medcalc software. The results were achieved are presented in table 3.

DISCUSSION:

This study highlights an important treatment option which has been used in many Covid patients in current pandemic

Table 1: The demographic variables, disease severity, modes of ventilation and outcome of plasma therapy Vs. Conventional therapy in Covid cases (n=100)

Variables	Amongst all n=100	Plasma therapy group n=50	Conventional therapy group n=50	*p-value*
Age (mean + SD years)	57.88 +11.95 28-83 years	60.7+10.26	55 +12.9	0.081
Duration of Hospital stay (mean + SD days)	14.17 + 7.79 5-45 days	15.46 + 8.71	12.88 + 6.59	0.133
Gender - Females - Males	 44(44%) 56(56%)	 22(50%) 28(50%)	 22(50%) 28(50%)	1.000
Obesity - Obese - Non-obese	 34(34%) 66(66%)	 18(52.9%) 32(48.5%)	 16(47.1%) 34(51.5%)	0.673
Smoking - Smokers - Non-smokers	 9(9%) 91(91%)	 04(44.4%) 46(52.3%)	 05(55.6%) 42(47.7%)	0.193
COVID Severity - Moderate - Severe	 74(74%) 26(26%)	 39(52.7%) 11(42.3%)	 35(47.3%) 15(57.7%)	0.362
Outcome - Discharged - Expired	 71(71%) 29(29%)	 30(42.3%) 20(69%)	 41(57.7%) 09(31%)	0.015
Modes of Ventilation - None - Nasal canula - High flow nasal canula - NIV - Invasive ventilation	 05(5%) 17(17%) 11(11%) 42(42%) 25(25%)	 0(0%) 04(23.5%) 07(63.6%) 21(50%) 18(72%)	 05(5%) 13(76%) 04(36.4%) 21(50%) 07(28%)	0.004
Co-morbids - Diabetes Mellitus - HTN - IHD - Asthma - COPD - CKD - Hypothyroid	 55(55%) 62(62%) 17(17%) 11(11%) 05(5%) 05(5%) 07(7%)	 29(52.7%) 32(51.6%) 09(52.9%) 05(45.5%) 01(20%) 02(40%) 02(28.5%)	 26(47.2%) 30(48.4%) 08(47.1%) 06(54.5%) 04(80%) 03(60%) 05(71.4%)	0.546 0.680 0.790 0.749 0.362 1.000 0.436

(Test of significance; Chi-square, Fisher's exact test, student t-test; significant p < 0.05)

Figure 1: Bar graph representing expiry in Moderate Vs. Severe Covid cases (n=100)

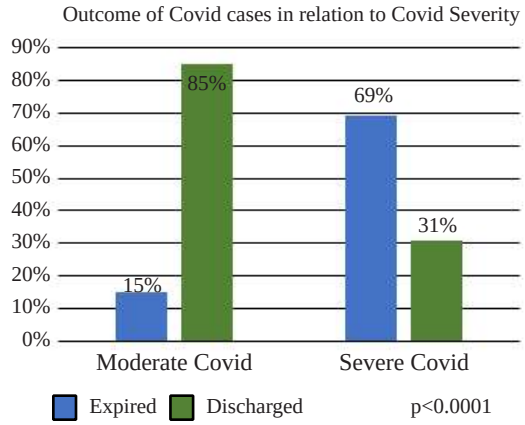

Figure 2: Bar graph representing expiry in Obese Vs. Non-obese Covid cases (n=100)

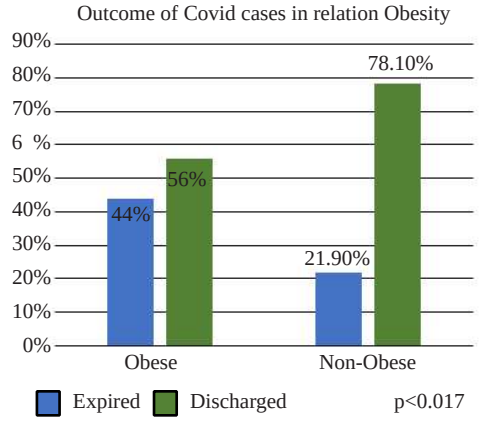

Table 2: Outcomes of covid cases managed by various modes of ventilation (n=100)

Modes of Ventilation	Among all (n=100)	Expired (n=29)	Discharged (n=71)	P-value
Invasive Ventilation	25(25%)	19(76%)	06(24%)	*<0.0001*
Non-invasive ventilation	42(42%)	05(11.9%)	34(81%)	
High flow oxygen	11(11%)	05(45.5%)	06(54.5%)	
Nasal canula	17(17%)	0(0%)	17(100%)	
None	05(5%)	0(0%)	05(100%)	

(Test of significance, Fisher's exact test; significant p<0.05)

Table 3: The table representing relative risk ratio calculated by Medcalc software.

Relative risk	2.2222
95% CI	1.1235 to 4.3956
Z static	2.294
Significance level	P=0.0218
NNT (Harm)	4.545

scenario in Pakistan. The study was done in a public setup hospital which is reflective of the resource limited hospital's management plans amid the Covid Crisis. There were two groups of Covid patients who were well matched in terms of the confounding factors like age, gender, obesity, smoking status and Covid severity. The *P-value* calculated showed more than 0.05 value in each factor, which showed no statistical significance. The mean age was fifty-seven years. Thus, it can be inferred that the age group above 50 years have higher tendency for need of admission. The strong age gradient has been observed by Varity et al as a risk factor for covid associated mortality.[12] Both of the groups were comparable in terms of age and gender. Among all cases there were 56% males as compared to 44% females.

There was high burden of co-morbid conditions, particularly diabetes and hypertension in our admitted cases. This reflects the overall regional prevalence of diabetes and hypertension. Studies have demonstrated that patients with these co-morbids are prone to be admitted and develop the severe forms of disease. However, both groups were comparable in terms of co-morbids, minimizing the likelihood of this as a contributory factor for mortality.

There was no significant difference in mean hospital stay between plasma therapy and conventional therapy groups. A study by RECOVERY collaborative group found no benefit of convalescent plasma regarding the proportion of patients discharged within 28 days.[13]

Certain confounding factors, other than age and gender were disease severity and need for ventilation. Both the groups had no statistical difference in disease severity. However, the plasma transfusion group had more cases that required invasive ventilation (i.e., 73%) as compared to lesser number of conventional therapy group cases (27%) requiring ventilation. Hence, the need for invasive ventilation may be interpreted as one of the contributing factors for poor outcome in plasma therapy group.

The indications for invasive ventilation include hypoxia, severity of lung involvement, multi-organ failure, the rapid progression of disease, deteriorating GCS due to hypoxia and other metabolic causes.[14] Authors recommend that these should be studied in future research. The higher number of patients in plasma group required invasive ventilation as compared to the conventional group as calculated P was less than 0.05. It can be inferred as the group which received plasma was sicker, thus requiring the ventilator support as compared to the other group. A total of 100 patients were included in the study out of which a group of 50 patients were given conventional treatment and the other group of 50 patients was given Convalescent plasma in addition to Conventional treatment. The donor plasma antibody titer was confirmed before administration of the plasma. The results showed statistical significance in the primary outcome of both groups.

Contrary to the clinical assumption the mortality was higher in the plasma group as compared to the conventional group. The Relative Risk ratio was more than 1 which means that the plasma group was having more mortality as compared to the other group. 95% confidence interval (1.12-4.39) calculated showed a wide range thus there is limited precision of the result value. It could be because of small number of patients and may be the study was underpowered. Or the patients with plasma group were sicker than the conventional group.

The plasma acquired from the screened donors had a wide range of antibodies titer ranging from 1.82 to 78.79. The variability of antibody titer could have changed the effectiveness of therapy among the plasma group.[15] Certain contraindications to donor and recipient eligibility also played a role in difficulty in selecting the appropriate candidates for plasma therapy.[16] There were no acute events or major adverse reactions during plasma transfusion, we may conclude that though it's a safe procedure, yet its efficacy is questionable that needs to be further evaluated.

We observed a death rate of 29%. Sheng et al observed a higher death rate of 38% in moderate to severe Covid cases in a study conducted in Wuhan China that is considered as epicenter of epidemic.[17] The reasons of such higher mortality could be that moderate to severe Covid cases were included, while mild and outdoor cases were excluded. Patients who require indoor care are already sick and high-risk cases. Also, during the earlier phase of epidemic, there was no vaccine available or approved that could have led to severe disease, need for ventilation and involvement of lung parenchyma.[18] The mortality of Severe Covid disease requiring mechanical ventilation has been found to vary in different studies. Namendy et al has reported a very high mortality of 73% in a Mexican study.[19] However, Mitra et

al has reported a comparatively lower mortality (15%) in a Canadian study.[20] There has been a debate regarding the modes of ventilation and settings of the ventilator as well; particularly in Covid cases.[21] Most of guidelines suggest the ventilator settings as recommended for ARDS cases earlier. We had approx. 1/4th of our patients on invasive ventilation (25%) and there was significant association of invasive ventilation with mortality ($p<0.0001$). Higher number of patients in plasma group received invasive ventilation, this is additional contributory factor to higher mortality in plasma group.

This study provides us data about the treatment modality used in a novel disease that is yet to be explored and needs urgent and worldwide research in view of its high mortality and global burden. Limited regional data is available, though several international studies have been conducted that show variety of outcomes. This may act as a benchmark for future studies as well as comparison to international data. There were certain limitations of the study like being a single centered study. The day of illness on which each patient of plasma group received the convalescent plasma was not observed in the study which could also affect the results. The antibodies titer post administration of plasma could not be measured due to budget constraints. It was an open labelled trial with no randomization due to ethical issues regarding consent of the plasma administration. The study was underpowered because of resource limitation in a public sector hospital therefore type 2 error cannot be excluded. The results of moderate severity plasma group cannot be extrapolated as the moderate severity patient would have recovered without the plasma due to lesser severity of the disease. Hence authors suggest careful interpretation of data and suggest further research in this context.

CONCLUSION:

There was no therapeutic benefit found in Covid patients treated with convalescent plasma as compared to conventional treatment. Although further research is required to have a clear understanding, but the use of convalescent plasma shouldn't be considered as a treatment of choice.

Authors Contribution:
Lubna Meraj: Data Collection, Conception, design analysis
Muhammad Usman: Data collection, design, analysis
Nadia Shams: Data collection. Analysis/interpretation of data
Muhammad Umar: Data collection, literature review, write up, referencing
Sidra Tahir: Data collection, conception, design
Nasim Akhtar: Data collection, conception, design
Muhammad Khalid Mehmood Randhawa: Data collection, write up, plasma preparation, donor selection
Asif Majid: Data collection, write up, recipient selection
Ashar Alamgir: Data collection, write-up plasma preparation donor selection

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