

Prognosis of Severe Covid-19 patients after treatment with Therapeutic Plasma Exchange (TPE)

Maliha Khalid¹, Faheem Feroze², Saad Bin Qamar³, Naseem Abbas⁴, Saeed Farooq⁵, Aisha Siddiqui⁶

¹ Post Graduate Trainee,

PAF Hospital, Mushaf, Sargodha

² Head of Department of Anesthesia,

PAF Hospital, Mushaf, Sargodha.

³ Consultant ENT,

PAF Hospital, Mushaf, Sargodha.

⁴ Consultant Anesthesia,

CMH Hospital, Abbottabad.

⁵ Medical Officer, Tehsil Head Quarter Hospital, Bhagtanwala.

⁶ Consultant Pathology,

PAF Hospital, Mushaf, Sargodha.

Author's Contribution

^{1,4} Conception of study

¹ Experimentation/Study conduction

^{1,2,3} Analysis/Interpretation/Discussion

² Manuscript Writing

^{5,6} Critical Review

¹ Facilitation and Material analysis

Corresponding Author

Dr. Maliha Khalid,

Post graduate trainee,

Anaesthesia,

PAF Hospital, Mushaf,

Sargodha.

Email: dowite18malyha@yahoo.com

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Abstract

Objective: To demonstrate the effective role of plasmapheresis in the treatment of Cytokine Release Syndrome associated with severe Covid-19 pneumonia.

Introduction: Covid-19 disease is a highly infectious disease with milder symptoms to a more severe form with acute respiratory distress syndrome leading to even death. Literature study showed that the initial viral infection in severe Covid 19 patients can cause a hyper-inflammatory response which can accelerate to severe hyper-cytokinaemia that can contribute to underlying endothelial dysfunction and multiple organ dysfunction. Thus, removal of these inflammatory cytokines by Therapeutic Plasma Exchange is considered to be an important part of the treatment of critically ill patients in order to improve their survival rates.

Materials and Methods: Retrospective observational study which included 150 RT-PCR positive patients admitted in Covid ITC, PAF Hospital from the time period of 1st February 2021 to 31st July 2021 including serving personnel and their dependents residing in the premises of PAF Air Base, Mushaf, Sargodha. Data was analyzed using SPSS software version 16. Frequencies were calculated along with mean and standard deviation. Chi square and ANOVA test was applied to the data. P value <0.05 was considered statistically significant. Linear regression study was applied to predict the prognosis.

Results: Out of 150 patients, 51 patients (34%) were of severe ARDS category of whom 13 (25.5%) developed Cytokine Release Syndrome. They received plasmapheresis therapy subsequently and 7 out of those 13 (53.8%) patients got improved. P-value was found to be significant (<0.05). Overall, the mortality rate was low with 120/150 (80%) getting discharged successfully.

Conclusion: Our findings suggest that Therapeutic plasma exchange is beneficial in Cytokine storm caused by SARS-CoV2 removing the inflammatory cytokines and improving symptoms, thereby, avoiding intubation.

Keywords: Therapeutic plasma exchange, Hypercytokinaemia, Cytokine Release Syndrome.

Introduction

The SARS-CoV-2 virus has created global panic due to its huge impact on public health world-wide. Currently, there is no permanent treatment plan for COVID-19 infection, and after several trials, present treatment strategies focus on palliative care, disease control, and investigational therapies.^(1,2,3) Most Covid-19 patients with severe ARDS on laboratory investigation show increased neutrophil and low lymphocyte counts suggesting that there can be a pathological increased inflammatory response to initial Covid-19 infection, which further accelerates a severe hyper cytokinaemia, that can lead to signal the presence of an underlying endothelial dysfunction, resulting in Cytokine Release Syndrome (CRS) in that subset of patients.^(4,5,6,7,8,9) Cytokine release syndrome CRS, also known as Cytokine Storm, is a life threatening condition with an extremely high mortality rate (>90%) in severely ill Covid-19 patients. Therefore, removal of these inflammatory cytokines by Therapeutic Plasma Exchange (TPE) of critically ill patients, admitted in Intensive Care Unit (ICU), is essential in order to improve their survival rates. During Covid-19 pandemic, research shows that the combined use of Therapeutic Plasma Exchange (TPE), also known as Plasmapheresis, along with strong antibiotics, anti-inflammatory medications, antiviral/immune modulatory therapy and anticoagulation therapy has been shown to improve clinical outcomes by effectively treating severe ARDS caused by Covid-19 disease, thereby, avoiding mechanical ventilation.⁽¹⁰⁾ Thus, this present study was conducted to document the effect of Therapeutic Plasma Exchange (TPE) on the outcome of patients having cytokine storm associated severe pneumonia caused by SARS-CoV2.

Materials and Methods

This study was retrospective observational and single center which enrolled laboratory tested PCR positive patients in Covid ITC, PAF Hospital, Mushaf, Sargodha for the time period of 6 months from 1st February 2021 to 31st July 2021 including serving personnel and their dependents, retired and the civilians of all age groups and both genders residing in the premises of PAF Air Base, Mushaf, Sargodha. Convenience sampling method was used and a total of

150 patients met the below mentioned criteria and were included in the study.

Inclusion Criteria: All those patients who were laboratory tested PCR positive having mild (PaO₂/FiO₂ <300), moderate (PaO₂/FiO₂ <200) and severe (PaO₂/FiO₂ <100) ARDS had been included in the study.

Exclusion Criteria: The following patients were excluded from the study:

1. Bacterial pneumonia was found as confirmed by sputum bacterial culture.
2. Patients suffering from interstitial pneumonia having previous radiological record of their disease.
3. Patients with prior heart failure, associated with pulmonary edema, not caused by Covid-19.

According to W.H.O criteria⁽¹⁶⁾, Severe disease has been operationally defined as patients presenting with fever, respiratory symptoms such as shortness of breath, radiological findings consistent with SARS-CoV2 infection on HRCT chest scan along with:

1. Flow rate of more than 15L/min for 90% oxygen saturation.
2. HRCT chest scan showing more than 50% involvement
3. Septic shock leading to multiorgan dysfunction or failure.
4. Blood culture test confirming a secondary bacterial infection.
5. Mean arterial blood pressure raised above 65mmHg by the use of inotropics such as norepinephrine and vasopressor.
6. PaO₂/FiO₂ ratio less than 100 mmHg or PaO₂ less than 80 mmHg on ABGs.

Following data was collected from the patients: Their age, gender, comorbidities, degree of HRCT involvement, PaO₂/FiO₂ ratio to categorize Covid-19 patients into mild/moderate or severe ARDS, their laboratory tests especially TLC count with specific emphasis on leukocyte (neutrophil) count and lymphocyte count so to divide the former by the latter to obtain NLR ratio, D-dimers, Lactate levels, ferritin, Interleukin 6 (IL-6) and pro-calcitonin levels, need of mechanical ventilation and the general patients' ITC stay outcome. As per protocol, all those who showed impending respiratory failure (respiratory rate >35 and the usage of accessory muscles), unstable hemodynamic status, or were fatigued and lethargic were intubated after taking informed and written consent.

Description of plasma exchange procedure:

Plasmapheresis was performed using the Spectra Optia®Apheresis System (TermuBact, Japan), a standard plasma exchange kit, with fresh frozen plasma (FFP) being used as a replacement solution. Citrate dextrose solution, solution A (ACD-A), was used as an anticoagulant. The total volume of plasma to be replaced was calculated by the following formulae: plasma replacement (L) = body weight (kg) × (1/13) × (100-hematocrit). TPE was performed through a standard double lumen catheter placed in femoral vein. Each patient underwent a total of three or more procedures. TPE’s effect on clinical and laboratory parameters was noted after the completion of the four cycles.

Treatment success is defined as weaning off of patients successfully and their discharge from Covid ITC while the proportion of severe Covid 19 patients with CRS who died after receiving TPE therapy or got intubated will be defined as treatment failure.

Statistical Analysis: Data was analyzed using SPSS software version 16. Frequencies were calculated along with mean and standard deviation. Chi square and ANOVA test was applied to the data. P value <0.05 was considered statistically significant. Linear regression study was applied to predict the prognosis.

Results

Total 150 patients tested Real Time PCR positive for Covid-19 disease, out of which 86.7% of the patients belonged to the middle age group (50-70 years). 113 (75.3%) subjects were males and 37 (24.7%) were females. Majority of the subjects had multiple comorbidities such as Diabetes Mellitus and Hypertension both existing in 16.7% of this study’s population. Hyper Resonance Computed Tomography (HRCT) chest scans taken at the time of admission showed majority (40%) of the patients having 50-70% lung involvement. 20% and 46% of subjects had mild (n= 30) to moderate (n= 69) ARDS while severe ARDS was observed in 51 participants (34%). Out of these 51 subjects who had severe ARDS, only 13 patients (25.5%) developed CRS and thus, received TPE therapy subsequently, revealing a significant relationship between the subset of patients who had ARDS only vs those having ARDS and CRS (P-value <0.005). After TPE treatment, 7 out of 13 patients (53.8%) got discharged successfully, the results of which when compared via Chi Square test and ANOVA test between the number of patients, who developed CRS-associated severe ARDS, and their subsequent treatment with TPE therapy, and the

general outcome of ITC patients revealed a significant relationship (P-value <0.005), thus, highlighting the importance of TPE therapy as one of the effective treatment modalities in the treatment of severely ill Covid-19 disease by slimming those patients’ mortality rates and thereby, avoiding intubation and mechanical ventilation. See Figure 1 and Table 1,2. Overall, the mortality rate of total 150 patients was low (20%) with 120 patients (80%) successfully surviving and getting discharged from Covid ITC at the end of their treatment. Linear regression study revealed a straight line relationship indicating a positive impact on outcome of CRS patients when treated with plasmapheresis therapy. See Figure 2.

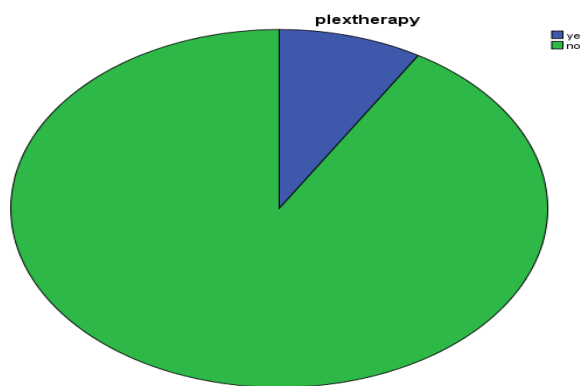


Figure 1:

Table 1: Test Statistics

	Outcomeofptnts	plextherapy
Chi-Square	54.000 ^a	102.507 ^a
Df	1	1
Asymp. Sig.	.000	.000

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 75.0.

Table 2: ANOVA^a

Model	Sum of Squares	df	Mean Square	F	Sig.
1 Regressi on	.807	1	.807	10.788	.001 ^b
Residual	11.067	148	.075		
Total	11.873	149			

a. Dependent Variable: plextherapy
 b. Predictors: (Constant), outcomeofptnts

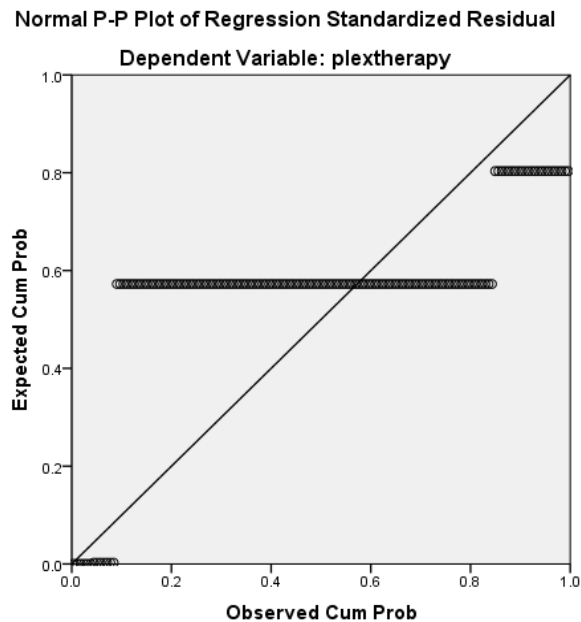


Figure 2:

Discussion

In this retrospective observational study, we found that TPE therapy when started early as soon as the inflammatory markers increased exponentially, after pre-treatment with antibiotics, steroids, antiviral/immune modulatory therapy and anticoagulation therapy, showed satisfactory outcome of those Covid-19 patients who were suffering from severe ARDS and then developed Cytokine Release Syndrome CRS consequently.

Literature review has suggested similar mortality benefit in severe Covid-19 patients who were treated successfully with TPE. ^(10,11,12,13,14,15) Khamis et al, reported in his study that mortality was significantly higher in the group not on TPE as compared to the group on TPE at 14 days (35% versus 0; $p=0.033$) and 28 days (35% versus 0; $p=0.033$) following the procedure.⁽¹⁵⁾ Gucyetmez et al, also reported a similar trend of increase in the mortality rate of patients who were in the control group (58.3%) versus those who received therapeutic plasma exchange (8.3%) ($p=0.009$).⁽¹⁰⁾

The reason may be that in Covid-19 infection, treatment by TPE removes toxins and injurious inflammatory cytokines such as TNF, IL-1, IL-6, G-CSF and other inflammatory parameters. These inflammatory cytokines can trigger a cytokine storm-mediated immune injury to the different target organs, resulting in capillary leak syndrome, deteriorating

lung injury, respiratory failure and ARDS, shock, acute brain and kidney injury and liver dysfunction.^(10,14,15)

Thus, there are several benefits of TPE therapy in such patients. Furthermore, studies have indicated that multiple sessions can significantly alter the discourse of critically ill Covid-19 patients.⁽¹³⁾ It is, therefore, essential to recognize the timely administration of this treatment plan as well as the correct duration and volume to avoid unwanted side effects.

Conclusion

Our results indicate that Early TPE therapy is beneficial in severe ARDS caused by Covid-19, suspected of down spiraling to Cytokine Release Syndrome CRS, when given along with antibiotics, steroids, antiviral/immune modulatory therapy and anticoagulation therapy, thereby, avoiding intubation.

Study Limitation

This study was conducted in a single hospital with a small sample size; therefore, more studies such as large randomized clinical trials are necessary to practice these relationships clinically.

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