Efectiveness of Therapeutic Plasma Exchange in Patients Suffering from COVID-19 Requiring Admission in Critical Care Setting

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ABSTRACT

***Objective*:** To determine the efficacy of therapeutic plasma exchange in patients suffering from COVID-19 requiring admission in the critical care setting.

***Study Design*:** Comparative cross-sectional study.

Setting and Duration of Study: Critical Care Unit, Pak Emirates Military Hospital Rawalpindi, from Apr 2020 to Jun 2020.

***Methodology*:** The study was carried out on 160 patients managed at the Critical Care setting of our hospital in three months. Data were extracted from the record regarding the patients who underwent therapeutic plasma exchange and others who were only given supportive management. Overall mortality, duration of hospital stay, duration of Intensive Care Unit stay and duration of oxygen supplementation was compared in both the groups.

Results: A total of 160 patients met the inclusion/exclusion criteria. Of these, 100 (62.5%) underwent therapeutic plasma exchange, while 60 (37.5%) did not undergo this procedure. The mean age of participants was 62.19 ± 5.192 years. Out of 15 (15%) patients died who underwent therapeutic plasma exchange, while 51 (85%) patients died who did not undergo plasma exchange (p-value <0.001). Length of hospital and Intensive Care unit stay and duration of oxygen supplementation were significantly less among those who underwent therapeutic plasma exchange than those who did not undergo this procedure (p-value <0.05).

***Conclusion*:** Therapeutic plasma exchange emerged as an effective procedure for patients of COVID-19 requiring Critical Care admission and organ support due to complications of this infection. Overall mortality and other clinical parameters were also significantly improved among patients undergoing therapeutic plasma exchange.

Keywords: COVID-19, Efficacy, Therapeutic plasma exchange.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) started as an outbreak in one province of China.[1] Pakistan had its first case reported on Feb 26, 2020. The spectrum of COVID-19 in adults ranges from asymptomatic infections to severe pneumonia with acute respiratory distress syndrome.[2,3]

There is no convincing evidence to support the use of plasma exchange therapy in COVID-19 patients.[4] Management usually revolves around supportive treatment as per symptoms and complications.[5] Immune-mediated response to viral infection and cytokine storm among the patients have rung the bells in the ears of clinicians.[6]

The SARS-CoV2 causing COVID-19 is a new disease with ever-evolving concepts. Guidelines and recommendations are evolving regarding optimal therapeutic options. Considering high mortality in critically ill patients, there is an unmet need to run trials for assessing the efficacy of novel treatments.[7] Therapeutic plasma exchange (TPE) has been used in several studies to manage severe infection. Recently, TPE, which is not a novel therapy, has been used in several studies to manage severe COVID-19 infection and is effective in a few case reports.[8] Therapeutic plasma exchange uniquely offers benefits in all the stages and is effective at multiple levels by removing virus particles, inflammatory cytokines, activated comp-lements, stabilizing endothelial membranes, and resetting the hypercoagulable state.[9]

Until vaccines or some definitive treatments for COVID-19 become available, it is evident that novel treatment options for increasing severe cases are urgently required to reduce mortality and morbidity related to this disease.[10] We, therefore, did this analysis to look for the efficacy of the TPE procedure among the patients of COVID-19 who developed complications and required critical care unit admission.

METHODOLOGY

This cross-sectional comparative study was conducted at the Critical Care Unit of Pak Emirates

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Military Hospital Rawalpindi from Apr 2020 to June 2020. The sample size was calculated by the WHO sample size calculator using the population prevalence of effectiveness of TPE as 9.1%.[11] The study was approved by the Ethical Committee of Pakistan Emirates Military hospital and written informed con-sent was obtained from the patient or (if intubated) next of kin and coding was done.

Inclusion Criteria: Patients of either gender, with age 18 to 60 years who were PCR positive for COVID-19 were included in the study.

Exclusion Criteria: Pregnant women, patients with pulmonary embolism and hemodynamic compromise/ instability, patients with acute coronary syndrome were excluded from the study.

Patients were selected from the computer-based and manual records and divided into two groups based on undergoing therapeutic plasma exchange. Both groups received standard management as per protocol. However, patients from group-A received TPE. Adult patients who were PCR positive for COVID 19 were admitted to the critical care unit either with ARDS or severe pneumonia or any other manifestation of cytokine release syndrome (CRS).

Berlin criteria of ARDS defined a case of ARDS, i.e., PaO2/FiO2 ratio ≤300 and >200 is mild ARDS; PaO2/FiO2 ratio 100-200 is moderate ARDS; PaO2/ FiO2 ratio <100 is severe ARDS In this criteria, the minimum level of PEEP required for diagnosing ARDS is 5cmH2O.[11,12]

Severe pneumonia in adults was defined as fever or suspected respiratory infection plus one of the following: respiratory rate of >30 breaths/minute, severe respiratory distress and SpO2 of <93% on room air.[13] Cytokine release syndrome was defined as per the definition of Chatenoud *et al*.[14]

Patients underwent 3-5 sessions of plasma exchange. Laboratory parameters: which were taken from all the patients included CRP, LDH, ferritin, D-dimer, (absolute lymphocytic count (ALC), neutrophil to lymphocyte ratio N/L ratio. Radiological parameters included CT severity Index (CTSI). Standard therapy given to all the patients (both groups) included Injection Vitamin C 1500mg IV 8 hourly, Vit D 200,000 U orally weekly, tablet Zinc 20mg daily, tablet Azithromycin 500mg daily for seven days, tablet Aspirin 75mg daily, tablet Atorvastatin 40mg daily, injection Enoxaparin 60mg twice daily or injection Heparin 5,000 U8 hourly, injection Dexa-methasone 6-12 mg daily and injection remdesivir 100 mg daily for ten days (optional).

Plasma exchange was carried out by standard procedure. Fresh frozen plasma (75%) and 5% human albumin (25% if less than 30) have been used. Exchange volume was calculated as: Plasma Replacement (L)=0.07 x body weight (kg) x (1–haematocrit).[15] Three to five sessions were carried out using a standard double-lumen catheter in a femoral or internal jugular vein over 7-10 days. Schedule of plasma exchange as per clinician discretion was daily or on alternate days. Primary outcome measure was overall mortality while secondary outcome measures included length of hospital stay, length of ICU stay, days on ventilator and days of oxygen supplementation.

Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. Quantitative variables were summarized as mean ± SD and qualitative variables were summarized as frequency and percentages. Chi-square test was applied to find out the association. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 160 patients fulfilled the inclusion/ exclusion criteria. Of these, 100 underwent therapeutic plasma exchange, while 60 did not undergo this procedure. The mean age of participants was 62.19 ± 5.192 years (Table-I).

Table-I: Characteristics of study participants (n=160).

Factors	n (%)
Age (Years)	
Mean ± SD	62.19 ± 5.192 years
Range (min-max)	20 - 74 years
Gender	
Male	120 (75%)
Female	40 (25%)
Mean Hospital stay	18.3 ± 2.41 days
Mean intensive care unit stay	9.8 ± 7.16 days
Therapeutic Modality	
Therapeutic plasma exchange	100 (62.5%)
Standard Treatment	60 (37.5%)
Overall Mortality	
Recovered	94 (58.75%)
Died	66 (41.25%)

120 (75%) patients were males while 40 (25%) were females. 15 (15%) patients died who underwent therapeutic plasma exchange, while 51 (85%) patients died who did not undergo plasma exchange (*p*-value <0.001).

Table-II showed that length of hospital and ICU stay and duration of oxygen supplementation were significantly less among those who underwent therapeutic plasma exchange than those who did not undergo this procedure (*p*-value <0.05).

Table-II: Difference of primary and secondary outcomes in both the groups.

Factors	Patients With Therapeutic Plasma Exchange	Patients with Standard Treatment Only	*p*-value
Overall Mortality			
Alive	85 (85%)	09 (15%)	<0.001
Deceased	15 (15%)	51 (85%)	
Length of Hospital Stay			
<2 weeks	68 (68%)	30 (50%)	0.024
>2 weeks	32 (32%)	30 (50%)	
Intensive Care Unit Stay			
<7days	82 (82%)	37 (61.7%)	0.005
>7 days	18 (18%)	23 (38.3%)	
Days on Ventilator			
<7 days	89 (89%)	36 (60%)	<0.001
>7 days	11 (11%)	24 (40%)	
Days on Oxygen Support			
<7days	81 (81%)	35 (58.3%)	0.002
>7 days	19 (19%)	25 (41.7%)	

DISCUSSION

Most of the patients who suffer from COVID 19 usually recover in few days with mild symptoms. Some patients may need oxygen or, in severe circumstances, may need ventilatory support and critical care management. Multiple options from vaccination to organ support have been tried in various world centres.

Kamran *et al,* published a study recently from a similar setting regarding the efficacy of therapeutic plasma exchange on patients of COVID-19 having complications. They came up with the conclusion that the use of therapeutic plasma exchange was associated with superior overall survival, early cytokine release syndrome resolution, and time to discharge as compared to standard therapy for COVID-19.[16] Our results supported their findings. There was a strong statistically significant relationship with lesser mortality and use of TPE among patients of COVID-19 admitted in the Critical Care Unit. Other parameters like hospital admission duration and days on the ventilator were also significantly less among the patients who received therapeutic plasma exchange.

Khamis *et al*, earlier published a study on data from a tertiary care hospital of Oman regarding the efficacy of therapeutic plasma exchange among severe adult patients of COVID-19. They concluded that the use of TPE in severe COVID-19 patients had been associated with improved outcomes.[11] Our patients also responded well to therapeutic plasma exchange compared to supportive treatment, but study design and method of study may not be sound enough to generalize these results.

Duan *et al*, earlier this year published data from China to establish the effectiveness of convalescent plasma therapy in severe COVID-19 patients. The findings of their study showed that convalescent plasma therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases. [17] Our results established that TPE was superior to supportive management in both primary and secondary outcomes.

Zhang *et al*, highlighted the role of this therapeutic option for the management of severely ill patients of COVID-19 and came up with the findings that therapeutic plasma exchange could be used as a strategy to attenuate circulating cytokines and inflammatory mediators.[18] Overall mortality, hospital stay, ICU stays, days on ventilator and oxygen support, and all the parameters were found better among the pa-tients who underwent therapeutic plasma exchange in our study.

STUDY LIMITATIONS

Multiple reasons attributed to the patients not undergoing TPE. Long term follow-up and complications among patients discharged from ICU or hospital were not taken into account. Adverse effects of the procedure were also not documented in this study.

CONCLUSION

Therapeutic plasma exchange emerged as an effective procedure for patients of COVID-19 requiring critical care admission and organ support due to complications of this infection. Overall mortality and other clinical parameters were also significantly reduced among patients undergoing therapeutic plasma exchange.

Conflict of Interest: None.

Authors' Contribution

MA: Direct contribution, AN:,KS:,AZ:,SB: Peer review, N: Data collection.

REFERENCES

1. CDC Weekly C. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19)-China, 2020. China CDC Wkly 2020; 2(8): 113-122.
2. Abid K, Bari YA, Younas M, Tahir Javaid S, Imran A. Progress of COVID-19 Epidemic in Pakistan. Asia Pac J Public Health 2020; 32(4): 154-156. doi:10.1177/1010539520927259
3. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD. Features, Evaluation and Treatment Coronavirus (COVID-19) In:

StatPearls. Treasure Island (FL): StatPearls Publishing; 2020, [Internet] Available at: https://www.ncbi.nlm.nih.gov/books /NBK554776/
4. Ali I, Alharbi OML. COVID-19: Disease, management, treatment, and social impact. Sci Total Environ 2020; 728(1): 138861. https://pubmed.ncbi.nlm.nih.gov/32344226/
5. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit care 2020; 24(1): 128.
6. Busund R, Koukline V, Utrobin U. Plasma-pheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intens Care Med 2002; 28(10): 1434-1439.
7. Patel P, Nandwani V, Vanchiere J, Conrad S, Scott L. Use of therapeutic plasma exchange as a rescue therapy in 2009 pH1N1 influenza A-An associated respiratory failure and hemodynamic shock. Pediatr Crit Care Med 2011; 12(2): e87-e89. https:// pubmed.ncbi.nlm.nih.gov/20453703/
8. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). Med Rxiv 2020; 2(10): 20021832.
9. Chang J. Sepsis and septic shock: endothelial molecular pathogenesis associated with vascular microthrombotic disease. Thromb J 2019; 17(1): 10.
10. Nguyen T, Carcillo J. Bench-to-bedside review: Thrombocy-topenia-associated multiple organ failure-a newly appreciated syndrome in the critically ill. Crit Care 2006; 10(6): 235.
11. Khamis F, Al-Zakwani I, Al-Hashmi S, Al-Dowaiki S, Al-Bahrani M, Pandak N et al. Therapeutic Plasma Exchange in Adults with Severe COVID-19 Infection. Int J Infect Dis 2020; 99(1): 214–218.
12. Diamond M, Peniston Feliciano HL, Sanghavi D. Acute Respiratory Distress Syndrome (ARDS). In: StatPearls Treasure Island (FL): StatPearls Publishing; 2020, [Internet] Available at: https://www.ncbi.nlm.nih.gov/books/NBK436002/
13. Jain V, Vashisht R, Yilmaz G. Pneumonia Pathology. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020, [Internet] Available at: https://www.ncbi.nlm.nih.gov /books/ NBK526116/
14. Chatenoud L, Ferran C, Reuter A, Legendre C, Gevaert Y, Kreis H, et al. Systemic reaction to the anti-T-cell monoclonal antibody OKT3 in relation to serum levels of tumor necrosis factor and interferon-gamma. N Engl J Med 1989; 320(7): 1420–1421.
15. Bobati SS, Naik KR. Therapeutic plasma exchange - an emerging treatment modality in patients with neurologic and non-neurologic diseases. J Clin Diagn Res 2017; 11(8): ec35-ec37.
16. Kamran SM, Mirza ZH, Naseem A, Liaqat J, Fazal I, Alamgir W, et al. PLEXIT - Therapeutic plasma exchange (TPE) for COVID-19 cytokine release storm (CRS), a retrospective propensity matched control study. medRxiv 2020; 07(23): 20160796.
17. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020; 117(17): 9490-9496.
18. Zhang L, Zhai H, Ma S, Chen J, Gao Y. Efficacy of therapeutic plasma exchange in severe COVID-19 patients. Br J Haematol 2020; 190(4): e181-e183.

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