THE EFFICACY OF PLASMA EXCHANGE IN COVID-19 PATIENTS WITH COMORBID DIABETES MELLITUS

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ABSTRACT

Objective: To explore the use of therapeutic plasma exchange as adjunctive therapy in COVID-19 patients with and without diabetes mellitus.

Study Design: Prospective, observational study.

Place and Duration of Study: Pakistan Emirates Military Hospital Rawalpindi, from Jan to Feb 2021.

Methodology: A total of 90 male patients with laboratory-confirmed coronavirus infection were selected based on our inclusion criteria and their management and outcomes were recorded. The data were analyzed using SPSS-22 and Microsoft Excel.

Results: The mortality rate was lower in patients who received 1 or more sessions of plasma exchange compared to those who did not receive plasma exchange (7.5% vs 12%). A lower mortality rate was seen in patients without diabetes who received therapeutic plasma exchange in addition to standard therapy compared to patients who received standard therapy alone (0 vs 14.82%, p=0.112). In patients with diabetes, a higher mortality rate was found in the group that had received therapeutic plasma exchange in addition to standard therapy instead of standard therapy alone (20% vs 8.7%, p=0.365).

Conclusion: Overall our study supports the use of therapeutic plasma exchange in COVID-19 patients. However, although statistically insignificant, there appears to be a higher mortality rate in patients with diabetes who received therapeutic plasma exchange in addition to standard therapy. As such, we recommend further investigation of this aspect.

Keywords: COVID-19, Diabetes, Mortality rate therapeutic plasma exchange.

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INTRODUCTION

According to the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) and the weekly epidemiological update by the World Health Organization (WHO), the COVID-19 pandemic has claimed over 2.2 million lives worldwide till now.[1,2] As the pandemic continues to grow and affect more people than ever, and the especially vulnerable population at risk of developing severe infection and complications, including death, is the geriatric population and those with comorbidities, such as diabetes mellitus. Several mechanisms have been proposed for the higher risk in the patients with diabetes including immuno-deficiency and altered inflammatory responses such as a reduced capacity to tolerate systemic cytokines.[3,4] COVID-19 mortality in these patients has been shown to be linked not only to the cardiovascular and renal complications of diabetes but also directly to the degree of glycemic control and Body Mass Index (BMI).[5,6]

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Although preventing exposure to the virus and controlling the underlying risk factors remains the best way to prevent severe illness, a number of adjunctive therapies have been tried and studied since the start of the pandemic. These include plasma exchange, Remdesivir, and Tocilizumab.[7] The potential benefits of plasma exchange in the setting of well-recognized complications, such as cytokine storm and coagulopathy, have been reported by multiple studies.[8,9] In one such study, it was shown to be particularly effective when used multiple times and early in the course of the infection.[10] However, few studies have commented directly on the efficacy of plasma exchange in patients with diabetes.

In our study, we aim to explore Therapeutic Plasma Exchange (TPE) as an adjunctive therapy and its potential effectiveness in male patients with and without diabetes who developed Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2).

METHODOLOGY

The study was prospective and single center, conducted at Pak Emirates Military Hospital (PEMH) in Rawalpindi. It was approved by the ethical review

committee at PEMH (certificate number: A/28/EC/246/2021) and spanned 4 weeks, from 6th January 2021 to 3rd February 2021.

Inclusion Criteria: Male patients, aged 40-79 years, with laboratory confirmed SARS-CoV-2 infection and severe disease at the time of admission were included in the study.

Exclusion Criteria: Patients with moderate or critical disease severity at the time of admission were not included. Patients, who had comorbids other than diabetes mellitus, including hypertension, ischemic heart disease, chronic kidney disease, obstructive lung disease, liver disease and/or malignancy, were excluded from the study.

Convenience sampling was used and a total of 121 patients met the above-mentioned criteria during the duration of the study. The study was not interventional and all patients were managed at the discretion of their treating physicians: individuals who showed signs of cytokine release storm received Therapeutic Plasma Exchange (TPE) in addition to standard therapy; the remaining subjects received standard therapy alone. As such, no special informed consent process was required for the study apart from consent for use of patient data. Patients who received adjunctive therapies other than TPE, including Tocilizumab, Remdesivir, convalescent plasma therapy and/or mesenchymal stem cell therapy, during the course of their treatment were excluded from the study. This left behind 90 patients from the original sample.

Laboratory confirmed SARS-CoV-2 was defined as COVID-19 infection confirmed by RT-PCR sampling of nasopharyngeal and oropharyngeal swabs, at the time of admission or subsequently during the first week of admission in patients with high clinical pretest probability.

Severe disease was operationally defined as COVID-19 pneumonia with evidence of hypoxemia (ie, respiratory rate >30/minute or PaO2 <80 mmHg on arterial blood gas sampling or PF ratio [Horowitz index for lung function] <300 or lung infiltrates involving >50% of the lung fields on a chest x-ray), according to the criteria designed by the World Health Organization.[11]

In accordance with PEMH's Institutional COVID-19 Management Guidelines, the following constituted standard therapy: all patients, regardless of disease severity, received a standard protocol of aspirin, oral vitamins C and D, zinc, famotidine, melatonin, anticoagulation, awake proning (if PaO2 <80 mmHg) and corticosteroids. All patients suffering from a Cytokine Release Storm (CRS) or hypoxemia received either methylprednisolone 1 mg/kg or dexamethasone 6-12 mg/day irrespective of overall disease severity. Respiratory support was given for hypoxemia and consisted of supplemental oxygen therapy, non-inva-sive ventilation (in the form of continuous positive airway pressure at 8-10 cmH2O in 2-4 hours sessions to maintain O2 saturation at 90-94%) or invasive ventilation.

The patients' data was recorded in spreadsheets on Microsoft Excel and IBM SPSS version 22. The data was then analyzed using SPSS-22 and a two-sided Fisher's Exact test was used to determine whether any differences in patient outcomes between different groups were statistically significant or not. Charts were generated on Microsoft Excel.

RESULTS

The total study population was 90 male patients, aged 40-79 years (mean age: 57.28 ± 10.33 years), with laboratory confirmed SARS-CoV-2 infection. The age distribution of cases is shown in Table-I.

About 52 (57.8%) patients did not have diabetes and 38 (42.2%) patients had diabetes. Among patients without diabetes, 27 patients did not receive Therapeutic Plasma Exchange (TPE) while 25 patients did receive TPE. Among the population with diabetes, 23 subjects did not receive TPE while 15 did receive TPE (Table-II). The total number of subjects who did not receive TPE was 50. The remaining 40 subjects received 1 or more TPE sessions (Table-III).

Table-I: Demographic information.

Age Group	n (%)
40-49 years	25 (27.8%)
50-59 years	22 (24.4%)
60-69 years	26 (28.9%)
70-79 years	17 (18.9%)

Table-II: Case distribution.

Patient Category	n (%)
Patients with Diabetes who received Therapeutic Plasma Exchange	15 (16.7%)
Patients with Diabetes who did not receive Therapeutic Plasma Exchange	23 (25.6%)
Patients without Diabetes who received Therapeutic Plasma Exchange	25 (27.8%)
Patients without Diabetes who did not receive Therapeutic Plasma Exchange	27 (30%)

Nine subjects (10% of the study population) died in the study. Of these, 6 did not receive Therapeutic

Table-III: Therapeutic plasma exchange (TPE) sessions.

Number of Therapeutic Plasma Exchange Sessions	n (%)
0	50 (55.6%)
1	12 (13.3%)
2	13 (14.4%)
3	9 (10%)
4	5 (5.6%)
5	1 (1.1%)

Plasma Exchange (TPE). The case fatality rate in the group that did not receive TPE was 12% compared to 7.5% in the group that received 1 or more TPE sessions (Figure-1). The relative risk reduction was 37.5%.

As shown in Figure-2, patients without diabetes who did not receive TPE had a mortality rate of 14.82% compared to 0% in patients who received TPE (p= 0.112). Whereas in patients with diabetes, 2 out of the 23 subjects (8.7%) who did not receive Therapeutic Plasma Exchange died compared to 3 out of 15 subjects (20%) who did receive TPE (p=0.365).

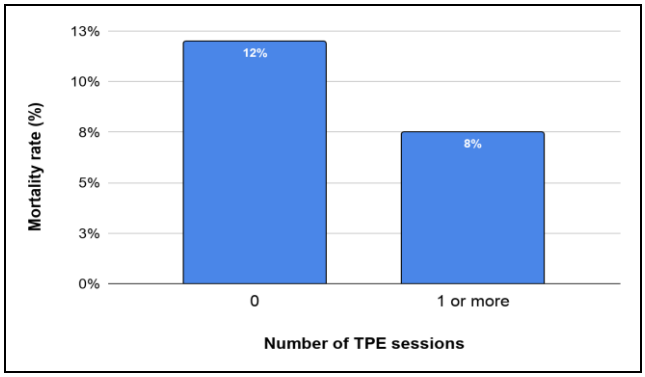

Figure-1: Number of TPE sessions and mortality rate (%).

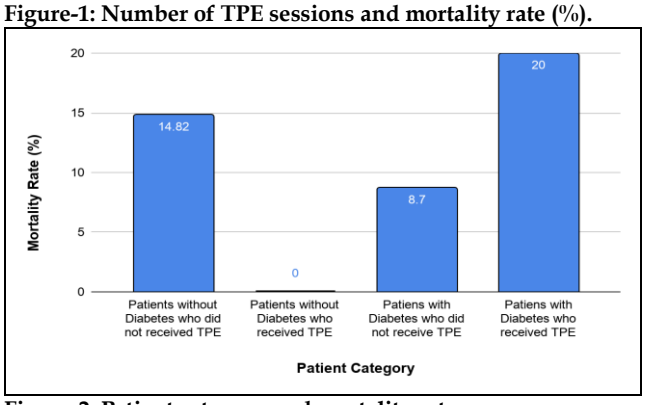

Figure-2: Patient category and mortality rate.

DISCUSSION

In our study, the mortality rate for patients who received 1 or more sessions of TPE was lower than the mortality rate for patients who received no TPE with a relative risk reduction of 37.5%. Many other studies have shown a similar mortality benefit with the use of plasma exchange in COVID-19 patients.[8,12,13] In one such study, Khamis *et al*, reported that mortality was lower in the group on TPE compared to the group not on TPE at 14 days (0 versus 35%; p=0.033) and 28 days (0 versus 35%; p=0.033) following the procedure.[12] Gucyetmez *et al*, also reported a similar trend of decrease in mortality rate in patients who received therapeutic plasma exchange (8.3%) as compared to the control group (58.3%) (p=0.009).[8]

As Kamran *et al,* pointed out, this mortality benefit may be explained by the fact that the cytokine profile in COVID-19 patients closely resembles that of secondary hemophagocytic lymphohistiocytosis (sHLH) and is often accompanied by features of coagulopathy and septic shock; the use of therapeutic plasma exchange has been established in all of these conditions.[9,14] Adeli *et al,* has further reiterated this point and attributed the improvement in respiratory status and reduction in pulmonary involvement of patients with COVID-19 to the elimination of cytokines.[13]

We found a similar trend among patients in our study who did not have diabetes where mortality in the group receiving TPE was considerably lower than the group not on TPE. However, this difference was not statistically significant (0 versus 14.82%; p=0.112). These results are similar to a study conducted by Faqihi *et al* Which showed that while therapeutic plasma exchange did significantly reduce ICU length-of-stay and the need for mechanical ventilation in patients, the effect on reduction of the mortality rate was statistically insignificant (p=0.09).[15]

The mortality rate in patients with diabetes who received TPE was higher than in patients with diabetes who did not receive TPE. This result was found to be statistically insignificant as well (20% vs 8.7%; p= 0.365). The reason for the increased mortality with TPE in COVID-19 patients who have diabetes is not clear because plasma exchange has been shown to be beneficial not only in the treatment of SARS-CoV-2 but also in reducing complications of metabolic syndrome, particularly severe hypertriglyceridemia and the micro-vascular complications associated with type 2 diabetes.[16,17] In contrast to our study, Fernandez *et al,* demonstrated therapeutic plasma exchange as effective rescue therapy in 4 patients with multiple comorbidities, including type 2 diabetes mellitus, who had failed treatment with conventional treatment options such as antiviral agents.[18]

A potential reason for the statistically insignificant results reported by our study is a small sample

size, which can lead to more type II errors and low statistical power.[19] The paradoxical increase in mortality in COVID-19 patients with comorbid diabetes mellitus who received TPE as compared to patients who did not receive TPE in our study, albeit statistically insignificant, could hold clinical value and must be further looked into in future studies.

As such, we recommend that TPE should be used judiciously in patients with diabetes mellitus until further research can demonstrate therapeutic efficacy. Future studies should include larger patient populations and experimental studies should be designed to further explore the efficacy of TPE in patients with diabetes mellitus who are infected with the coronavirus.

CONCLUSION

The results of our study support the use of therapeutic plasma exchange in SARS-CoV-2 patients. There seems to be an overall reduction in mortality with the use of TPE especially in patients without diabetes mellitus. Although statistically insignificant, the mortality rate in patients with diabetes mellitus appears to be higher in those who received plasma exchange in addition to standard therapy.

Conflict of Interest: None.

Authors' Contribution

KA: Manuscript, data collection & analysis. ZH: Article review, data collection. SMK: Manuscript review. IK: Manuscript review. ST: Manuscript, data analysis.

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