Received: 24 September 2021 | Revised: 13 December 2021 | Accepted: 26 April 2022

DOI: 10.1111/1744-9987.13862

ORIGINAL ARTICLE

Therapeutic Apheresis and Dialysis

WILEY

How effective is rescue therapeutic plasma exchange in treatment of SARS-Coronavirus-2?

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Abstract

Introduction: After the FDA gave emergency approval for the use of therapeutic plasma exchange in treatment for SARS-Coronoavirus-2, we analyzed its efficacy in patients who had failed all other known therapies.

Methods: This was a prospective observational study of 42 patients with SARS-Coronoavirus-2 who had failed conventional therapy and were treated with therapeutic plasma exchange. Pre- and postexchange clinical and laboratory parameters were monitored. The patients were then also compared with a group of 147 patients with SARS-Coronoavirus-2 who were referred for stage 3 acute renal failure and dialysis from SARS-Coronoavirus-2.

Results: After therapeutic plasma exchange, there were significant improvements in some clinical parameters but mortality remained high; although better than the renal failure group (43.9% vs. 50.7%, $p = 0.004$).

Conclusion: SARS-CoV-2 patients who failed all other therapies had significant mortality with therapeutic plasma exchange; however, their survival was better than SARS-CoV-2 patients with stage 3 acute renal failure.

KEYWORDS

acute renal failure, coronavirus, cytokines, microangiopathy, plasmapheresis, survival

1 | INTRODUCTION

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became pandemic, the world searched for curative or stabilizing treatments in the face of discouraging clinical outcomes in critically ill patients. Although there were no approved drugs for treatment of this infection, many possible treatment targets were identified and various drugs were re-purposed in an attempt to halt viral entry, replication and cytokine activation [1, 2], but the results were equivocal to disappointing [3–5]. Then others showed that cell entry of coronaviruses depends on binding of the viral spike proteins to cellular receptors and on S protein priming by host cell proteases [6, 7] through a mechanism by which anti-spike protein antibodies were responsible for the immune system cells infection [8, 9]. Since a one volume plasma exchange can remove nearly 70% of cytokines, antibodies or circulating factors, it was suggested that therapeutic plasma exchange (TPE) might be a life-saving therapy [10], and several small case series of a few patients were consistent with that hypothesis [11–15]. That prompted the FDA to give emergency use authorization for the use of TPE for SARS-Coronoavirus-2, and we then chose to examine the possibility that TPE might be an appropriate rescue therapy for those who failed conventional pharmaceutical and supportive treatments [16].

2 | METHODS

This was a prospective observational study conducted from July, 2020 through March, 2021. Hospitalized patients who had failed conventional therapy with the most commonly used pharmaceuticals (Table 1) while yet remaining critically ill who were felt to have no further hope for survival by infectious disease service, were offered TPE as a possible rescue treatment. Forty-two patients accepted the offer of an intervention with TPE as rescue therapy. Since with IRB consideration, it was felt unethical to withhold potentially life-saving therapy from these individuals, there was no randomization or an appropriate control group; however, the TPE patients were compared with a group of 147 patients who were referred to the renal service for stage 3 acute renal failure (ARF) from SARS-CoV-2 infection but as of that time had not failed any therapy and were still considered eminently treatable. The demographics of race, body mass index (BMI) sex, and age as well as risk factors for morbidity and mortality in SARS-CoV-2 including: diabetes, chronic obstructive pulmonary disease, smoking, chronic renal failure, history of vaping, atherosclerotic coronary vascular disease, psychiatric illnesses, prior Human Immunodeficiency Virus, and the use of vasodilators, proton pump inhibiters (PPI), erythropoietin, and potassium sparing drugs [17–25] were recorded. Since fresh frozen plasma was employed for replacement fluid due to the COVID microangiopathy, we also evaluated the effect of blood type. No patients in either group were treated with extracorporeal membrane oxygenation.

While the TPE group was younger ($p < 0.001$) and less likely to have cancer (myeloma, breast and prostate cancer, but none with pulmonary involvement) ($p = 0.002$), there were no other statistically different baseline characteristics. Although the nearly two thirds of both groups were African-Americans, there were no significant differences (Table 2). Mortality, hospital days, mean arterial pressures, respiratory and renal function were studied as variables of

TABLE 1 Drugs that had failed before starting plasmapheresis

Azithromycin
Hydroxychloroquine
Methylprednisolone
Anakinra
Remdesivir
Tocilzumab
Dexamethasone
Convalescent plasma

Note: These were the therapies that all patients in TPE group failed as their status continued worsen before they were offered a chance of attempting TPE.

TABLE 2 Baseline characteristics of the groups studied

	TPE	Stage 3 AKI	Significance
Number of patients	42	147	
Median age ± SD	60.9 ± 12.9	66.7 ± 15.3	$\mathbf{p < 0.001}$
Sex (male) %	70.7	51	$p = 0.32$
Race (African-American) %	65.8	65	$p = 0.41$
Diabetics %	31.7	49.2	$p = 0.66$
Body mass index ± SD %	35.8 ± 10.0	29.2 ± 8.8	$p = 0.66$
Smoking history %	12.2	19.5	$p = 0.18$
Cancer %	4.9	13.8	$p = \mathbf{0.002}$
Dementia %	0	4.6	–
Psychiatric disorder %	0	3.1	–
Chronic renal failure %	7.3	42.1	$p = 0.23$
Chronic obstructive pulmonary disease %	29	18.4	$p = 0.23$
Cardiovascular disease %	17	46.1	$p = 0.06$
Prior human immunodeficiency virus %	0	1.5	–
Erythropoietin use %	4	0	–
Proton pump inhibitor %	48.8	55.3	$p = 0.92$
Vasodilator %	48.8	33.8	$p = 0.24$
Potassium sparing drug %	0	4	$p = 0.11$

Note: While the TPE group was younger and less likely to have cancer, there were no other statistically different baseline characteristics. Bold indicates $p < 0.05$.

efficacy in addition to markers of inflammation such as ferritin, and CRP levels.

The TPE patients underwent daily one volume TPE for 5 days using both the Braun Apheresis Machine 36.0065 (B. Braun, Medical Inc., Renal Therapies Division, Melsungen Germany) and the Terumo Spectrum Optia Centrifuge Systems (Terumo BCT, Inc., Lakewood, CO). All patients underwent 5 consecutive days of one plasma volume TPE. Fresh frozen plasma was chosen as a replacement fluid in all TPE patients since microangiopathy similar to thrombotic thrombocytopenic purpura [26] needs plasma factors to be successful in restoring vascular health and convalescent plasma with documented SARS-CoV-2 antibodies was used as the last 1-L return bag in all patients. We do not have data on how many antibodies were present/L. Heparin was used as an anticoagulant.

In Compliance with Ethical Standards: As the work was purely observational by the physicians following the patients after renal failure began and no treatment intervention was either given or withheld by the observers, no other approval was necessary.

Both groups were evaluated by Chi Square and Kolmogorov–Smirnov for normality while ANOV (Analysis of Variance), Pearson Correlation and Cox Proportional Hazards Model with Kaplan Meir survival curves were employed to discern significant differences of inflammatory markers, in renal and respiratory function as well as survival.

TABLE 3 Comparison of TPE patients before and after TPE course

	Before	After	Significance
Ventilator %	24	44	$p = 0.003$
Prone %	24	34	$p = 0.10$
Oxygen saturation%	89.3 ± 14.7	91.3 ± 21.5	$p = 0.48$
F_iO_2%	86.2 ± 29.0	73.1 ± 30.5	$p = 0.001$
Mean arterial pressure mmHg	89.0 ± 17.2	80.6 ± 23.6	$p = 0.01$
Serum creatinine mg/dl	1.4 ± 1.7	1.2 ± 1.5	$p = 0.23$
Hemodialysis %	4.8	7.3	$p = 0.32$
Ferritan ng/ml	657.6 ± 466.3	374.7 ± 373.6	$p < 0.001$
CRP mg/dl	6.6 ± 6.6	4.6 ± 8.1	$p = 0.177$
Platelets/1000	259.4 ± 123.1	216.1 ± 105.3	$p = 0.003$

Note: Only the ferritin showed a significant improvement after course of TPE.

TABLE 4 Comparison of TPE patients with the plasma exchange with stage 3 ARF patients

	TPE	Stage 3 AKI	Significance
Number of patients	*42*	*147*	
Ventilator %	24	38	$p = 0.41$
Prone	24	29	$p = 0.72$
Oxygen saturation%	89.3 ± 14.7	92.2 ± 12.6	$p = 0.25$
F_iO_2%	86.2 ± 29.0	54.2 ± 30.3	$\mathbf{p = 0.03}$
Mean arterial pressure mmHg	89.0 ± 17.2	91.3 ± 20.1	$\mathbf{p = 0.003}$
Serum creatinine	1.4 ± 1.7	4.6 ± 3.0	$\mathbf{p = 0.003}$
Hemodialysis (after) %	7.8	38	$\mathbf{p < 0.001}$
Ferritin ng/ml	657.6 ± 466.3	907.8 ± 547.9	$p = 0.40$
CRP mg/dl	6.6 ± 6.6	13.5 ± 10.1	$\mathbf{p = 0.006}$
Platelets/1000	259.4 ± 123.1	205.7 ± 90.7	$\mathbf{p = 0.03}$
Hospital days (overall)	24.1	14.3	$\mathbf{p < 0.001}$
Hospital days (survived)	30.1	15.1	$\mathbf{p < 0.001}$
Hospital days (expired)	16.6	14.5	$\mathbf{p = 0.53}$
Mortality %	43.9	50.7	$\mathbf{p = 0.004}$

Note: Mean Arterial pressure, serum creatinine, CRP, the need to initiate hemodialysis and mortality were significantly lower and the platelet count and FiO_2 requirements were significantly higher in the TPE group. Bold indicates $p < 0.05$.

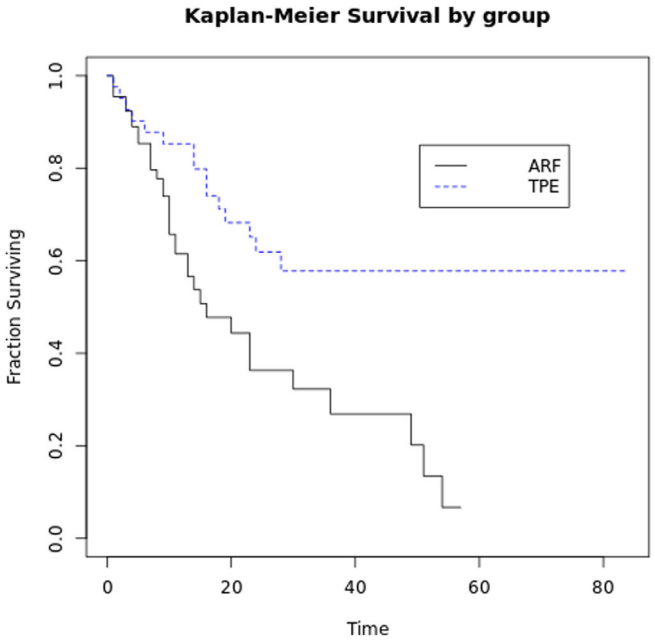

FIGURE 1 The TPE group had lower mortality (43.9% vs. 50.7%, $p = 0.004$) than the Stage 3 ARF patients. Time is in days.

3 | RESULTS

During the study period, 42 patients received TPE after one patient refused and died within 24 h. There were no TPE patients who died before completing TPE. There were two patients with minor reactions to the plasma replacement. The results are listed in Tables 3 and 4. As seen in Table 3, while the TPE patients had significantly decreased oxygen requirements, significantly more had required mechanical ventilation by the end of the TPE treatments. Similarly, while the ferritin levels significantly fell after treatment, so did the blood pressure and the platelet counts. When comparing the baseline characteristics of the TPE patients to the Stage 3 ARF patients (Table 4), the renal failure group had higher CRP levels, serum creatinines values and were more likely to have cancer and need initiation of dialysis; however, the TPE group had lower platelet counts, significantly worse mean arterial pressures with higher oxygen requirements as represented by the FiO_2. Nevertheless, the TPE group had lower mortality (43.9% vs. 50.7%, $p = 0.004$, Figure 1), although a significantly longer hospital stays (24.1 vs. 14.3, $p < 0.001$). The stage 3 ARF patients were much more likely to be dialyzed ($p < 0.001$). The initial serum creatinine, CRP, initiation of dialysis, presence of COPD, cardiovascular disease, Body Mass Index, male sex, cancer, the use of erythropoietin or a vasodilator all correlated significantly with mortality, while surprisingly the initial oxygen saturation, percentage of inspired oxygen, ventilator use, mean arterial blood pressure, prior hemodialysis or history of human immunodeficiency virus were not associated with mortality (Table 5). There was no significant effect of blood type on mortality and the only suspected transfusion reaction occurred in one blood type O patient whose fever increased after TPE (Table 5). The one patient who refused TPE also died.

TABLE 5 Variables correlation with mortality

	Significance
Initial ventilator	$p = 0.172$
Initial prone	$p = 0.175$
Initial oxygen saturation %	$p = 0.120$
Initial F_iO_2%	$p = 0.215$
Initial mean arterial pressure mmHg	$p = 0.101$
Initial serum creatinine	$\mathbf{p = 0.023}$
Initial hemodialysis	$p = 0.113$
Hemodialysis (after)	$\mathbf{p = 0.007}$
Ferritan ng/ml	$p = 0.130$
CRP mg/dl	$\mathbf{p = 0.023}$
Platelets/1000	$p = 0.081$
Age	$p = 0.140$
Chronic renal failure	$\mathbf{p = 0.029}$
Chronic obstructive pulmonary disease	$\mathbf{p = 0.048}$
Sex (Male)	$\mathbf{p = 0.036}$
Race (African-American)	$p = 0.060$
Diabetic	$p = 0.135$
Body mass index	$p = 0.031$
Smoking history	$p = 0.125$
Cancer	$\mathbf{p = 0.043}$
Dementia	$p = 0.064$
Psychiatric disorder	$p = 0.144$
Cardiovascular disease	$\mathbf{p = 0.014}$
Prior human immunodeficiency virus	$p = 0.102$
Erythropoietin use	$\mathbf{p = 0.007}$
Proton pump inhibitor	$p = 0.144$
Vasodilator	$\mathbf{p = -0.032}$
Blood type	$p = 0.092$
Potassium sparing drug	$p = 0.093$

Note: The initial serum creatinine, CRP, initiation of dialysis, presence of COPD, cardiovascular disease, body mass index, male sex, cancer, the use of erythropoietin or a vasodilator all correlated significantly with mortality, while surprisingly the initial oxygen saturation, percentage of inspired oxygen, ventilator use, mean arterial blood pressure, prior hemodialysis or history of human immunodeficiency virus were not associated with mortality. Bold indicates $p < 0.05$.

4 | DISCUSSION

Early in the pandemic there were calls to action to develop new treatments because of a dearth of therapeutic options [27–29].Since there are similarities between the spike antigens of SARS-CoV and SARS-CoV-2 viruses, it was expected that those similarities of structure and affinity to the receptor of ACE2 binding domain (ABD) could lead to the same pathophysiological activity of the virus by the use of ACE2 and the antibody-dependent enhancement mechanism through which viruses take advantage of anti-viral humoral immune responses to infect host target cells primarily mediated by anti-spike antibodies [8] that could be removed by therapeutic plasma exchange towards a potentially therapeutic effect [27]. Therefore, some felt TPE should be "employed on patients that have no significant response for typical anti-viral, ARDS and conservative therapies, and the disease persists or progresses despite sufficient therapies [27]." A recently published critical analysis of all previous case series has concluded that despite some individual successes with TPE in SARS-CoV-2 virus infection, we still do not know how or if it is really effective [30]. Furthermore, a soon to be published metanalysis of all available published use of therapeutic plasma exchange found that only a total of 49 critically ill patients with SARS-CoV-2 have been treated with therapeutic plasma exchange but yet they have concluded that the treatment is helpful [31]. The paucity of data for just 49 patients in this life threatening situation leaves one dubious. While our study was not a randomized double-blind trial (RCT), we will now add almost as much data as had previously been reported in the world's literature to lend perspective to that proposal. To our knowledge this is the largest single center prospective observational study on this important topic.

As this was not an RCT with no real control group, we cannot come to definite conclusions but merely wish to share our data with those who are considering TPE as a rescue therapy. In an attempt to put our data in proper perspective we have gathered another group of patients to substitute as a control group since it was considered unethical to withhold potentially life-saving therapy for an appropriate control group. As nephrologists, our main reason for consultation was renal failure. Since patients with ESRD are known to survive SARS-CoV-2 well [23], we chose to compare our TPE patients with stage 3 acute kidney failure (ARF) patients because of their known high mortality and the fact that we were seeing large numbers of patients with that diagnosis. ARF has been reported as a severe complication and a predictor for poor clinical outcomes of different coronavirus infections, including SARS-CoV-2 [32–37]. Recent analyses indicate ARF mortality with Sars-CoV-2 is higher than Middle East Respiratory Syndrome but lower than SARS-CoV-1 infections [33]. Thus while patients with ARF from SARS-CoV-2 may not be a perfect comparison group, the fact that their average mortality rates of 78% in metanalysis [35] for stage 3 ARF shows that they could be thought to be a suitably dire comparison for the TPE group [36] who were felt to otherwise have no chance of survival. Although the TPE group had significantly less mortality ($p = 0.004$), they also were younger and less likely to have cancer or be smokers; however, only cancer had an effect on mortality. Since the cancers were multiple myeloma, breast and prostate cancers without any pulmonary involvement, it is more likely that the severity of the underlying disease rather than the SARS-CoV-2 infection was responsible. The age difference may be more significant. As this study was performed before the emergence of the delta variant, the fewer angiotensin converting enzyme 2 receptors in youth would be protective not only against infection, but also the severity of infection without the increased hydrogen bonding and Van der Waal binding to ABD provided by the delta variant mutation [38]. Similarly, the improved oxygenation requirements after TPE (86.2–73.1%, $p = 0.001$) might be seen as a benefit from TPE except that it is offset by the increased need for ventilator use ($p = 0.003$) indicative of the fact that there continued to be deterioration for the period immediately after TPE. That led to prolonged hospital stays. Overall, the TPE patients had statistically longer hospital stays than the ARF patients (24.1 vs. 14.3 days, $p < 0.001$), mainly due to the TPE patients who recovered compared with ARF patients (30.1 vs. 15.1, $p < 0.001$) who recovered, since the TPE patients who died did so just as quickly as the ARF patients (16.6 vs. 14.5, $p = 0.53$). Given the ventilator and bed shortage during the pandemic, that may be an undesirable, even, if necessary, requirement for survival. Nevertheless, although a 43.9% mortality might be thought to be a success in a group who were thought to otherwise have no chance of survival, we cannot be sure that TPE as rescue therapy was successful as their CRP levels were lower which did predict mortality. Even though the oxygen requirements and laboratory parameters of inflammation did become significantly improved after TPE, we cannot guarantee that this was not an effect of the TPE because a similar improvement was seen in the Stage 3 ARF patients who did not undergo TPE in the same time period. The only significant laboratory difference in changes between the two groups at this interval was the expected drop in platelet count caused by the TPE procedure itself [37] was not observed in the stage 3 ARF patients. A similar series of 31 patients whose ventilatory parameters significantly improved while their overall mortality did not

[39], might be viewed with the same skepticism. Since more recent cases suggest that TPE may be more effective early in the first week [40, 41], TPE may not be the optimum rescue therapy for the most critically ill who have failed all other therapy; however, we did find improved survival compared with a very ill group of ARF patients.

5 | LIMITATIONS

This was not a randomized clinical trial. With an imperfect control group, we are greatly limited in conclusions. Although all patients whom the department of infectious disease requested TPE as rescue therapy for SARS-CoV-2 patients who had failed all previous therapy were included as TPE patients and compared with all patients with stage 3 ARF from who presented in the same time frame, we cannot exclude a selection bias. We therefore merely wish add our data to the world's literature in order to provide more insight at present and accuracy of future metanalyses by others.

6 | CONCLUSION

SARS-CoV-2 patients who failed all other therapies still had significant mortality with TPE; however, their survival was better than SARS-CoV-2 patients with stage 3 ARF. While the results may be encouraging, the efficacy of TPE as a rescue therapy in SARS-CoV-2 can only be answered by a randomized controlled trial.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Diskin CJ, Maldonado R, Leon J, Dansby LM, Carter TB, Radcliff L, et al. How effective is rescue therapeutic plasma exchange in treatment of SARS-Coronavirus-2? Ther Apher Dial. 2022. https://doi.org/10.1111/1744-9987.13862