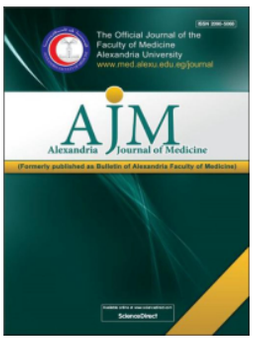

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Does therapeutic plasma exchange have a role in resistant cytokine storm state of COVID-19 infection?

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ABSTRACT

Introduction: Among the main causes of mortality in COVID-19 patients is cytokine storm (CS) state. Few treatment options with variable efficacy results are available for its management. We aimed to illustrate the efficacy of Therapeutic Plasma Exchange (TPE) treatment in COVID-19 patients with resistant CS.

Material and methods: This research is a prospective pilot study which included ten COVID-19 positive patients with CS state with no response after two doses of tocilizumab. Each patient received three to five TPE sessions according to his/her response. Respiratory status {oxygen (O_2) requirements and data of mechanical ventilation} and laboratory markers (IL-6, CRP, ferritin, D dimer, LDH) were assessed before and after TPE. We reported mortality at 28 day of illness.

Results: Six males and four females were enrolled in the study with a mean age of (52.9 years). Seven patients (70%) were on mechanical ventilation (MV). After TPE, oxygenation parameters and most laboratory markers improved significantly in all patients ($p < 0.05$). Four patients survived and were discharged (40%). One was on MV and three were not. The four patients had better hypoxic index (PaO2/FiO2 ratio) (>100 vs <100), started TPE sooner after tocilizumab failure (2–3 vs 5–6 days), needed fewer TPE sessions (3 vs 4–5, $p = 0.03$), and less duration in ICU (6.5 vs 12.5 days) compared to those who did not benefit.

Conclusions: In patients with CS state who did not respond well to tocilizumab and steroids, TPE could be a good option. Larger randomized clinical trials are needed to support its use.

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COVID-19; cytokine storm; therapeutic plasma exchange; TPE

1. Introduction

In early December 2019, several pneumonia cases of unknown origin were observed in Wuhan (China). A novel enveloped RNA β coronavirus was isolated and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The new virus rapidly spread across China and worldwide. On March 11th, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic [2]. As of December 27, 2020, COVID-19 has been confirmed in over 79.2 million individuals globally with deaths reaching 1.75 million with a morality of 2.2%. Egypt has 131,315 confirmed cases and 7352 deaths [3].

The virus mainly spreads through respiratory droplets from infected patients [4]. The clinical spectrum of COVID-19 infection ranges from asymptomatic forms to severe pneumonia requiring hospitalization and isolation in critical care units with the need of mechanical ventilation due to acute respiratory distress syndrome (ARDS). Severe COVID-19 conditions are usually due to an aggressive inflammatory response known as cytokine storm (CS) that is characterized by the release of a large amount of proinflammatory cytokines [5,6]. Treating this cytokine storm state improves morbidity and mortality [7]. Immunomodulators, cytokine antagonists, and cytokine removal are potential options to manage cytokine storm [8].

Therapeutic plasma exchange (TPE) removes pro-inflammatory cytokines mediating cytokine storm condition. TPE had been used successfully in severe H1N1 influenza A infection [9]. Steroids are the most used drug to treat cytokine storm of COVID-19. Tocilizumab [interleukin (IL) 6 antagonist] also is used widely with promising results. But a considerable percentage of patients do not respond to it leaving physicians with very limited options and usually patients deteriorate rapidly with very high mortality. Hence, we decided to test the efficacy of TPE in those patients who did not respond to tocilizumab.

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2. Patients and methods

2.1. Participants

This research included 10 patients from the COVID-19 isolation hospitals in Alexandria, Egypt who had CS state with no improvement after two doses of tocilizumab. Criteria of failure (resistance) of tocilizumab were: persistent high IL-6 and C reactive protein (CRP), persistent worsening of respiratory symptoms (dyspnea, tachypnea, increased oxygen (O_2) requirements or even need for mechanical ventilation), partial arterial pressure of oxygen to fractional inspired concentration of oxygen (PaO2/FiO2) ratio <150, persistent fever (>38.5°C) despite normal procalcitonin level. Patients with refractory septic shock were excluded. Patients were treated according to the COVID 19 management protocol of the Egyptian ministry of health [10]. The study protocol was approved by the medical ethics committee in our hospital. This research was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and informed consent was obtained from each patient. In unconscious patients, consent was obtained from legal guardians.

2.2. Methods and study outcomes

All patients were subjected to full history taking, full clinical examination, assessment of oxygen (O_2) requirements, and data of mechanical ventilation. Laboratory investigations included serum IL-6, complete blood picture (CBC) including lymphocytic and neutrophilic counts, erythrocyte sedimentation rate (ESR), CRP, Lactate dehydrogenase (LDH), ferritin, D-dimer, procalcitonin, serum albumin, blood urea, serum creatinine, liver enzymes, sodium, potassium, calcium, PT, PTT, INR. Chest x-ray, computed tomography (CT) chest were used to assess lung affection.

TPE was done through filtration technique using a plasma filter (Plasmart 600, Medica company, Italy) at a dose of (1–1.5) plasma volume/session. Fresh frozen plasma or albumin 5% was used to replace plasma. Each patient received two to five sessions according to their response. Clinical, laboratory and radiological parameters were assessed before and after TPE.

Primary outcome was to assess 28-day mortality. Secondary outcomes included changes in oxygenation parameters, clinical status and laboratory markers of CS condition.

2.3. Statistical analysis

Data were analyzed using IBM SPSS version 22. Data were presented as range, median, and interquartile range for quantitative variables and number and percentage for qualitative variables. Paired comparisons as regard quantitative variables were conducted using Wilcoxon-signed rank test at 5% level of significance.

3. Results

3.1. Baseline characteristics of patients

This research enrolled 10 patients with a mean age of 52.90 ± 10.48 years ranging from 37 to 68 years. Sixty percent of studied patients were males. The majority were having a chronic disease or obese. Seven patients (70%) were on mechanical ventilation (MV), two (20%) patients were on mask reservoir, one (10%) patient was on high flow nasal cannula.

3.2. Clinical course, laboratory parameters, and mortality before and after TPE

After TPE, oxygenation parameters (O_2 requirements and data of mechanical ventilation) and most of laboratory markers (IL-6, ferritin, LDH, and D dimer) improved significantly in all patients ($p < 0.05$). In addition, CRP and lymphocytic count improved after TPE but not significantly with p value of 0.093 and 0.074, respectively (Table 1). Regarding clinical outcome assessed by 28-day mortality, six patients (60%) died and four patients (40%) survived and discharged. All patients on mechanical ventilation (MV) had severe ARDS (100%). Patients who survived (4/10) (3 without MV and 1 on MV), had better hypoxic index (PaO_2/FiO2 ratio) (>100 vs <100), started TPE sooner after tocilizumab failure (2–3 vs 5–6 days), needed fewer TPE sessions (3 vs 4–5, $p = 0.03$) and less duration in ICU (6.5 vs 12.5 days) compared to those who did not benefit. From mechanically ventilated patients (7), only one (15%) was extubated 2 days after TPE. Regarding TPE safety, one patient suffered from bradycardia during one session near its end. Full data for each patient regarding demographic, laboratory parameters, oxygenation data, and clinical outcomes before and after TPE are shown in Table 2.

4. Discussion

COVID-19 pandemic has affected the whole world due to very rapid spread of the virus in communities causing many deaths. A lot of health sectors have

Table 1. Biochemical and clinical parameters before and after TPE for all patients.

Parameter	Baseline	After TPE	p value
IL-6 (pg/ml)	57–637	2.3–116	0.005*
Min-Max	269(105–397)	15.7(5.97–35.25)	
Median±IQR			
LDH (u/l)	245–923	220–723	0.005*
Min-Max	735(642–834)	440(310–605)	
Median±IQR			
D-Dimer (ng/ml)	349–2410	156–1382	0.007*
Min-Max	857(630–1267)	602(412–922)	
Median±IQR			
Serum ferritin (ng/ml)	833–1674	285–1314	0.005*
Min-Max	1258(927–1477)	421(336–761)	
Median±IQR			
Lymphocytic count ($\chi 10^9$/l)	0.3–1.3	0.7–1.7	0.074
Min-Max	0.65(0.47–1.05)	1.05(0.75–1.32)	
Median±IQR			
C.R.P (mg/l)	53–261	11–264	0.093
Min-Max	148(75–203)	31(20.2–128)	
Median±IQR			
PaO_2/FiO_2 ratio	57–144	86–292	0.005*
Min-Max	90(71–111)	162(118–265)	
Median±IQR			

Data were expressed in range and median (Min.-Max.).
*: Statistically significant at $p \leq 0.05$.
CRP: C-reactive protein, IL 6: interleukin 6, LDH: lactate dehydrogenase, PaO_2/FiO_2: Partial arterial pressure of oxygen to fractional inspired concentration of oxygen.

collapsed due to shortage of critical care beds and mechanical ventilators compared to the huge number of patients with severe disease. This health catastrophe has led the worldwide economy to go down. An increasing number of vaccines against COVID-19 infection got the approval to be used in many countries hoping to provide immunity and limit number of severe infections.

One of the main causes of death from COVID-19 infection is CS state with disproportionate rise in many cytokines like IL-6, IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α that correlated with the disease severity [1,11]. So, attacking this pathway was a target by scientists to prevent the deleterious effects of this immune dysregulation. The most widely used drugs were corticosteroids and tocilizumab with variable efficacy.

A considerable percentage of patients do not respond to these drugs opening the gate for cytokine removal strategies like TPE to be used. Some have used TPE from the start [12] and others tried it after failure of other options [13] with very promising results.

In our study, we started TPE only after failure of two doses of tocilizumab to improve disease condition. Oxygenation status (O_2 requirements and PaO_2/FiO_2 ratio) and laboratory markers improved in all patients (100%). This finding had been described in recently published data [14–16]. But the reflection of that clear improvement (clinically and serologically) on patient mortality was not clearly identified with 40% survived and 60% died at 28 day of illness.

Analyzing our data, we found that patients who lived (n = 4) 3 patients not on MV and one mechanically ventilated, had moderate ARDS and started TPE earlier than others. Non mechanically ventilated patients had obvious clear benefit on 28-day mortality (0 vs 85%) compared to patients on MV. In contrast to our mortality data on MV patients, Khamis et al. [17] in their study which included 31 patients with severe COVID-19 infection found that patients on TPE had a lower 14 days (0 vs 35%; p = 0.033) and 28 days (0 vs 35%; p = 0.033) post plasma exchange mortality compared to patients not on TPE. However, all-cause mortality was only marginally lower in the TPE group compared to the non-TPE group (9.1% vs 45%; p = 0.055). Similar results had been described by others [13,18].

The explanation for higher mortality rates in our patients on MV compared to others might be the delayed start of TPE and longer duration on MV before beginning TPE therapy in our cohort waiting the failure of tocilizumab use, so the chest condition became worse. What support this hypothesis is that 100% of our patients who were not on MV survived and discharged and the patient on MV who survived started TPE after 1 day of intubation.

Considering TPE safety, bradycardia occurred in one patient at the end of session and improved within one hour. But none had suffered from hypotension, cramps, nor bleeding events reflecting safety of this procedure.

The main cause of death in most patients was respiratory failure. Septic shock in one patient.

Table 2. Individual patient's data regarding demographic, laboratory parameters, oxygenation data, and clinical outcomes before and after TPE.

Patient no.	Age (ys)	Sex	Medical history	IL 6 (pg/ml)		Ferritin (ng/ml)		D dimer (ng/ml)		CRP (mg/l)		LDH (u/l)		Lymphocytic count ($\times 10^9$/l)		TPE sessions (No)	Respiratory status		(PaO_2/FiO_2) ratio		ICU stay (days)	28-day mortality
				Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		Pre	Post	Pre	Post		
1	54	M	HTN	340	116	1189	332	2410	1382	76	21	923	723	0.6	0.75	4	MV, PEEP 12	PEEP 8	88	170	13	Died
2	49	M	DM	250	2.3	1477	730	1230	902	200	45	563	307	0.7	1.2	3	Mask Reservoir 8 l/min	nasal cann 4 l/min	130	264	7	Survived
3	63	F	Asthmatic	115	7.3	1356	857	836	573	171	34	245	220	1.3	0.8	4	MV, PEEP 15	PEEP 10	73	135	14	Died
4	38	M	free	637	26	882	345	692	471	212	18	671	421	0.5	1.3	4	Mv, PEEP 14	PEEP 8	66	111	13	Died
5	51	F	HTN, obese	316	32	833	376	1378	838	53	124	783	603	1.2	0.9	5	MV, PEEP 10	PEEP 6	92	155	12	Died
6	48	F	Free	289	19.4	1479	662	349	156	75	11	854	434	0.9	1.2	3	Mask Reservoir 8 l/min	Nasal Cann 4 l/min	144	270	5	Survived
7	64	M	DM, HTN	78	5	942	285	943	632	125	24	669	311	0.4	1.4	4	MV, PEEP 8	Extubated	85	255	10	Survived
8	57	F	Obese ,IHD	569	6.3	1293	466	444	238	261	29	779	476	1	1.7	3	High flow Nasal cann	Nasal Cann 5 l/min	105	292	6	Survived
9	68	M	IHD	167	12	1224	338	878	983	179	141	692	612	0.3	0.7	4	MV, PEEP 18	PEEP 14	57	86	10	Died
10	37	M	Dyslipidemic	57	45	1674	1314	723	544	122	264	828	446	0.6	0.75	5	MV, PEEP 14	PEEP 10	95	121	11	Died

DM: diabetes mellitus, F: female, HTN: hypertension, ICU: intensive care unit, IHD: ischemic heart disease, M: male, MV: mechanical ventilation, nasal cann.: nasal cannula, PEEP: positive end-expiratory pressure, TPE: therapeutic plasma exchange.

The main limitation of our study is the small sample size (n = 10), but it revealed promising results on TPE use.

5. Conclusion

In patients with CS state who did not respond well to tocilizumab and steroids, TPE could be a good option. Larger randomized clinical trials are needed to support the evidence of TPE efficacy in resistant cytokine storm conditions complicating COVID-19 infection.

Disclosure statement

No potential conflict of interest was reported by the author (s).

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