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The effect of therapeutic plasma exchange and intravenous immunoglobulin therapy on biomarkers and 28-day mortality in patients with COVID-19 in intensive care unit

Korgün Ökmen, Asiye Demirel, Ilkay Ceylan

Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Turkey

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Corresponding author:
Asiye Demirel.
E-mail: dr.asiyedemirel@hotmail.com;
ORCID: 0000-0003-1694-2265

Abstract

Background: The aim of our study was to determine the effectiveness of the co-administration of therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIg) therapy in intensive care patients with COVID-19.

Material and methods: In the propensity-matched study 46 patients were evaluated. The groups were defined as patients who received TPE + IVIg and standard treatment, and patients who received only standard treatment. The primary outcome of the study was determined as a 28-day mortality rate. Secondary outcome measures; were biomarkers of inflammation at admission and treatment days.

Results: In the evaluation of 23 patients in 2 groups, no statistically significant difference was found between demographic data, vital and respiratory status, additional diseases and treatments applied (p>0.05) .There was no difference in 28-day mortality rates between the two groups (p:0.688). CRP, IL-6 and Ferritin Lymphocytes values in the TPE+IVIg group were lower when compared to the control group in the values measured after the treatment (p<0.05). All inflammatory markers applied in the Cox regression model were associated with survival and no association was found.

Conclusion: In the results of this study, in which we applied TPE and IVIg treatment in combination, it was determined that this treatment method did not provide an additional benefit to the standard treatment. More clear information can be obtained by testing treatment applications in different doses and regimens and by randomized controlled studies.

Key words: SARS-CoV 2, COVID-19, intravenous immunoglobulins, therapeutic plasma exchange, intensive care

Introduction

With the definition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]) as a pandemic infection by the World Health Organization (WHO), many countries have started studies for the diagnosis and treatment of this disease [1]. Coronaviruses (CoV) can cause infections ranging from the common cold to severe disorders such as the Middle East Respiratory Syndrome (MERS) and the Severe Acute Respiratory Syndrome (SARS-CoV) [2,3]. SARS-CoV-2 infection can be transmitted through droplets and mostly asymptomatic and/or self-limited, patients can become critically ill, as manifested by acute respiratory distress syndrome (ARDS), thromboemboli, hyperinflammation and multi-system organ failure (MSOF), which may require intensive care treatment [2-8]. This situation, which occurs due to COVID-19, is related to the cytokine release syndrome, is caused by the late and excessive reaction of the immune system. Since no effective therapy is available, clinicians can use different treatments for this challenging condition in the treatment process. In addition to standard care of treatments (SOC) (Hydroxychloroquine, favipiravir, azithromycin), immunomodulatory treatments,

steroids, intravenous immunoglobulin (IVIg) and extracorporeal treatments are some of them. These treatments, which try to prevent the occurrence of cytokine release syndrome, can be used both as a supportive treatment and to reduce the resulting burden. Among these treatments, therapeutic plasma exchange (TPE) [9] and IVIg can be used in the treatment of different diseases. Apart from removing the abnormal components (immune complexes, toxins, allo/autoantibodies, lipoprotein, monoclonal antibodies, etc.) that play a role in the pathogenesis of diseases, TPE has also been found to have an immunomodulatory effect [10]. IVIg is a liquid preparation containing IgG antibodies with antiviral, bacterial, or other pathogens. IVIg has been identified as a potential mechanism of action, increasing the level of IgG, neutralizing exogenous antigens, and immune regulation. IVIg and TPE have been used in the treatment of bacterial, viral infection, and sepsis in different viral diseases other than COVID-19 [11-13].

Although IVIg and TPE treatments have been used in the treatment of systemic hyperinflammatory response in COVID-19 patients due to this uncontrolled immune response against SARS-CoV-2, the effectiveness of these treatments has not been clearly demonstrated [14-17]. TPE and IVIg combination therapy has been used for immunosuppression [18].

This study hypothesized that TPE and IVIg combination therapy might be effective in preventing systemic hyperinflammatory responses. For this purpose, we investigated the effects on 28-day mortality and biochemical inflammatory markers of patients who received TPE and IVIg combined treatment beside SOC in addition to SOC.

Material and methods

After obtaining ethics committee approval (The decision number is 2011-KAEK-25 2021/07-08) for this trend-oriented retrospective cohort study, the files of patients hospitalized in the intensive care unit (ICU) with the diagnosis of COVID-19 between May 2020 and June 2021 were reviewed.

Severe COVID-19 patients between the ages of 18 and 70 was defined by SARS-CoV-2 positive real-time polymerase chain reaction (RT-PCR test) and requirement for intensive care, based on the presence of the following criteria: (a) respiratory rate >30/min, (b) signs of dyspnea and respiratory distress, (c) SpO2 < 90% and PaO2 < 70 mmHg, despite nasal oxygen support of >10 L/min, or >15 L/min reservoir oxygen mask support (d) PaO2/FiO2 < 300 (mild acute respiratory distress syndrome (ARDS), (e) lactate >2 mmol/L, (f) bilateral infiltrations, multi-lobular involvement or pleural fluid in lung, (g) hypotension (systolic blood pressure <90 mmHg or drop >40 mmHg, mean arterial pressure <65 mmHg), tachycardia >100/min, (h) signs of renal, hepatic, hematologic (thrombocytopenia) or cerebral (confusion) dysfunction (sepsis or septic shock), (i) immunosuppression, (j) troponin elevation and (k) arrhythmia. Exclusion criteria were defined as having a previous allergic reaction to plasma exchange or its ingredients and patients who died 24 hours after administration to ICU. The patients who underwent TPE and IVIg were matched using propensity score matching at a ratio of 1:1 [19]. Matching was performed to equate potential factors affecting patients' mortality for the 2 groups. Tendency scores were calculated using the logistic regression model in which treatment modality was used as a dependent variable. As independent variables, 5 risk factors that were considered to have a direct effect on mortality were determined. Risk factors (1) Age, (2) Gender, (3) Diabetes mellitus, (4) Hypertension, (5) APACHE II score [20]. Trend matching was done using the 1:1 nearest neighbour algorithm. Matches within the limit range of 0.2 standard deviations of the logit of the propensity score were included [21]. All analyzes were restricted to patients compatible with this trend set. After propensity score matching, 2 groups of 23 people were matched. The groups were defined as patients who received TPE+IVIg with SOC, and patients who received only SOC. Initial SOC was planned in accordance with the local pandemic treatment guideline [22], hydroxychloroquine (800 mg loading dose, LD, 400 mg/day maintenance for 5 days) and favipiravir (3200 mg loading dose, 1200 mg/day maintenance for 5 days) were started as first-line therapy. Anticoagulant treatment with Low Molecular Weight Heparine (LMWH) and antithrombotic treatment with acetyl salicylic acid were applied for their admission from the ICU. Considering biochemical markers of inflammation and vital signs, tocilizumab/anakinra, methylprednisolone (1 mg/kg/day), and antibiotherapy were administered as a result of the culture specimen of the patients' body fluids (tracheal aspirate, urine, blood) and the visit made with the infection specialists.

TPE+IVIg treatment were applied to patients who did not find clinical improvement in the treatment protocol described above.

TPE+IVIg therapy; was planned as 5 sessions. It was performed using Fresenius apheresis devices (Fresenius AG, Germany) by subtracting 1.5 times the predicted plasma volume every other day. Body surface area, hematocrit, and gender were used to calculate plasma volumes. During the 4-hour procedure, a 1:1 mixture of fresh frozen plasma (FFP)/human albumin 5% and normal saline was applied as reserve fluid. After the TPE procedure, 10 g of IVIg Octagam® (Octapharma Aglachen, Switzerland) was administered intravenously to each patient with a 6-hour infusion.

The primary outcome of the study was determined as the 28-day mortality rate. Secondary outcome measures were, APACHE II score, observing the changing the biomarkers of inflammation; C-reactive protein (CRP), ferritin, D-Dimer, interleukin (IL) 6 and lymphocyte count (LYM) at admission and on treatment days.

Statistical Method

Descriptive statistics (mean, frequency, percentage, median, min-max, standard deviation,) were used. The Shapiro-Wilk test was used to evaluate the distribution model. Wilcoxson test or Mann-Whitney U test was used for comparison between groups and in-group measurement times. A main effect logistic regression model was used to examine the effect of treatment on overall survival. The effect of biochemical values on survival times was evaluated using Cox regression models. The Kaplan-Meier test was used for survival analysis and log-rank was used to compare the difference between the two groups. A p-value less than 0.05 was determined as the level of significance.

Results

In this study, the data of 46 patients were subjected to statistical analysis. In the evaluation of 23 patients in two groups, no statistically significant difference was found between demographic data, vital and respiratory status, additional diseases and treatments applied ($p>0.05$) (Table 1). There was no difference in 28-day mortality rates between the two groups. Kaplan–Meier survival distributions in the TPE+IVIg and control groups patients (log-rank test, P=0.688; Cox regression model, Hazard Ratio=0.81 confidence interval (95% CI 0.335-2.029, P=0.62) (Figure 1). There was no significant difference

Table 1 Patient characteristics

	TPE+IVIg *n =23*	Control *n =23*	*p*
Sex (M/F)	8/15 (65/35)	10/13 (74/26)	0.621
Age (years)	45.3 ± 18.2	48.3 ± 12.2	0.657
BMI (kg/m^2)	25.8 ± 5.3	24.9 ± 4.1	0.633
Vital and respiratory status			
APACHE II score	24.3 ± 5.3	25 ± 7.9	0.681
Respiratory rate (/min)	36 ± 9	35 ± 7	0.678
PaO2/FiO2 ratio	121 (90–165)	128 (90–195)	0.137
High-flow nasal cannula	17	16	0.844
Mechanical ventilation	6	7	0.708
Systolic blood pressure (mmHg)	109.8 (116-84)	108.88 (104-84)	0,742
Diastolic blood pressure (mmHg)	68.72 (94-34)	67 (99-44)	0,436
Additional diseases			
Hypertension	11 (47.0%)	12 (52.1%)	0.893
Diabetes	8 (34.7%)	10 (43.4%)	0.729
Cardiac disease	5 (21.7%)	6 (26%)	0.722
Pulmonary disease	3 (13%)	1 (4.3%)	0.347
Treatments			
Favipiravir	23 (100%)	23 (100%)	N/A
Hydroxychloroquine	21 (91.3%)	20 (86.9%)	0.981
Azithromycin	3 (13%)	4 (17.3%)	0.943
Tocilizumab	10 (43.4%)	12 (52.1%)	0.637
Anakinra	8 (34.7%)	6 (26%)	0.577
LMWH	23 (100%)	23 (100%)	N/A
Corticosteroids	21 (91.3%)	22 (95.6%)	0.781
ICU day	16.5(7-28)	18.7(9-36)	0.559
Mortality on Day 28 [n (%)]	13 (56.5%)	14(60%)	0.767

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, Body mass index; FIO2, Fraction of inspired oxygen; ICU, Intensive care unit; PaO2, Arterial partial pressure of oxygen;
Values are means ± SD (n) or N (%), except ,median (interquartile range) due to non-normal distribution. p-values <0.05 in bold.

Table 2 Change in Biomarkers before and after treatment

	TPE+IVIg * *n =23*	Control* *n =23*	*p**
CRP mg/L			
Baseline	129 (35–302)	122 (31–189)	0.648
Post treatment	57 (19–100)	82 (14–216)	**0.044**
p	**0.000**	0.246	
IL-6 µg/L			
Baseline	104 (16–194)	108 (15–176)	0.723
Post-treatment	21 (1–76)	55 (7–477)	**0.001**
p	**0.000**	0.84	
Ferritin mg/L			
Baseline	1061 (336–2000)	1141 (31–1890)	0.677
Post-treatment	590 (285–889)	924 (285–2000)	**0.013**
p	**0.001**	0.078	
D-dimer mg/L			
Baseline	2.1 (0.46–8.8)	3.3 (0.92–8.9)	0.703
Post-treatment	1.94 (1.1–4.6)	3.2 (2.2–6)	0.530
p	0.940	0.573	
Lymphocytes 10^9/L			
Baseline	0.4 (0.18–0.63)	0.31 (0.17–0.45)	0.364
Post-treatment	0.41 (0.17–1.32) (n =22)	0.41 (0.16–0.63)	0.276
p	**0.002**	**0.033**	

Post-treatment: 8 days after initiation of treatment
*median (interquartile range)

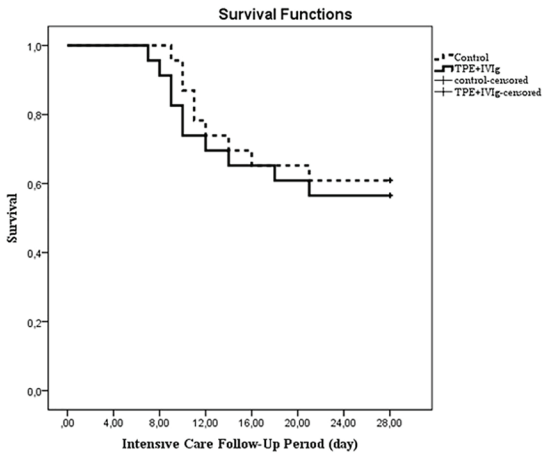

Figure 1 - Kaplan–Meier survival distributions in the TPE+IVIg and control groups patients

Table 3 Cox proportional hazards model for biochemical markers for 28-day mortality in patients (n=46)

	HR p	95% CI	p
IL-6 µg/L	1.003	0.993-1.012	0.580
Ferritin mg/L	0.999	0.998-1.008	0.237
CRP mg/L	1.002	0.997-1.008	0.383
D-dimer mg/L	0.982	0.995-1.009	0.175
Lymphocytes 10^9/L	0.890	0.156-8.488	0.890

CRP, C-reactive protein; PCT, Procalcitonin;IL-6, Interleukin 6; significant differences between groups in bold. HR:Hazard Ratio

between the initial values in the measurements of CRP, IL-6, D-Dimer, Lymphocytes and Ferritin, which are used to monitor the follow-up and treatment response ($p>0.05$) (Table 2). When the values before and after the treatment were evaluated, the CRP, IL-6, D-Dimer and Ferritin values of the patients in the TPE+IVIg group were found to be low after the treatment, while in the control group, only Lymphocytes values were lower than the initial values after the follow-up ($p<0.05$) (Table 2). When the values measured after treatment were compared, TPE+IVIg group had lower CRP, IL-6 and Ferritin values ($p<0.05$) (Table 2). CRP, IL-6 and Ferritin values in the TPE+IVIg group were lower when compared to the control group in the values measured after the treatment ($p<0.05$) (Table 2). All inflammatory markers applied in the Cox regression model were associated with survival and no association was found (Table 3).

Discussion

In the results of this study, no statistically significant difference was found in the 28-day mortality of the patients in the control group treated with SOC in combination with TPE + IVIg combined treatment with SOC. The mortality of the patients was associated with the cytokine storm and acute respiratory failure caused by COVID-19. Although IL6, Ferritin, and CRP values, which are biochemical markers showing inflammation, were lower in the follow-ups of patients treated with TPE+IVIg, they were not associated with mortality.

TPE was started to be used for the first time in the early 1900s and started to be used in the treatment of different diseases in 2013 under the name of therapeutic plasma exchange. Theoretically, it is aimed to reduce the immune load in the body by separating the plasma from the blood and applying replacement fluid instead. Its immunomodulatory effect has been demonstrated in different studies [10]. It has been determined that this immunomodulatory effect occurs in the form of stimulating proliferation of B cells and plasma cells, removal of immune complexes with macrophage/monocyte function, replacement of deficient plasma components such as ADAMTS13, removal of cytokines, changes in lymphocyte counts, and correction of the modified T helper cell type 1/2 (Th1/Th2) ratio that supports Th1 dominance [10]. The American Society for Apheresis (ASFA) periodically updates and publishes guidelines on which diseases TPE can be beneficial and can be used. For sepsis and macrophage activation syndrome, it has been reported that TPE can be used in certain patients whose Category 3 grade 3c efficacy cannot be determined in this guideline [10]. There are few studies at a similar level in the literature. In their retrospective, observational study and review results, Ketih et al. showed an improvement in 28-day survival with adjunctive TPE compared to standard care alone in adult patients with septic shock and multi-organ failure [13]. It has been reported that hemodynamics, organ dysfunction, and fluid balance can be corrected with additional TPE, and survival times can be increased [13].

A limited number of studies in the literature provide information about the effectiveness of TPE application in the treatment of COVID-19. While there are studies indicating that TPE is effective in treatment and survival, some studies found that it does not affect mortality. In the study in which the results of 11 patients who underwent TPE were shared, it was stated that mortality and extubation time decreased with the application of TPE compared to the patients used as the control group [23]. In addition, they found a decrease in SOFA scores, IL-6, CRP, D-dimer, and ferritin levels after TPE application [23]. Another study, sharing the results of 15 COVID-19 patients after TPE treatment additionally used convalescent plasma in 4 patients. In this study, in which TPE treatment was determined to be effective on mortality, they determined a decrease in inflammatory markers [20]. Patidar et al. shared an opinion that TPE can be used as a treatment option in the guideline for its use in infectious diseases and COVID-19. They stated that the weak side of the guideline is the absence of RCT [24].

On the other hand, in a randomized controlled study in the literature, Faqihi et al. evaluated 83 patients and reported that TPE added to standard treatment in life-threatening COVID-19 patients provided clinical improvement compared to standard treatment alone, but did not significantly affect 35-day mortality [15]. Low baseline PaO2/FiO2 ratio, ADAMTS-13 activity, higher SOFA score, increased D-dimer levels and IL-6 were determined as predictors of mortality [15]. While the number of TPE treatments applied in the examined studies varied between 4-5, it varied according to the availability of fluids used for replacement and the conditions of the country. The fact that it is a device-dependent treatment and the need for additional personnel can reduce usability in pandemic conditions. On the other hand, it can be said as an advantage that the IVIg treatment option can be applied more easily. Therefore, the literature data also includes more studies. Shao et al., from 2 different studies designed retrospectively from these studies, reported that 28-day mortality and inflammation could be reduced in patients treated with IVIg and SOC in their cohorts. In the subgroup analysis, they found a better response in patients who started early treatment (before 7 days) with a high dose of more than 15 g/day [17]. In other retrospective study results, the dose of IVIg was determined as 30 g/day at 5% concentration for 5 days. In this study, in which they found a significant decrease in survival times compared to the patient group that they applied standard treatment, they emphasized that the decrease

in CRP values was significant in the follow-up. On the other hand, they found that the decrease in IL-6 and the increase in D-dimer were not significant [17]. In the RCT found in the literature, it was stated that the use of 400 mg/kg IVIg for 3 days and hydroxychloroquine, lopinavir/ritonavir as an additional treatment did not have an effect on mortality and did not affect the radiological changes. In addition, it was emphasized that early IVIg treatment may shorten the length of hospitalization [26]. In their study, Bongomin et al. reached similar results and stated that it did not provide additional benefit in non-severe COVID-19 and that IVIg could help treatment in combination with other drugs such as corticosteroids or antibiotics [27].

When the literature information is examined, it does not seem possible to reach definitive data on the effectiveness of TPE and IVIg treatment options alone on the hyperinflammatory state caused by SARS-CoV-2. Considering the global pandemic, the fact that physicians are courageous about alternative treatments should be taken into consideration. Dosing times and procedures differ between the two treatment options, and the impact of this on study results is debatable. The differences in the medical treatment applied by countries during the pandemic limit the comparison of studies. TPE+IVIg combination treatment method used in our study did not provide more survival when compared to the control group patients. On the other hand, when compared to the studies in the literature, the late treatment initiation and the severe clinical condition of selected patient groups may have affected the results.

Limitations

Although the patients in the study were matched, the retrospective design is the main limitation of this study. In addition, due to small sample size of our study and the differences in the medical treatments applied for immune modulation during the treatment of both groups of patients stands out as another limitation.

Conclusion

In the results of this study, in which we applied TPE + IVIg treatment in combination, it was determined that this treatment method did not provide an additional benefit to the standard treatment. More clear information can be obtained by testing treatment applications in different doses and regimens and by randomized controlled studies.

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Ethical Statement: Written consent was obtained from each patient to use their hospital data. The Ethics Board of University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital received the study approval [The decision number is 2011-KAEK-25 2021/07-08].

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