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Research Article

Intravenous Immunglobulins Are Not Effective in the Treatment of COVID-19

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Abstract

Objectives: The COVID-19 disease caused a pandemic. Pneumonia and related hypoxia are known to be the most important causes of mortality. An effective treatment is needed until extensive utilization of the vaccines. We report the effect of intravenous immunoglobulins in COVID-19 patients.

Methods: As an observational case control study, demographic, clinical, laboratory, treatment, and outcome data of patients from Covid-19 ICU were obtained from records of the electronic medical archive of the hospital. Univariable and multivariable logistic regression methods were used to investigate the risk factors related to the length of hospital stay and in-hospital death.

Results: All patients were treated with both corticosteroid and favipravir. Patients who received IVIG had a lesser amount of lymphocytes before treatment start. Eleven of the patients were died and 15 were alive. In alive patients, a significant increase in lymphocyte and decrease in ferritin levels were observed after high dose IVIG therapy.

Conclusion: Increase in lymphocyte count and decrease in ferritin levels were observed in patients who survived after high dose IVIG therapy. COVID-19-related mortality toll is very high so an urgent effective treatment modality is still needed. However, IVIG therapy was not found to decrease mortality rate in severe COVID-19 patients.

Keywords: SARS-CoV-2 Infection, renal functions, prognosis, mortality rate, immunoglobulin

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SARS-COV2 pandemic has arised in 2019. The COVID 19 agent causes illness of primarily respiratory tract resulting in many deaths. Worldwide total COVID-19-related mortality toll is very high so an urgent effective treatment modality is still needed.

COVID-19 mainly affects the respiratory system by rapidly progressing to acute respiratory distress syndrome (ARDS) in some of the patients.[1] Pneumonia and related hypoxia are known to be the most important causes of mortality.[2] Besides mortality, hypoxia also leads to acute renal injury.[3] Hypoxia induced renal injury and ischemia-reperfusion usually causes irreversible renal fibrosis resulting in CKD.

Intravenous immunoglobulin (IVIG) is a blood product of the serum pooled from healthy donors. IgG is the major component of IVIG preparations is the serum.[4] IVIG targets soluble and cellular mediators of the inflammatory immune response. by complement scavenging, neutralisating the autoantibodies and inhibiting of activation of innate immune cells like dendritic cells, monocytes, macrophages and neutrophils.[5]

C-reactive protein (CRP) is a member of the pentraxin superfamily. It is an important component of immunity and inflammation.[6] CRP levels were found to increase in COVID-19 patients. and it has been shown that survivors had median CRP values of approximately 40 mg/L and non-sur-

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vivors had median values of 125mg/L. A strong correlation seems to be between CRP and prognosis.[7]

Ferritin is a shell protein that contains iron in its core. The shell is composed of heavy and light chain ferritin. Serum ferritin is an acute-phase reactant and its levels show the degree of acute and chronic inflammation during infections, rheumatologic and malignant diseases. The serum levels of ferritin are also correlated with poor outcome in COVID-19 patients. Elevated ferritin levels and cytokine storm syndrome were found in severe COVID-19 patients.[8]

Lymphopenia and increased levels of some cytokines are known to be closely associated with the disease severity.[7] We evaluated the effects of IVIG therapy on CRP and ferritin as acute phase reactants, and also on mortality and renal functions of severe COVID-19 patients.

Methods

This study was conducted in severe COVID 19 patients who were followed up in Edirne Sultan 1. Murat State Hospital. The participants were the patients whose COVID-19 PCR test results were positive and were hospitalized in our COVID-19 ICU. All the patients were treated according to the COVID-19 guidelines that were suggested by the Health Ministery of Turkey. All the patients received antiviral therapy (favipiravir). Oxygen therapy, antipyretic therapy, deep venous thrombosis prophylaxis, gastrointestinal ulcer propylaxis oral and/or intravenous hydration were used in every patient in need. Additional therapies include antibiotics and steroids as per guidelines of Turkey.

It was a retrospective observational research study.and the approval was received from the local ethics committee. The data of the patients were obtained from the record analysis of COVID-19 ICU inpatients of either sex without any age bar.

Demographical data of the patients including age and gender were noted. Comorbidities including hypertension, Diabetes Mellitus, coronary artery disease, active malignancy and any other immunsuppresive condition or disease data were recorded. The medication history of all patients were taken.

The medical records were noted at the beginning, just before and 48-72 hours after the application of intravenous immunoglobulins. These records included the medical data of the patients. Serum biochemical tests including serum urea, creatinine, sodium, potassium, chlorine, CRP, SGPT, SGOT, complete blood count which had been analyzed at our central laboratory were obtained. Trakya University Microbiology Laboratory was responsible for SARS-CoV-2 infection detection in respiratory specimens by real-time RT-PCR methods.

Data analysis was performed via SPSS version 22. Numeric variables were expressed as median (Inter-Quartile Range, IQR) and comparisons were made with the Mann-Whitney U test. We presented Categorical variables as number and percentage (%) and compared with the Chi-square test. The survival probability of the patients were calculated using the Kaplan-Meier method. The significance and the hazard ratio of the variables were estimated by fitting a Cox proportional hazards model. A significance level was considered statistically significant when $p<0.05$.

Results

A total of 26 severe COVID-19 patients who were treated with or without high dose IVIG in ICU were enrolled. Median follow up time was 28 days. Eleven of the patients were died and 15 were alive. Table 1 shows the baseline clinical characteristics of the study subjects. The median age was 60 years (53-69) and men were more affected than women (3:7). Hypertension was the most common morbidity and median length of the ICU stay was 18 (14-30) days. All patients were treated with both corticosteroid and favipiravir during inpatient service stay. Patients who received IVIG had a lesser amount of lymphocytes before treatment start.

In addition, baseline neutrophil, c-reactive protein and ferritin levels were comparable in both groups. In alive patients, a significant increase in lymphocyte and decrease in ferritin levels were observed after high dose IVIG therapy, whereas those values of died patients did not change significantly ($p>0.05$ for all). Table 2 shows that change in serum inflammatory marker levels between baseline.

Discussion

IVIG is a blood derivative that has been used for over 30 years. It contains polyclonal immunoglobulin G isolated and pooled from healthy individuals. It has been used in medicine as a safe and potent immune modulator. We investigated the effects IVIG in patients that were administered high-dose IVIG at 0.3–0.5 g per kg weight daily for five days in our COVID-19 ICU. We found no survival advantage of IVIG in the treatment of COVID-19 disease.

Administration of IVIG has a role on innate and adaptive immunity and it has been used in some immune mediated diseases due to its immunomodulating effects.[9] High dose IVIG is a choice of immunomodulatory therapy in some autoimmune and inflammatory diseases and sometimes for prophylaxis and treatment of infections, particularly in immunocompromised patients.[5, 10]

The novel coronavirus has a high infection rate and mortality. The major cause of morbidity and mortality is severe pneumonia in COVID-19. An effective single antiviral thera-

Table 1. Demographic and clinical characteristics of the study subjects

	All (n=26)	Non-IVIG (n=16)	IVIG (n=10)	p
Age, year				
Median (Interquartile range)	60 (53-69)	59 (53-69)	60 (46-69)	0.67
Gender, n (%)				
Female	8 (30.8)	4 (25)	4 (40)	0.42
Male	18 (69.2)	12 (75)	6 (60)	
Comorbidity, n (%)				
HT	12 (46.2)	6 (37.5)	6 (60)	0.26
DM	7 (26.9)	5 (31.3)	2 (20)	0.52
COPD	5 (19.2)	2 (12.5)	3 (30)	0.27
CAD	3 (11.5)	3 (18.8)	-	0.15
Length of hospital stay, day				
Median (Interquartile range)	28 (18-36)	25 (17-40)	30 (18-36)	0.91
Length of ICU stay, day				
Median (Interquartile range)	18 (14-30)	17 (12-25)	25 (14-32)	0.47
Prior treatment, n (%)				
Favipravir	26 (100)	26 (100)	26 (100)	0.99
Dexamethasone (6 mg/day)	26 (100)	26 (100)	26 (100)	
Baseline C-reactive protein				
Median (Interquartile range)	78 (41-135)	56 (39-105)	104 (65-186)	0.09
Baseline white blood cell count				
Median (Interquartile range)	7.1 (5.5-10.4)	7.7 (5.8-11.6)	6.3 (4.7-8.5)	0.26
Baseline neutrophil				
Median (Interquartile range)	5.8 (4.3-8.9)	5.9 (4.1-10.2)	5.8 (4.3-7.8)	0.91
Baseline lymphocyte				
Median (Interquartile range)	1.3 (0.8-3.6)	1.1 (0.6-1.2)	0.2 (0.1-0.4)	0.001
Baseline NLR				
Median (Interquartile range)	13.7 (4.5-18.3)	7.0 (3.4-16.4)	19.1 (14.0-31.0)	0.01
Baseline ferritin				
Median (Interquartile range)	1395 (775-2000)	1223 (745-1841)	1741 (775-2000)	0.52

peutic agent lacks. In addition, vaccination of large populations looks like it will take a long time. So IVIG has been used on the assumption of being a safe and effective agent.

IVIG may limit the hyperactive immune response defined as cytokine storm syndrome in the properly selected patients. These are the ones who had lymphopenia and inflammatory cytokine storm.[11,12] However the effect of IVIG in COVID-19 patients was suggested to be succesful when administered on time.[13]

In a randomized placebo-controlled double-blind clinical trial, the use of intravenous immunoglobulin gamma for the treatment of severe COVID-19 patients was found to decrease the mortality rate.[14] Shao et al. also found that utilization of IVIg in COVID-19 patients decreased 60-day mortality rates in their multicenter retrospective cohort study. They also detected both higher IVIg dosage and earlier administration could improve the results.[15]

Severe COVID-19 patients have hyperinflammation so associated biomarkers may be beneficial to see the effects of drugs. IVIG is known to reduce inflammatory mediators. CRP and ferritin levels have been used as general markers of inflammation despite not being specific for COVID-19 disease. Several studies have reported that CRP and ferritin declines after IVIG therapy.[16]

Lymphocytopenia is a frequent feature of COVID-19 patients. Additionally, a continuing decrease in the absolute lymphocyte count (ALC) is accepted as a risk factor for mortality. COVID-19 patients with lower lymphocyte counts had poorer outcomes so a clear correlation between lymphopenia and COVID-19 severity is known to be present.[17] In addition, patients with lymphocytopenia were found to be more likely to develop an AKI as an important organ failure.[18] We found no correlation between lymphocytopenia and AKI development.

We have investigated pre and post-IVIG levels of CRP, ferritin and lymphocyte count as possible biomarkers of IVIG

Table 2. Association between study subjects and mortality of the patients with severe COVID-19

	Mortality			Unadjusted OR (95% CI)	p
	No	Yes	p		
Age, Median (IQR)	57 (45-61)	62 (57-70)	0.10	1.05 (0.98-1.14)	0.14
Gender, n (%)					
Female	6 (40)	2 (18.2)	0.39	Ref	0.24
Male	9 (60)	9 (81.8)		3.00 (0.47-19.03)	
HT, n (%)	7 (46.7)	5 (45.5)	0.63	0.95 (0.20-4.53)	0.95
DM, n (%)	5 (33.3)	2 (18.2)	0.65	0.44 (0.06-2.88)	0.39
COPD, n (%)	2 (13.3)	3 (27.3)	0.62	2.43 (0.33-17.90)	0.38
CAD, n (%)	2 (13.3)	1 (9.1)	0.61	0.65 (0.05-8.22)	0.73
Neutrophil, Median (IQR)					
Baseline	5.1 (4.4-7.8)	7.1 (3.8-9.6)	0.79	1.00 (1.00-1.00)	0.70
After IVIG	8.9 (6.6-12.1)	9.7 (7.5-18.3)	0.33		
p	0.09	0.05			
Lymphocyte, Median (IQR)					
Baseline	0.6 (0.2-0.9)	0.6 (0.3-1.1)	0.68	1.44 (0.30-6.81)	0.64
After IVIG	1.2 (0.8-1.5)	0.7 (0.4-0.8)	0.03		
p	0.01	0.82			
NLR Median (IQR)					
Baseline	13.5 (4.4-20.8)	14.9 (7.0-16.6)	0.89	1.00 (1.00-1.00)	0.68
After IVIG	7.1 (4.0-17.3)	15.0 (10.2-23.8)	0.10		
p	0.14	0.47			
Ferritin Median (IQR)					
Baseline	1648 (952-2000)	1341 (745-1841)	0.54	1.00 (0.99-1.00)	0.46
After IVIG	894 (557-1271)	1020 (904-1688)	0.34		
p	0.01	0.64			
CRP Median (IQR)					
Baseline	88 (47-131)	69 (39-125)	0.77	0.99 (0.98-1.00)	0.67
After IVIG	54 (17-130)	158 (44-214)	0.11		
p	0.17	0.18			
Treatment group, n (%)					
IVIG	7 (46.7)	3 (27.3)	0.42	0.42 (0.08-2.27)	0.32
Non-IVIG	8 (53.3)	8 (72.7)			

response in order to understand the relationship between inflammatory markers and COVID-19 prognosis. We found no relationship between CRP and IVIG therapy. We found a significant increase in lymphocyte and decrease in ferritin levels in alive patients with the use of high dose IVIG therapy in the treatment of COVID-19 disease. Lymphocyte and decrease in ferritin values of died patients did not change significantly. Despite those promising results on laboratory values, IVIG therapy was not found to increase arterial oxygen saturation and decrease mortality rate of severe COVID-19 disease.

The limitations of this study include the small numbers of patients enrolled and it was focused on one community hospital. More randomised controlled studies are needed to confirm the results. In addition, we could not collect all data of some patients. For example; there were some missing data in APACHE scores so we did not include those parameters into the statistical analysis.

In conclusion, IVIG therapy does not decrease the mortality rate of SARS-CoV-2 but observing the changes in the lympohocyte count and ferritin values after IVIG therapy seems to be useful to predict the prognosis of severe COVID-19 patients.

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