Research Article

Efficacy of intravenous immunoglobulin therapy in hospitalised patients with COVID-19: A randomized controlled trial

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ABSTRACT

Objectives: Acute respiratory distress syndrome (ARDS) is one of the life-threatening complications of COVID-19. The occurrence of ARDS is due to overactivation of the host immune response to the virus. The purpose of this study is to investigate whether administration of intravenous immunoglobulins (IVIG) could enhance the outcomes of severely ill COVID-19 patients with ARDS.

Methods: In this randomized controlled trial at Milad Hospital of Isfahan, Iran, 88 patients were randomly assigned between May and October 2020. The patients had no significant differences in age and sex. The patients were divided into two groups: the group who received IVIG and routine treatment (n=44, 50%) and the control group who were just treated with routine treatment (n=44, 50%). The outcomes of patients, including hospitalization duration, ICU admission period, and total death occurrence, besides clinical and laboratory parameters, were followed and compared between the two groups.

Results: Primary outcomes of patients, including hospitalization duration (P=0.18), ICU admission period (P=0.35), and mortality (P=0.621), had no significant difference between the IVIG group and the control group. At day 3 and day 5 of IVIG administration, clinical and laboratory outcomes were screened. The clinical parameter that improved was oxygen saturation compared to the control group (87.56 ± 6.72 vs. 86.72 ± 7.52). In the cardiovascular system, IVIG significantly decreased diastolic blood pressure (P=0.02). In terms of coagulation parameters, IVIG treatment decreased PTT while it increased D-dimer, but no effect on platelet count and PT was seen. The inflammatory parameters, including ESR, CRP, and IL6, had no superior changes between the IVIG group and the control group.

Conclusion: Our study demonstrated that there were no superior advantages in COVID-19 patients with ARDS who were treated with IVIG..

Keywords: IVIG, COVID-19, coronavirus, ARDS

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Introduction

Coronavirus disease 2019 (COVID-19) has been declared a worldwide pandemic with more than 600 million confirmed cases and more than 6 million deaths reported by the World Health Organization (WHO) by November 2022 (1). Respiratory failure caused by acute respiratory distress syndrome (ARDS) is one of the most common complications of severe COVID-19 infection, which is the main cause of death in these patients (2). ARDS associated with COVID-19 results not only from viral infection but also from severe host inflammatory responses (3). Studies have shown that in patients with severe COVID-19 infection, serum levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin-2 (IL-2), IL-6, IL-7, monocyte chemoattractant protein-1 (MCP-1/CCL2), and interferon (IFN)-γ increase (4-6). Therefore, effective treatment that modulates the inflammatory response can improve mortality. Dexamethasone was the first anti-inflammatory drug to reduce the risk of death in hospitalized patients with COVID-19 receiving invasive mechanical ventilation by about 12.1% (7). Baricitinib is a Janus Kinase (JNK) inhibitor that has been associated with increased recovery rates and reduced risk of mortality in COVID-19 patients (8). In addition, tocilizumab, an IL-6 receptor antagonist, has been reported to have beneficial effects on factors associated with COVID-19, such as C-reactive protein, ferritin, d-dimer, and lymphocyte levels (9). However, despite these advances, the mortality associated with ARDS related to COVID-19 remains significant, suggesting the evaluation of other immunomodulatory approaches (10).

Intravenous immunoglobulin (IVIG) is a blood product containing polyclonal gamma immunoglobulin, which is prepared from the collected serum of 1,000 to 15,000 healthy donors. IVIG plays an immunomodulatory function by neutralizing autoantibodies, inhibiting the complement cascade, disrupting the dendritic function of cells, preventing the proliferation of T helper cells, and expanding the population of regulatory T cells (11). Since its discovery, this drug has had beneficial effects in the treatment of a wide range of inflammatory and autoimmune diseases such as dermatomyositis, Guillain-Barré syndrome, thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, and vasculitis (12, 13). Due to its anti-inflammatory function, IVIG may moderate the inflammatory response caused by severe COVID-19 pneumonia and improve the disease. In a randomized, double-blind study of 59 patients with severe, refractory COVID-19 infection, it was shown that administration of IVIG compared with placebo could improve disease-related complications and reduce mortality (14). A meta-analysis published in April 2021 by Xiang H. et al. demonstrated the role of IVIG in reducing mortality in hospitalized critically ill patients with COVID-19 (15). In contrast, a more recent meta-analysis published in January 2022 by Focosi D. et al. concluded that the use of IVIG was not associated with a significant reduction in the risk of death, but showed that IVIG significantly reduced the length of hospitalization in moderate COVID-19 patients (16). Therefore, according to the previous studies on the use of IVIG as an adjunct for the treatment of severe pneumonia of COVID-19 and presenting some contradictory results, more research is needed to evaluate IVIG for the management of severe cases of coronavirus (16-19). On the other hand, although most studies have shown the usefulness of IVIG in the treatment of patients with COVID-19, the exact mechanism of the effect of this treatment is not known. Therefore, the aim of this study was to investigate the effectiveness of IVIG therapy in COVID-19 patients with pneumonia and also to determine the effect of IVIG on various clinical and laboratory parameters such as hematological, hepatic, renal, and inflammatory factors.

Materials and Methods

This randomized controlled trial (n=88) was carried out by Isfahan University of Medical Sciences at the Milad Hospital of Isfahan, Iran, from May to October 2020 on patients hospitalized with COVID-19-associated acute respiratory distress syndrome (ARDS). This clinical trial was conducted according to the principles of the Helsinki protocol. Informed consent was obtained from patients or their legal representatives. The research protocol was approved by the Medical Ethics Committee of Isfahan University of Medical Sciences (IR.ARI.MUI.REC.1400.058) and was registered with the registration number IRCT20220213054013N1 in the Iranian Registry of Clinical Trials.

Study sample

Patients older than 18 years were eligible for admission in this study if they had acute respiratory syndrome and a definite diagnosis of COVID-19. The criteria for a definitive diagnosis included reverse transcription-polymerase chain reaction (RT-PCR) and computed tomography (CT) scan findings (involvement of more than 30% of both lungs). Exclusion criteria included age less than 18 years, viral pneumonia with viruses other than COVID-19, pregnancy and breastfeeding, coagulation disorders, history of sensitivity to IVIG, severe heart failure (left ventricular ejection fraction less than 35%), and lung diseases such as pulmonary fibrosis, sarcoidosis, and history of lung surgery.

In total, 88 eligible patients were randomly assigned to receive IVIG + routine treatments (test group) or routine treatment alone (control group).

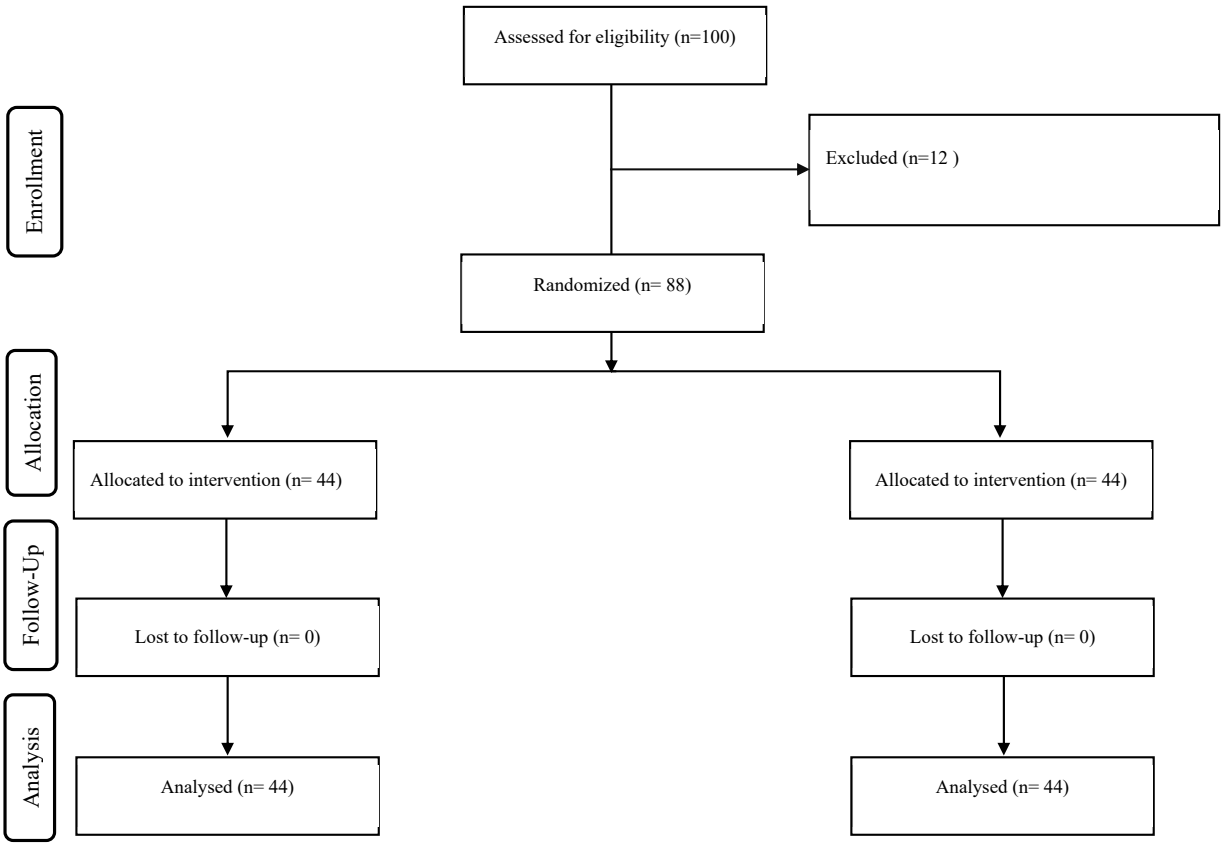

Figure 1: Summary of patient flow diagram

Outcome

The primary outcome was the number of days from the start of treatment to hospital discharge. Secondary outcomes included time to improvement in clinical parameters such as the number of days to normalization of body temperature (<37°C), oxygen saturation (>94% on room air), radiological improvement on CT lung scan, as well as the concentration of inflammatory factors (ESR, CRP, and IL6), coagulation factors (PT and PTT), d-dimer, troponin, and lymphocyte count on day zero (pre-treatment) and days 2 and 4 after treatment. Five milliliters of blood were collected for biomarker measurements at the baseline of the intervention. Available commercial kits were used to determine the following tests: serum creatinine, BUN, LDH, AST, ALT, ALP, and CRP concentrations (Pars Azmun, Tehran, Iran). Serum IL-6 levels were quantified using an available ELISA kit (Monobind, Lake Forest, California).

Statistical analysis

The Kolmogorov-Smirnov test was used to determine if the data were normally distributed. To detect the differences in study variables between the two groups, we used the independent-samples t-test. Chi-square tests were used for quantitative and categorical variables. The results were analyzed using SPSS v.26.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 88 patients were included in the study and randomized into two groups: the IVIG group (n=44) and the control group (n=44). There were no significant differences in age (58.07 ± 12.14 vs. 59.11 ± 11.56) or sex (31.8% females vs. 47.7% females) between the two groups (Table 1). Primary outcomes in each treatment group, including hospitalization duration, ICU admission period, and total death occurrence, demonstrated that IVIG treatment did not show significant superiority over standard treatment, with P-values of 0.18, 0.35, and 0.621, respectively (Table 2). Six deaths occurred in each group, indicating no significant difference in mortality rates between the two groups.

The patients in each group were screened for various clinical (Table 3) and laboratory parameters (Table 4) at baseline, after 3 days, and after 5 days of receiving IVIG or standard-of-care treatment. The most noticeable beneficial effect seen in the IVIG group was the improvement in the oxygen saturation of patients. Despite significantly lower baseline oxygen saturation in the patients of the IVIG group (66.89 ± 14.22 vs.

Table 1: Information on age and gender of treatment and control groups

Variables	IVIG group (n = 44)	Control group (n = 44)	P-value
Age (mean ± SD)	58.07 ± 12.14	59.11 ± 11.56	0.340
Gender (female)	14 (31.8%)	21 (47.7%)	0.095

Table 2: Primary outcomes of treatment and control groups

Variables	IVIG group (n = 44)	Control group (n = 44)	P-value
Days of hospitalization (mean (min-max))	12.95 (5 – 30)	11.75 (4 – 26)	0.181
Days of ICU admission (mean (min-max))	3. 32 (0 – 15)	2.93 (0 – 21)	0.35
Number of deaths	6 (13.6%)	6 (13.6%)	0.621

Table 3: Comparison of the clinical parameters between treatment and control groups

Variable	Control group (Mean ± SD)	IVIG group (Mean ± SD)	p-value
Systolic Blood pressure (mmHg)			
SPB at baseline	120.91 ± 16.75	125.36 ± 14.41	0.16
SBP on day 3	110.98 ± 21.15	120.55 ± 14.13	0.01
SBP on day 5	116.28 ± 10.72	120.91 ± 16.40	0.10
SBP change (Between baseline and day 5)	-4.63 ± 17.93	-4.45 ± 20.75	0.98
Diastolic blood pressure (DBP) (mmHg)			
DBP at baseline	72.48 ± 9.50	79.64 ± 7.87	0.00
DBP on day 3	71.32 ± 10.22	73.27 ± 9.73	0.36
DBP on day 5	75.00 ± 8.67	72.73 ± 9.81	0.33
DBP change (Between baseline and day 5)	2.23 ± 13.82	-6.91 ± 12.67	0.02
Heart rate (HR)(beats/minute)			
HR at baseline	74.65 ± 26.34	80.73 ± 10.25	0.21
HR on day 3	68.60 ± 23.77	79.82 ± 10.25	0.00
HR on day 5	68.02 ± 23.97	82.68 ± 10.59	0.00
HR change (Between baseline and day 5)	-7.00 ± 12.26	1.95 ± 12.62	0.00
Respiration rate (RR)(breaths/minute)			
RR at baseline	22.14 ± 8.9	19.59 ± 2.39	0.07
RR on day 3	22.23 ± 9.2	19.77 ± 1.82	0.08
RR on day 5	22.56 ± 9.14	19.45 ± 1.77	0.03
RR change (Between baseline and day 5)	0.48 ± 3.62	-0.14 ± 2.57	0.36
Temperature (T)(^{0}C)			
T at baseline	36.88 ± 0.60	36.69 ± 0.56	0.12
T in day 3	36.79 ± 0.53	36.62 ± 0.38	0.98
T in day 5	37.36 ± 7.24	36.70 ± 0.53	0.54
T change (Between baseline and day 5)	0.49 ± 7.24	0.00 ± 0.60	0.66
O2 saturation (SatO2)(%)			
SatO2 at baseline	87.64 ± 4.84	66.89 ± 14.22	0.00
SatO2 on day 3	86.43 ± 6.81	82.26 ± 10.05	0.02
SatO2 on day 5	86.72 ± 7.52	87.56 ± 6.72	0.59
SatO2 change (Between baseline and day 5)	-0.74 ± 7.54	21.00 ± 12.46	0.00

Table 4: Comparison of the lab tests between treatment and control groups

Variable	Control group (Mean ± SD)	IVIG group (Mean ± SD)	p-value
Blood pH (mmHg)			
pH at baseline	7.37 ± 0.07	7.41 ± 0.04	0.00
pH on day 3	7.36 ± 0.04	7.37 ± 0.06	0.13
pH on day 5	7.38 ± 0.05	7.39 ± 0.03	0.31
pH change (Between baseline and day 5)	0.00 ± 0.07	-0.02 ± 0.05	0.41
Blood HCO3(mEq/l)			
HCO3 at baseline	23.73 ± 5.22	26.66 ± 5.32	0.01
HCO3 on day 3	25.88 ± 6.67	25.54 ± 7.96	0.82
HCO3 on day 5	26.49 ± 7.29	26.47 ± 6.18	0.99
HCO3 change (Between baseline and day 5)	2.55 ± 5.75	0.45 ± 7.26	0.16
Pressure of O2 (PO2)(mmHg)			
PO2 at baseline	47.27 ± 20.90	43.44 ± 14.85	0.33
PO2 on day 3	48.39 ± 19.95	52.03 ± 18.00	0.37
PO2 on day 5	51.59 ± 18.85	59.35 ± 20.61	0.08
PO2 change (Between baseline and day 5)	3.23 ± 22.55	15.25 ± 25.23	0.03
Serum urea (Ur)(mg/dl)			
Ur at baseline	45.77 ± 34.56	45.27 ± 19.42	0.93
Ur in day 3	55.63 ± 31.42	55.73 ± 23.55	0.98
Ur in day 5	55.86 ± 30.07	58.27 ± 21.74	0.66
Ur change (Between baseline and day 5)	9.53 ± 27.32	13.00 ± 19.31	0.49
Serum creatinine (Cr) (mg/dl)			
Cr at baseline	1.99 ± 3.09	1.03 ± 0.28	0.04
Cr in day 3	1.44 ± 1.16	1.02 ± 0.25	0.02
Cr in day 5	1.30 ± 0.88	0.95 ± 0.20	0.01
Cr change (Between baseline and day 5)	-0.71 ± 2.86	-0.07 ± 0.18	0.15
Serum sodium (Na)(mEq/l)			
Na at baseline	137.43 ± 4.16	137.41 ± 3.43	0.97
Na in day 3	138.81 ± 3.97	138.82 ± 3.04	0.99
Na in day 5	138.58 ± 3.98	138.64 ± 3.40	0.94
Na change (Between baseline and day 5)	1.30 ± 5.52	1.23 ± 4.41	0.94
Serum potassium (K) (mEq/l)			
K at baseline	4.48 ± 0.54	4.05 ± 0.41	0.00
K on day 3	4.63 ± 0.51	3.78 ± 0.49	0.00
K on day 5	4.46 ± 0.81	3.76 ± 0.58	0.00
K change (Between baseline and day 5)	-0.02 ± 0.87	-0.28 ± 0.68	0.12
Serum LDH(IU/L)			
LDH at baseline	616.42 ± 201.35	852.45 ± 294.05	0.00
LDH on day 3	638.43 ± 227.71	864.91 ± 342.84	0.00
LDH on day 5	595.53 ± 247.62	854.68 ± 447.29	0.00
LDH change (Between baseline and day 5)	-26.40 ± 224.84	-2.23 ± 455.67	0.71
Serum ALT(IU/L)			
ALT at baseline	45.43 ± 22.43	66.77 ± 31.80	0.00
ALT on day 3	39.45 ± 19.18	51.55 ± 17.10	0.00
ALT on day 5	37.65 ± 19.72	52.41 ± 19.28	0.00
ALT change (Between baseline and day 5)	-8.09 ± 21.59	-14.36 ± 34.89	0.31
Serum AST(IU/L)			
AST at baseline	46.77 ± 25.72	72.41 ± 37.03	0.00
AST on day 3	48.89 ± 29.68	72.05 ± 29.17	0.00
AST on day 5	62.00 ± 35.99	76.82 ± 28.87	0.03
AST change	14.95 ± 38.01	4.41 ± 34.09	0.17

Continued Table 4: Comparison of the lab tests between treatment and control groups

Variable	Control group (Mean ± SD)	IVIG group (Mean ± SD)	p-value
(Between baseline and day 5)			
Serum ALP(IU/L)			
ALP at baseline	163.34 ± 63.54	190.23 ± 75.33	0.07
ALP on day 3	154.24 ± 54.99	182.82 ± 59.43	0.02
ALP on day 5	165.53 ± 105.22	183.38 ± 69.06	0.35
ALP change	1.77 ± 102.28	-7.48 ± 59.15	0.61
(Between baseline and day 5)			
Serum troponin (Trop)(ng/L)			
Trop at baseline	8.80 ± 4.49	37.95 ± 127.90	0.13
Trop on day 3	14.27 ± 24.26	11.79 ± 24.99	0.65
Trop on day 5	7.12 ± 5.24	5.84 ± 6.67	0.33
Trop change	-1.56 ± 6.54	-32.11 ± 122.53	0.11
(Between baseline and day 5)			
Serum CRP(mg/dl)			
CRP at baseline	67.63 ± 37.25	58.23 ± 20.52	0.14
CRP in day 3	55.77 ± 39.51	39.80 ± 25.77	0.02
CRP in day 5	28.09 ± 37.28	26.11 ± 23.41	0.76
CRP change	-39.97 ± 46.10	-32.11 ± 25.27	0.32
(Between baseline and day 5)			
Serum IL6(pg/mL)			
IL6 at baseline	26.39 ± 34.17	37.30 ± 26.83	0.10
IL6 on day 3	18.53 ± 30.12	39.80 ± 25.77	0.02
IL6 on day 5	9.92 ± 10.85	37.73 ± 43.89	0.00
IL6 change	-16.41 ± 28.59	1.84 ± 46.83	0.37
(Between baseline and day 5)			
Serum ESR(mm/hr)			
ESR at baseline	41.09 ± 25.10	47.45 ± 19.56	0.18
ESR on day 3	45.20 ± 24.09	48.09 ± 23.02	0.56
ESR on day 5	37.84 ± 23.99	35.64 ± 17.97	0.66
ESR change	-3.55 ± 20.58	-11.82 ± 16.57	0.43
(Between baseline and day 5)			
Platelet count (PLT)(10^3/µl)			
PLT at baseline	162.61 ± 53.22	211.55 ± 55.42	0.00
PLT on day 3	190.30 ± 66.33	266.14 ± 73.04	0.00
PLT on day 5	226.42 ± 75.65	271.86 ± 80.57	0.00
PLT change	65.40 ± 61.91	60.32 ± 65.87	0.71
(Between baseline and day 5)			
Prothrombin Time (PT)(Sec)			
PT at baseline	13.06 ± 1.96	15.35 ± 7.38	0.05
PT on day 3	14.07 ± 10.41	15.36 ± 10.81	0.57
PT on day 5	12.49 ± 1.29	15.25 ± 11.06	0.10
PT change	-0.60 ± 2.26	-0.10 ± 4.01	0.48
(Between baseline and day 5)			
Partial Thromboplastin Time (PTT)(Sec)			
PTT at baseline	29.09 ± 4.06	34.22 ± 5.63	0.00
PTT in day 3	29.10 ± 2.07	31.36 ± 3.92	0.00
PTT in day 5	29.71 ± 5.40	31.54 ± 4.51	0.08
PTT change	0.59 ± 7.00	-2.68 ± 4.25	0.01
(Between baseline and day 5)			
Serum D-dimer (µg/L)			
D-dimer at baseline	1298.02 ± 801.04	909.18 ± 1513.02	0.13
D-dimer on day 3	1202.92 ± 460.41	1534.27 ± 1364.90	0.16
D-dimer on day 5	1210.31 ± 701.44	1552.29 ± 1190.85	0.11
D-dimer change	-90.68 ± 1084.38	642.67 ± 1227.69	0.00
(Between baseline and day 5)			
WBC count(in 1µL)			
WBC at baseline	7681.82 ± 4383.91	9135.00 ± 4370.85	0.12
WBC on day 3	8943.18 ± 3516.56	10238.18 ± 4704.13	0.14
WBC on day 5	9897.67 ± 3545.11	10611.82 ± 3204.35	0.32
WBC change	2490.70 ± 4820.63	1476.82 ± 4514.57	0.31
(Between baseline and day 5)			

Continued Table 4: Comparison of the lab tests between treatment and control groups

Variable	Control group (Mean ± SD)	IVIG group (Mean ± SD)	p-value
Lymphocyte count (Lymph) (in 1µL)			
Lymph at baseline	1261.77 ± 1731.31	792.00 ± 461.12	0.08
Lymph on day 3	1150.00 ± 833.48	563.05 ± 287.96	0.00
Lymph on day 5	1068.37 ± 641.72	546.64 ± 417.99	0.00
Lymph change (Between baseline and day 5)	-190.19 ± 1857.13	-245.36 ± 338.20	0.84

87.64 ± 4.84), after 5 days of treatment, they had higher oxygen saturation than the patients in the control group (87.56 ± 6.72 vs. 86.72 ± 7.52). These results were further corroborated by the analysis of the pressure of oxygen in patients' serum. However, the results were not reflected in the respiratory rate of patients as it remained relatively unchanged in both groups (P=0.36).

In terms of cardiovascular function, the IVIG and standard treatment both reduced systolic blood pressure in an identical manner (P=0.98). Nonetheless, compared to the standard of care, IVIG significantly decreased diastolic blood pressure (P=0.02) and increased the patient's heart rate (P=0.00). IVIG treatment also affected some coagulation parameters. Despite having no influence on platelet count and PT, IVIG treatment decreased PTT while it increased D-dimer.

Except for the aforementioned parameters, IVIG treatment does not appear to significantly affect other clinical or laboratory parameters differently compared to the standard of care. IVIG treatment did not have significantly beneficial effects regarding the inflammatory parameters, such as ESR, CRP, and IL6. Furthermore, laboratory data indicated no difference between pH, HCO3, urea, Cr, Na, K, ALK-p, AST, ALT, LDH, WBC, lymphocyte count, and troponin of patients from the IVIG and control groups.

Discussion

IVIG therapy is a treatment option for people with autoimmune and immune-mediated conditions. This therapy involves the direct infusion of immunoglobulin derived from healthy donors into the patient's bloodstream to provide the essential antibodies against infection (20). The COVID-19 pandemic has sparked increased interest in using IVIG therapy as a possible treatment option for patients with COVID-19, because of its capability to offer passive immunity and regulate the immune response (21). Several studies recently assessed the effect of IVIG therapy on the outcome, clinical, and laboratory relevance of COVID-19 patients (22, 23).

R. S. Raman et al. conducted a multicenter randomized controlled study on 50 COVID-19 patients who underwent IVIG administration compared to 50 COVID-19 patients with standard treatment. The traits of the patients in both groups were relatively equal. The results demonstrated that hospitalization duration was significantly reduced in the IVIG treatment group (7.7 days) compared to the control group (17.5 days). Also, during the period of 28 days, there was a significant decrease in hospitalization and length of stay in the intensive coronary care unit and duration of mechanical ventilation usage (24). Additionally, in comparison to the standard of care, the normalization period for oxygen saturation and mechanical ventilation was notably shorter with IVIG.

However, in another study that included individuals over 65 years old, those who had been given corticosteroids, and those who were obese (with a body-mass index ≥30 kg/m²), IVIG did not have any impact on the length of time they needed invasive mechanical ventilation or their mortality rate (23). Consistent with the latter study, our experience on 88 patients who were given IVIG vs. standard treatment showed no significant difference between the duration of hospitalization, ICU admission, and mortality. However, after 5 days of follow-up, the patients in the test group demonstrated an increase in their oxygen saturation levels.

The use of corticosteroid therapy in myocarditis associated with COVID-19 showed no significant difference in mortality and may delay virus clearance and increase the risk of secondary infections. IVIG therapy, on the other hand, has been shown to be effective in reducing mortality and improving left ventricular ejection fraction in patients with acute myocarditis, including those with COVID-19. The authors suggest that IVIG's benefits in myocarditis may be due to its ability to decrease cardiac inflammation and downregulate pro-inflammatory cytokines (25). In our study, IVIG therapy reduced diastolic blood pressure with no effect on systolic pressure and also increased the patient's heart rate. Additionally, systemic inflammation induced by COVID-19 increased the possibility of cardiac injury and was associated with a rise in the levels of CRP, leukocyte counts, interleukin, LDH, creatine kinase, and troponin (26, 27). The outcomes of our study demonstrated no meaningful effect of IVIG therapy on inflammatory cardiac-related markers. However, the role of IVIG treatment on other cardiovascular inflammatory markers such as procalcitonin, creatine kinase, globulin, myoglobin, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) has not been assessed

in our study, and further investigation might be needed to assess whether IVIG treatment is beneficial for COVID-19 patients with cardiac complications.

There is limited information available on the effect of IVIG therapy on coagulation parameters in COVID-19 patients. In one retrospective study on 850 COVID-19 patients who were divided into two groups, one with IVIG-treated and one with non-IVIG-treated patients, the results showed that the levels of D-dimer were decreased in the IVIG-treated group. However, there was no significant difference in diffuse intravascular coagulation between the tested and controlled groups (28). Based on our study, the levels of D-dimer have increased, and PTT was shortened, which may suggest that IVIG is an unfavorable anticoagulant treatment for COVID-19 patients.

IL-6 is a major inflammatory cytokine that increases during a cytokine storm in COVID-19 (29). Other associated cytokines include TNF-alpha, IFN-gamma, and IL-1beta (30). IVIG therapy is one of the treatment strategies suggested for cytokine storms in COVID-19 patients, along with anti-IL-6, anti-TNF-α, anti-IL-1, and corticosteroid therapy (32). However, our study demonstrated that IVIG has no effect on decreasing inflammatory components including IL-6, lymphocytes, ESR, and CRP, which reveals that IVIG therapy may not be an optimal option for the over-immune response induced by COVID-19.

There are some limitations in our study. Randomized clinical trials attempt to minimize selection bias by randomly assigning participants to treatment groups. However, certain types of patients may still be overrepresented or underrepresented in the study population, which can affect the generalizability of the results. Blinding both participants and researchers to the treatment group assignments is important to minimize bias, but it may be challenging in a study of IVIG therapy for COVID-19 patients due to the nature of the treatment. Inconsistencies in dosage, timing, and frequency of IVIG administration can make it difficult to draw meaningful conclusions about its effectiveness. Additionally, confounding variables such as age, comorbidities, and disease severity can also impact the validity of the study results. Finally, randomized clinical trials typically involve a highly controlled study population, which may not reflect the diversity of real-world patients, limiting the generalizability of the study results to other populations or settings.

Conclusion

The current study suggests that although IVIG therapy has been proposed as a potential treatment for COVID-19 patients, it may not be effective in improving clinical outcomes, including hospitalization duration, ICU admission period, and total death occurrence for ill COVID-19 patients with ARDS. As a result, given the restricted availability of IVIG and the possible risks associated with its use, it is crucial to carefully evaluate the potential benefits and disadvantages before administering it to COVID-19 patients with ARDS. However, the use of IVIG in the treatment of other complications of COVID-19 should be further investigated in future studies.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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