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International Immunopharmacology 90 (2021) 107205

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial

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ARTICLE INFO

Keywords:
IVIg
Intravenous Immunoglobulin
COVID-19
Coronavirus
Pulmonary infection

ABSTRACT

Background: The newly discovered coronavirus has turned into coronavirus disease 2019 (COVID-19) pandemic and it rages at an unprecedented rate. Considering the findings of previous studies on the use of Intravenous Immunoglobulin (IVIg) for treating severe H_1N_1 infection and the satisfying results for reducing viral load and mortality, this study aimed to investigate the potential usefulness of IVIg for the management of severe cases.
Methods: In this randomized controlled trial, 84 patients were included: 52 in the IVIg group and 32 in the control group. The intervention group received IVIg at a dose of 400 mg/kg, IV, daily for three days. Both groups received hydroxychloroquine, lopinavir/ritonavir and supportive care. The demographic data, mortality rate, the need for mechanical ventilation, length of stay in hospital and in Intensive Care Unit (ICU), and imaging findings were recorded and compared in terms of the mentioned factors.
Results: The mean time from admission to IVIg initiation was 3.84 ± 3.35 days. There was no significant difference between the two groups in terms of mortality rate (P-value = 0.8) and the need for mechanical ventilation (P-value = 0.39). The length of hospital stay was significantly lower for the control group than that of the intervention group (P-value = 0.003). There was a significant positive relationship between the time from hospital admission to IVIg initiation and the length of stay in the hospital and ICU among the survivors (P-value < 0.001 and =0.01, respectively).
Conclusions: Our findings did not support the use of IVIg in combination with hydroxychloroquine and lopinavir/ritonavir in treatment of severe COVID-19 cases.

1. Introduction

The newly discovered coronavirus, called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), first emerged in Wuhan, Hubei, China, and has surprisingly turned into coronavirus disease 2019 (COVID-19) pandemic at an unprecedented rate [1].

Currently, the number of confirmed cases of COVID-19 and the mortality rate continue to grow as a result of the high infectivity of the

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https://doi.org/10.1016/j.intimp.2020.107205
Received 24 September 2020; Received in revised form 29 October 2020; Accepted 10 November 2020
Available online 13 November 2020

disease, rapid respiratory progression, and lack of effective treatment options, hence imposing an enormous burden on clinicians and health-care system [2]. However, according to a report from the WHO-China, 80% of COVID-19 patients develop a mild to moderate disease and are less likely to require hospitalization. On the contrary, there are roughly 20% of cases which may develop severe disease or become critically ill [3].

Due to the lack of well-controlled studies and sufficient conclusive evidence, no consensus on treatment protocols has been achieved to date [4]. Moreover, the highly contagious nature of the disease, as well as the variability of clinical features and patient symptom severity make it challenging to control and manage the condition successfully [3,5,6]. Meanwhile, available options for the management of patients are limited to supportive interventions and empirical administration of several pre-existing therapeutic choices that are thought to have a potential for the treatment of COVID-19. Various medications consisting of antivirals, corticosteroids, immunomodulatory agents, and more recently, anti-helminthics are being examined in clinical settings. However, the optimal treatment strategy and definite cure, particularly in severe cases, are still unrecognized [4,7–9].

Despite a notable number of previous studies conducted on the use of Intravenous Immunoglobulin (IVIg) for severe H_1N_1 infection and the satisfying results for reducing viral load and mortality, further investigations to evaluate IVIg for the management of severe coronavirus cases are required [10]. Several studies have used IVIg as an adjunct to the treatment of severe COVID-19 pneumonia. However, its beneficial effect on the prognosis of patients with COVID-19 remains controversial [2,4,11]. This study evaluated the efficacy of IVIg in treating COVID-19 patients.

2. Materials and Methods

2.1. Setting

The current study is a randomized controlled trial conducted in Dr. Masih Daneshvari Hospital, a university affiliated and selected referral center for COVID-19 patients, Tehran, Iran.

2.2. Patients

Severely ill patients between 18 and 65 years old with COVID-19, confirmed based on the reports of Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or bilateral pulmonary infiltration in computed tomography (CT) scan of the chest were included in the study. Severe pneumonia cases were determined based on World Health Organization (WHO) case definitions for COVID-19 consisting of the following: respiratory rates: $\geq$ 30 breaths/min, SpO2 $\leq$ 93%, and $PaO_2/FiO_2 \leq 300$ mmHg.

The exclusion criteria were as follows: patients who denied signing the consent form; those with allergy reaction while injecting IVIg with severe extravasation and anaphylactic shock; mildly ill patients; patients recovering and improving upon Hydroxychloroquine, Lopinavir/Ritonavir, and supportive therapy; and pregnancy or breastfeeding.

2.3. Informed consent and approval

The patients who signed the consent form by themselves or their legal representatives were included in the study. This research was conducted according to the declaration of Helsinki and was approved with the ethics code number of IR.SBMU.NRITLD.REC.1399.143 by the ethics committee of Shahid Beheshti University of Medical Sciences. The trial was registered in Iranian Registry of Clinical Trials with the registration number of IRCT20151227025726N20.

2.4. Interventions

In total, this study analyzed 84 patients who were randomly assigned into IVIg and control groups (Fig. 1). Block randomization method was used for randomization. Eight blocks, including ten patients, were generated by the Online Randomizer website (www.sealesenvelop.com/simple randomizer). Patients in the IVIg group received Intratect® (Biotest), 400 mg/Kg daily for three doses, if they met necessary criteria for receiving the drug, while patients in the control group did not receive IVIg treatment. The time passed from hospital admission to IVIg infusion was recorded. All patients in the IVIg group were premedicated with 500 mg Acetaminophen, 100 mg Hydrocortisone, and 25 mg Diphenhydramine 30 min before the injection.

Patients in both groups received oxygen and fluid support, lopinavir/ritonavir (200/50 mg, Hetero labs), two tablets twice a day, and hydroxychloroquine (Tehran-Daru) 200 mg two times daily.

2.5. Outcomes

The primary outcomes included the need for invasive mechanical ventilation and oxygenation, the need for admission to the Intensive Care Unit (ICU), and the mortality rate. Secondary outcomes included length of stay in ICU and hospital, and radiological improvements in the CT scan. The data were collected from the patients' medical records, which included age, gender, underlying diseases, laboratory test results, and CT imaging findings.

2.6. Statistical analysis

The results were analyzed using SPSS v.25.0 software (IBM Corp., Armonk, NY, USA). Chi-square tests were performed to evaluate the difference in qualitative data. Shapiro-Wilk test was performed to assess the normality of data distribution. To compare the differences in the quantitative variables of both groups, the student-t or Mann-Whitney *U* test was carried out. The Pearson correlation test was applied to determine the relationships between different variables.

3. Results

Demographic characteristics of the patients are shown in Table 1. There were no significant differences between the two groups in terms of patients' age, gender, and past medical history.

The mean time (days) from hospital admission to IVIg infusion is shown in Table 2.

Chi-square test was performed to evaluate the differences between the two groups in terms of the need for invasive mechanical ventilation and oxygenation, the need for admission to ICU, the extent of improvements in CT scan findings, and mortality rate. To comparatively investigate the study population in terms of the length of stay in hospital and ICU, Mann-Whitney *U* test was performed. The results are shown in Table 3.

The results of the lab tests of the whole patients during a 14-day treatment are shown in Table 4. There were no significant differences regarding the lab data of the patients. The reported p-values represent the significance of differences between the two groups, including both survivors and non-survivors in each one.

We evaluated the relationships between the time from admission to initiation of IVIg and the length of hospital and ICU stay. This evaluation was done on the patients who received IVIg and survived. The Pearson correlation test results showed that there were significant relationships between the time from admission to initiation of IVIg and the length of stay in the hospital and ICU (P-value < 0.001 and $= 0.01$, respectively) (Pearson correlation $= 0.62$ and 0.72, respectively). The sooner the IVIg was started, the shorter the length of hospital and ICU were.

The results of the Pearson correlation test also showed that among all patients, there was a significant relationship between the age of patients

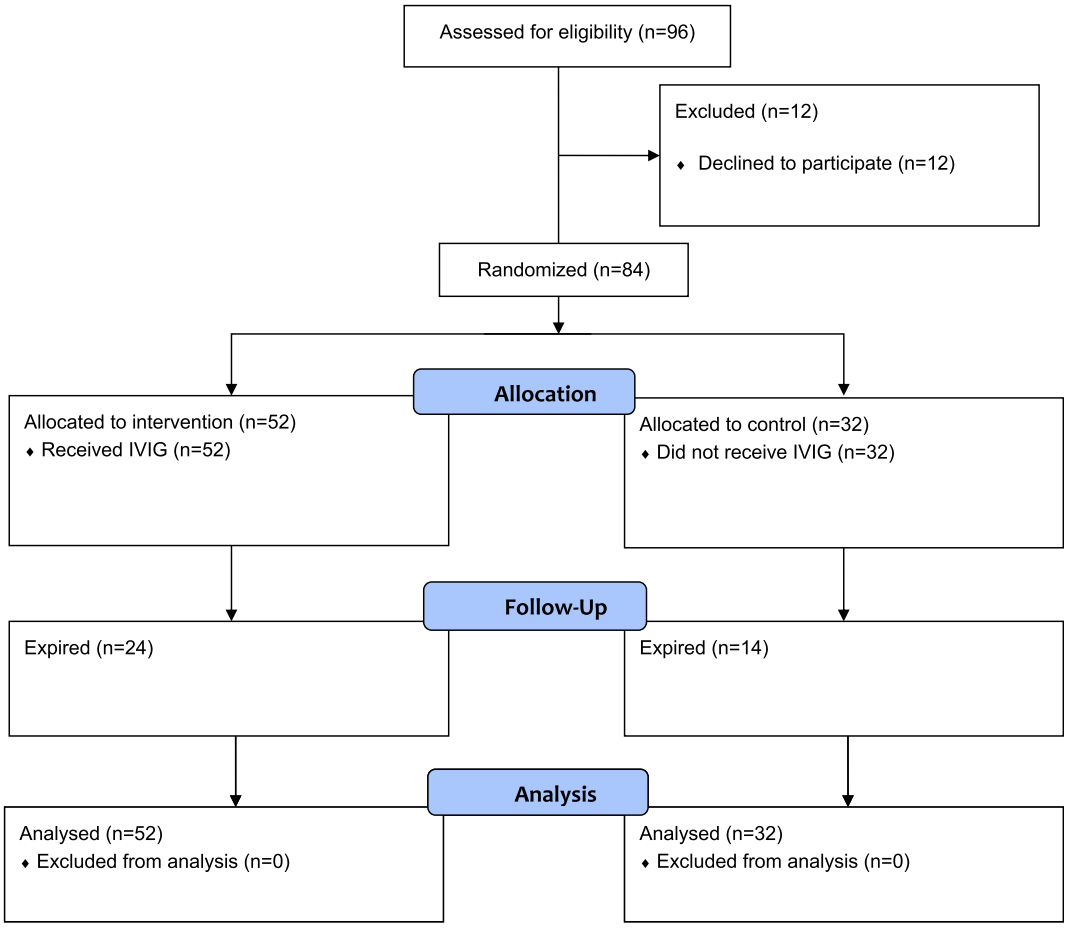

Fig. 1. CONSORT flowchart.

Table 1
Information on age, gender, and past medical history of the study population.

	IVIg group (n = 52)	Control group (n = 32)	P-value
Age	54.29 ± 12.85	52.47 ± 14.49	0.55
Gender (Male)	40 (76.92%)	25 (78.12%)	0.89
Smoking history	1 (1.92%)	0 (0%)	1
Hypertension	11(21.15%)	6 (18.75%)	0.79
Ischemic heart disease	3(5.76%)	2 (6.25%)	1
Chronic obstructive pulmonary disease	1 (1.92%)	0 (0%)	1
Malignancy	0 (0%)	1(3.12%)	0.38
Diabetes	10 (19.23%)	8 (25%)	0.53
Chronic kidney disease	3 (5.76%)	1(3.12%)	1
Rheumatoid arthritis	1 (1.92%)	0 (0%)	1

Data are presented as mean ± standard deviation for quantitative data and numbers (percent) for qualitative data.

Table 2
The time from the admission to administration of IVIg in the intervention group.

	Frequency	Minimum	Maximum	Mean ± SD
Time from admission to administration (days)	52	1	22	3.84 ± 3.35

SD: Standard deviation

and the mortality rate. This correlation was positive, suggesting that the higher the age of the patients is, the higher the mortality rate would be. However, this correlation was of moderate type (P-value < 0.001) (0.4 < Pearson correlation < 0.6). The need for mechanical ventilation had also a positive relationship with the age of the clients (P-value = 0.003).

Table 3
Differences between the two groups in terms of the need for invasive mechanical ventilation, the need for admission to the ICU, the extent of improvements in the chest CT scan, mortality rate and the, length of stay in ICU and hospital.

	IVIg group (n = 52)	Control group (n = 32)	P-value
The need for mechanical ventilation	21	10	0.39
Nasal or face mask oxygen therapy	23	15	0.63
The need for admission to the ICU	39	27	0.3
More than 50% improvements in chest CT scan	7	2	1
Length of hospital stay (day)	8.5 (6–12)	5.5 (4–8)	0.003
Length of ICU stay	5(3–7)	4(2–7)	0.72
Mortality (expired)	24	14	0.83

Data are presented in numbers for qualitative data and median plus 25%-75% percentile for quantitative data.
ICU: Intensive Care Unit; CT: Computed Tomography

4. Discussion

Despite a substantial number of severe COVID-19 cases in the world, the data about the potential therapeutic options remain limited. This study examined the therapeutic effects of IVIg on the confirmed COVID-19 cases and reviewed the previous valuable results of related articles.

Our study did not find any therapeutic benefits of administering IVIg for the severe cases of COVID-19. The need for mechanical ventilation,

Table 4
Comparison of the lab tests between the two groups.

	IVIg Group				Control Group				P-value
	Not-survived		Survived		Not-survived		Survived		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
WBC Baseline (10^3/μL)	9.70	7.87–11.96	7.36	4.85–11.60	9.95	7.40–13.30	6.40	5.00–8.80	0.69
WBC day 7 (10^3/μL)	14.33	13.45–23.00	9.94	7.70–11.76	13.10	10.10–19.40	8.15	7.20–9.60	0.56
WBC day 14 (10^3/μL)	.	.	10.90	10.88–10.99	13.90	13.60–15.20	10.05	7.15–12.45	0.7
Cr Baseline (mg/dL)	1.20	1.00–1.70	1.10	0.90–1.20	1.20	1.00–1.40	1.10	1.00–1.20	0.71
Cr day 7 (mg/dL)	1.60	0.90–3.20	1.00	1.00–1.50	1.20	1.00–1.50	1.05	0.90–1.10	0.62
Cr day 14 (mg/dL)	.	.	1.40	1.00–1.80	1.10	0.70–4.20	1.05	0.90–1.10	0.28
AST Baseline (Units/L)	63.00	42.00–79.00	51.00	39.50–63.50	55.00	33.00–95.00	47.00	26.00–66.00	0.32
AST day 7 (Units/L)	80.00	56.00–120.00	40.00	33.50–56.00	66.00	37.00–90.00	33.00	27.00–47.00	0.92
AST day 14 (Units/L)	.	.	24.00	22.00–28.50	67.00	35.50–341.50	32.00	23.00–112.00	0.07
ALT Baseline (Units/L)	33.00	25.00–58.00	30.00	23.50–50.50	45.00	21.00–59.00	38.00	22.00–61.00	0.64
ALT day 7 (Units/L)	36.00	20.00–58.00	53.50	30.00–108.00	78.00	33.00–139.00	23.50	18.00–59.00	0.89
ALT day 14 (Units/L)	.	.	35.00	17.50–49.50	57.50	32.50–434.00	81.00	35.00–338.00	0.16
ALP Baseline (Units/L)	200.00	155.00–258.00	141.00	132.00–272.00	164.00	141.00–198.00	189.00	129.00–221.00	0.55
ALP day 7 (Units/L)	295.00	181.00–503.00	188.00	141.50–222.50	345.00	171.00–361.00	155.00	94.00–175.00	0.71
ALP day 14 (Units/L)	.	.	183.00	127.00–187.00	308.00	201.50–499.50	192.00	144.00–197.00	0.18
CRP Baseline	62.00	62.00–62.00	39.00	39.00–39.00	56.50	37.50–60.00	52.50	28.50–55.50	0.71
CRP day 14	.	.	.	.	59.00	59.00–59.00	66.00	66.00–66.00	–

IQR: inter-quartile range; WBC: White blood cells; CRP: C-reactive protein; ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline-phosphatase; Cr: Creatinine

admission to the ICU, and the extent of improvements in the chest CT did not differ significantly between the two groups. The mortality rate remained unaffected as well. Surprisingly, the length of hospital stay was significantly shorter in the control group. However, this result is hard to interpret, as the need for admission to the hospital for IVIg administration may be a confounding factor.

There was a significant relationship between the time from admission to the administration of IVIg and the patients' length of stay in hospital and ICU among the surviving patients. This relationship was of positive and strong type, that shows the sooner IVIg be administered for patient, the shorter the length of stay in hospital and ICU might be.

Previous studies have proposed different mechanisms for IVIg immunomodulatory properties, such as Fc-mediated and Fab-mediated pathways [9,12]. Studies supporting the beneficial effects of IVIg on SARS-Cov-2 patients have emphasized the time of IVIg initiation. It can be mentioned that IVIg showcases its best results when administered at the beginning of the acceleration phase of the disease. Previous publications believed that IVIg might not be of any effective use following the development of systemic damage in patients [2].

In our study, the mean time from the hospital admission to IVIg initiation was 3.84 ± 3.57 days. It is possible for patients of our study to have received the intervention just after the acceleration phase of their disease has developed, which may has occurred at home or during their hospital admission. The achieved data might be invalidated for those cases who are struggling with the acceleration phase of the disease. The patients who have received IVIg at an earlier stage of clinical deterioration, had a shorter hospital and ICU length of stay.

Our results are not consistent with the case series published by Wei Cao et al. that was conducted on three patients and found that IVIg was a useful therapeutic option for treating severe COVID-19 cases. The results of Wei Cao et al. study showed that the five-day administration of IVIg led to satisfactory clinical outcomes and improved radiographic changes [2]. While patients in Wei Cao et al. study were given IVIg at a constant dose of 25 g/d for five days, our patients received the weight-based dosing (400 mg/kg, three doses) on a daily basis.

Another noteworthy finding in our study is the direct relationship between the patients' age and their need for mechanical ventilation and mortality rate. The older the patients were, the more urgent the need for mechanical ventilation and the higher the mortality rate would be. These data are in line with the reports of the Epidemiological Characteristics of the Outbreak of 2019 Novel Coronavirus Diseases (COVID-19), China, 2020 [13].

The main limitation of our study is that we can not exclude the potential benefits of IVIg monotherapy in the management of COVID-19 disease. Only the combination therapy of IVIg with hydroxychloroquine and lopinavir/ritonavir was not effective. The ethical challenges pushed us not to consider a control group without any treatment, and due to that fact, we could evaluate the effectiveness of IVIg in the combination regimens only.

There are two ongoing clinical trials (NCT04411667 and NCT04261426) that are evaluating the effectiveness of administering high dose of IVIg in confirmed SARS-CoV-2 patients. The administered dose in both of these trials is 0.5 g/kg daily, which is quite higher than the dose used in our study. In one trial, the duration of treatment is three days, while it is five days for the other one. The results of these trials must be evaluated before generalizing the results to the whole population. It is recommended that patients' plasma in the recovery phase be considered for determining the presence of adequate titers. Furthermore, it is recommended that the effects of IVIg administration on RT-PCR tests and symptom improvements be taken into account for future studies.

5. Conclusion

The obtained data did not support the beneficial effects of using IVIg in combination with hydroxychloroquine and lopinavir/ritonavir for SARS-Cov-2 patients, as the mortality rate, radiographic changes, and the need for mechanical ventilation did not show noticeable improvement. However, the length of the ICU and hospital stay might be shorter upon early IVIg initiation.

CRediT authorship contribution statement

Payam Tabarsi: Conceptualization, Methodology, Writing - review & editing. **Saghar Barati:** Methodology, Writing - original draft, Formal analysis. **Hamidreza Jamaati:** Conceptualization, Methodology, Writing - review & editing. **Sara Haseli:** Writing - review & editing. **Majid Marjani:** Methodology, Writing - review & editing. **Afshin Moniri:** Methodology, Writing - review & editing. **Zahra Abtahian:** Methodology, Writing - review & editing. **Alireza Dastan:** Writing - review & editing. **Sahar Yousefian:** Data curation, Software, Writing - review & editing. **Raha Eskandari:** Writing - review & editing. **Ali Saffaei:** Formal analysis. **Fatemeh Monjazebi:** Writing - review & editing. **Abdolbaset Vahedi:** Writing - review & editing. **Farzaneh**

Dastan: Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study was approved and supported by Shahid Beheshti University of Medical Sciences.

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