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ORIGINAL ARTICLE CARDIOLOGY

Investigation of cardiac adverse effects in COVID-19 ARDS patients treated with intravenous immunoglobulin

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ABSTRACT

OBJECTIVE: The popularity of intravenous immunoglobulin (IVIG) therapy in Acute Respiratory Distress Syndrome (CARDS) secondary to COVID-19 infection is increasing day by day. In this study, we aimed to retrospectively evaluate the possible cardiac effects in our CARDS patients treated with IVIG.

METHODS: Demographic and clinical characteristics, mortality, sequential electrocardiography (ECG), echocardiography, cardiac markers, and other laboratory parameters of CARDS patients who received IVIG treatment were recorded.

RESULTS: The mean age of the patients was 68.7±13.6%, and 70.5% were female. The mean number of days of hospitalization in the intensive care unit was 18.2±9.7, and the mortality rate was recorded as 35.2%. No pathological rhythm or ischemic change was observed in sequential ECG follow-ups. However, in consecutive ECO follow-ups, the sPAP values at the treatment end were numerically lower, although not statistically significant.

CONCLUSION: Our study suggests that IVIG therapy may be used safely in COVID-19 patients with cardiovascular side effects. However, due to the high risk of coagulopathy in these patients, the use of IVIG therapy in COVID-19 infection should be monitored with close monitoring, as it may increase the potential for cardiovascular risk. Furthermore, monitoring cardiac parameters are also essential as it may predict high cardiovascular risk in patients. For this reason, patients need lower infusion rates, steroid combination, adequate hydration, and effective anticoagulation therapy to avoid these side effects.

Keywords: Acute respiratory distress syndrome; adverse effects; COVID-19; drug effects; intravenous immunoglobulins; shock.

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The effectiveness of the proposed treatment methods in Severe Acute Respiratory Distress Syndrome (CARDS) associated with COVID-19 infection is still controversial. Unfortunately, a standard treatment regimen has not yet been determined [1]. Moreover, 15% of COVID-19 infections require hospitalization, and it has been reported that 5% of them cause a critical picture and require intensive care hospitalization [2]. In addition, it has been reported that CARDS is seen in 42% of patients hospitalized with COVID-19 pneumonia and 61–81% of the patients of CARDS require intensive care [3].

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Intravenous Immunoglobulin (IVIG) is the gammaglobulin fraction of blood plasma containing a wide range of antibodies. It has a wide variety of uses, as it has many effects such as preventing and treating diseases, neutralizing toxins, strengthening, and modulating the immune system [4]. Autoimmune and chronic inflammatory diseases are the main ones, and they have been used in the treatment of viral infections over the years. For example, it has been used to treat ARDS caused by the Severe Acute Respiratory Syndrome Virus, a previous coronavirus epidemic, with the hope of making positive contributions to immunity [5]. The rationale for the use of IVIG in COVID-19 infection is the modulation of inflammation. IVIG enhances regulatory T-cell proliferation. Evidence has shown that proinflammatory cytokines such as IL-17A and IL-6 decrease, Th17 cells are suppressed, and anti-inflammatory cytokines such as IL-10 increase. In addition, IVIG shows antiviral and anti-inflammatory effects by increasing the secretion of certain cytokines such as IL-2 to support T-cell and B-cell proliferation and differentiation. For all these reasons, it is recommended to be used in COVID-19 virus infection [4, 5].

However, some thromboembolic side effects have been observed despite its benefits [6, 7]. In studies reported on the use of IVIG in treating respiratory failure secondary to COVID-19 pneumonia, it has been reported that IVIG treatment reduces the length of hospital stay and the need for invasive mechanical ventilation in mild and moderate ARDS [8]. IVIG has also been recommended among the treatment options in the COVID-19 guideline in Turkiye [9].

It is known that the use of IVIG has some dose-related side effects, and most of these side effects are in the form of headache, weakness, fatigue, fever, and chills. In addition, less common but serious side effects are thrombosis, secondary acute ischemic stroke, acute myocardial infarction, arrhythmias, hemolytic anemia, transfusion-associated acute lung injury, and transfusion-related circulatory overload, also be observed. Due to these side effects, patients need to be treated. Therefore, close monitoring is recommended throughout the period [10].

This study aimed to retrospectively evaluate the possible cardiac effects in our CARDS patients treated with IVIG for 3 months in our clinic.

Highlight key points

- No echocardiographic or electrocardiographic changes to treat COVID-19 while using IVIG were observed.
- During IVIG treatment, thromboembolism prophylaxis, hydration, and slow infusion rates did not show significant D-dimer elevation, thrombotic complications, and ischemic changes in patients.
- When combined IVIG treatment with steroids, no significant neutropenia developed.

MATERIALS AND METHODS

This study was carried out with the permission of Eskisehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: June 01, 2021, Decision No: 35). All procedures were carried out following the Declaration of Helsinki's ethical rules and principles. This was a cross-sectional and retrospective study. In our study, COVID-19 patients hospitalized in our intensive care clinic at Eskişehir City Hospital between November 15, 2020 and Feburary 15, 2021 and received IVIG treatment were retrospectively examined.

Study Population

Between the specified dates, 14 of 102 patients hospitalized in the COVID-19 intensive care unit had negative PCR, and COVID-19 infection was confirmed by PCR positivity of 88 patients. Among them, 18 patients who received IVIG treatment were included in the study. One of the patients who received IVIG treatment died due to CARDS on the 1st day and was excluded from the study due to the absence of consecutive electrocardiography (ECG) and echocardiography (ECHO) values. Therefore, 17 patients in the study group were analyzed.

Treatment Protocol

Severe CARDS patients were treated with guideline recommendations prepared by the Turkish Ministry of Health and constantly updated with new literature [9]. IVIG treatment at a dosage of 0.4 g/kg/day for 5 days, based on ideal body weight, was given to unstable patients whose oxygen needs did not decrease with standard treatment. First of all, IVIG treatment was planned if the patients' urine output was at optimum level, and creatinine levels were within normal limits. Concomitant administration of loop diuretics to patients was avoided. The treatment was planned as an infusion, and adequate hydration was provided to the patients beforehand. Glycine preparations containing 10 grams of IVIG in 200 mL available in our hospital were used, and the infusion rate did not exceed 1.4 ml/kg/h. All pa-

tients received pre-infusion steroid therapy and pheniramine hydrogen maleate for 5 days, during which they received IVIG infusion. The patients were treated with steroids by calculating the dose of methylprednisolone, which corresponds to 0.5–1 mg/kg prednisolone dose, according to the guidelines recommendation. All patients were treated with low molecular weight heparin (LMWH) as 2*40 mg enoxaparin for thrombosis prophylaxis if there were no contraindications.

Data Collection

Demographic data, clinical characteristics, days, and grams of IVIG treatment of patients who received IVIG treatment were recorded retrospectively. During the period of IVIG, the patients were followed up closely. ECG, ECHO, cardiac markers, and other laboratory parameters were recorded before and after the treatment. After IVIG treatment, the necessity for inotropes, the quantity and quality of oxygen demand, mortality status, and the number of intensive care hospitalization days were also recorded.

Statistical Analysis

The distribution of each continuous variable was tested for normality using the Shapiro–Wilk test and was expressed as mean±standard deviation. Non-normally distributed variables were performed using the Wilcoxon Signed-Rank Test and were expressed as median values (25–75%). The categorical variables were expressed in frequencies and percentages. A $p<0.05$ was considered statistically significant. All analyses were performed using the SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 68.7±13.6%, and 70.5% were female. The mean number of days of hospitalization in the intensive care unit was 18.2±9.7, and the mortality rate was recorded as 35.2% (Table 1). In all of our patients who died, the cause was found to be COVID-19-related CARDS and septic shock. No additional cause of death was identified. As can be seen from Table 2, Complete Blood Count, C-reactive protein, procalcitonin, ferritin, D-dimer, troponin I, CK-MB, B-type natriuretic peptide (BNP), creatinine, and glucose values did not show any significant differences between groups ($p>0.05$) (Table 2) . ECG values followed during IVIG use were shown in detail in the table, and no pathological rhythm or ischemic change was observed (Table 3). Although it was not statistically significant in the ECHO results between groups, the sPAP values in Group 2 were numerically lower ($p=0.032$) . ECHO parameters before and after treatment were detailed in the table (Table 4) IVIG treatment was not given to 67 of the patients followed in the intensive care unit. In 44.8% of these patients (n=30), mortality was observed during the intensive care stay. None of our patients had a complication that we thought was due to IVIG treatment such as arrhythmiaand neutropenia.

Table 1. Demographic and clinic characteristics of the patients with COVID-19

Variables	Mean±SD
Age	68.7±13.6
Gender	
Male (%)	5 (29.5)
Female (%)	12 (70.5)
APACHE-II	15.8±5.8
Predictive mortality rate	25.6±15.6
Number of IVIG threatment, days	4.6±0.8
The amount of IVIG that patients take per day, gram	20.2±1.2
Duration of intensive care stay, days	18.2±9.7
Need for oxygen therapy, days	
Invasive mechanic ventilation	3.5±7.9
High flow oxygen therapy-NIV	3.5±6.1
Reservoir mask	5.3±4.2
Nasal cannula	1.6±1.7
Need for inotropic agents, days	1.6±2.8
Mortality status (%)	
Ex	35.2
Discharge	64.8

SD: Standard deviation; APACHE: Acute physiology and chronic health evaluation; IVIG: Intravenous Immunoglobulin; NIV: Non invasive mechanical ventilation.

DISCUSSION

Our study did not detect significant ECG and ECHO changes in CARDS patients with adequate hydration, low-rate infusion, and LMWH prophylaxis during IVIG treatment. As we know, there is no other study in the literature, in which cardiac effects were investigated and closely monitored during IVIG therapy in COVID-19 patients. In addition, there is no study on cardiac side effects in other patient groups receiving IVIG treatment,

Table 2. Laboratory parameters before and after treatment in COVID-19 patients

Variables	Before treatment	After treatment	p
Leukocytes $\times 10^3/\mu L$	13.0 (7.7–21.6)	11.9 (9.2–17.0)	0.463
Neutrophil $\times 10^3/\mu L$	11.6 (6.9–19.6)	10.5 (8.3–14.6)	0.523
Lymphocyte $\times 10^3/\mu L$	0.6 (0.4–1.1)	0.5 (0.4–1.2)	0.850
Haemoglobin	12.3 (10.9–12.9)	11.8 (10.7–12.9)	0.186
Platelets $\times 10^3/\mu L$	271.0 (239.0–376.5)	256.0 (224.0–323.0)	0.298
C-reactive protein, mg/dL	76.4 (45.3–148.6)	59.7 (26.7–87.7)	0.177
Procalcitonin	0.33 (0.11–0.84)	0.18 (0.10–0.54)	0.266
Ferritin	509.0 (295.5–1206.5)	687.0 (369.5–1085.0)	0.049
D-dimer	1.17 (0.8–2.7)	1.6 (0.7–3.7)	0.636
Troponin I, pg/mL	16.3 (6.3–30.7)	18.7 (5.1–124.3)	0.438
CK-MB	1.1 (0.3–3.8)	1.3 (0.5–4.5)	0.641
B-type natriuretic peptide, pg/mL	62.8 (26.2–162.3)	61.7 (15.1–129.5)	0.213
Creatinine, mg/dL	0.84 (0.74–0.93)	0.78 (0.69–0.94)	0.184
Glucose, mg/dL	144.0 (119.5–243.5)	170.0 (129.0–217.0)	0.722

Median value (25%–75%). CK-MB: Creatine kinase-isoenzyme MB.

Table 3. ECG findings and characteristics of the study patients

Variables	First day of treatment	Third day of treatment	p
HR (bPM)	75.0 (62.2–106.7)	86.0 (65.0–111.5)	0.530
PR interval (msec)	158.5 (143.5–178.0)	168.0 (155.5–184.5)	0.330
QT interval (msec)	379.0 (341.5–418.0)	390.0 (335.0–437.5)	0.530
QTc (msec)	421.0 (386.7–447.2)	435.0 (408.7–469.2)	0.258
QRS interval (msec)	95.0 (87.5–114.5)	95.0 (87.5–124.2)	1.000

Median value (25%–75%). ECG: Electrocardiography; HR: Heart rate; bPM; Beats per minutes; PR: PR interval; QTc; Rate-corrected QT interval; QRS: QRS complex duration.

and it is limited to case reports. Therefore, we think this study is a pilot study that could lead to other studies.

IVIG, although controversial, has been accepted as one of the effective treatment methods in COVID-19 infection [11]. In the study by Shao et al. [12], it was shown that the use of IVIG at high doses, especially in the early period of infection, provided a significant decrease in 28-day and 60-day mortality, shortened the hospitalization period, and improved organ functions. The effectiveness of IVIG treatment has been demonstrated by studies conducted in a short time on IVIG, and the COVID-19 guideline published by the World Health Organization has become one of the treatment options [13]. Large-scale observational studies could then be carried out. In a retrospective study conducted in Wuhan, the origin of COVID-19, IVIG treatment, which was admitted to the intensive care unit and applied in the early stage (within the first 48 h after admission to the intensive care unit), decreased the need for invasive mechanical ventilation, shortened the hospital-intensive care hospital stay, and found to be associated with a decrease in daily mortality rate [8]. In contrast, another retrospective study, in which 101 deceased CARDS patients were examined, it was emphasized that almost all of the patients received IVIG treatment, but it did not change the mortality [14]. We applied IVIG treatment to patients whose condition became unstable and whose oxygen requirement increased while under standard COVID-19 treatment, with the guide's recommendations.

Table 4. Conventional echocardiographic features of study patients before and after treatment initiation

Variables	Before treatment	After treatment	p
LVEDV mm	72.0 (54.2–92.7)	70.0 (53.7–101.2)	0.475
LVESV mm	23.5 (17.2–33.0)	22.5 (16.0–54.7)	0.241
LVEF %	62.2 (55.5–67.7)	59.0 (46.7–67.5)	0.236
LVESD	26.0 (23.5–31.0)	27.0 (23.5–30.5)	0.779
LVEDD	47.0 (39.7–49.0)	47.5 (41.0–49.5)	0.439
E wave, m/s	54.5 (43.2–78.0)	43.5 (40.5–72.2)	0.139
A wave, m/s	67.0 (36.7–74.5)	53.5 (46.0–79.7)	0.332
MDZ	162.0 (156.0–230.0)	204.0 (159.0–260.5)	0.262
IVRZ	70.0 (58.0–100.0)	63.5 (54.0–70.5)	0.249
e' Lateral, cm/s	8.0 (7.0–11.0)	8.0 (6.0–10.7)	1.000
e' Septal, cm/s	8.0 (7.0–10.0)	8.0 (6.0–10.0)	1.000
LA volume mm	35.5 (28.2–41.2)	35.0 (33.0–42.5)	0.212
LAV	25.0 (11.5–31.5)	21.0 (11.2–33.5)	0.528
RV	34.0 (28.0–36.7)	31.0 (24.0–37.7)	0.351
TAPSE , mm	22.5 (15.5–25.7)	19.5 (17.2–27.0)	0.833
sPAP (mmHg)	40.0 (30.0–53.7)	36.0 (15.0–51.2)	0.032
RA pressure, mmHg	33.5 (26.5–41.2)	34.0 (30.7–44.5)	0.073
IVS (mm)	12.5 (9.0–14.2)	12.0 (8.5–13.0)	0.344
PW	9.0 (8.75–12.0)	10.0 (8.5–12.0)	0.196

Median value (25%–75%). LVEDV: Left ventricle end-diastolic volume; LVESV: LV end-systolic volume; LVEF: LV ejection fraction; LVESD: LV end-systolic diameter; LVEDD: LV end-diastolic diameter; MDZ: Mitral deceleration time; IVRZ: Isovolumetric relaxation time; LA: Left atrium; LAV: Left atrium volume; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; RA: Right atrium; IVS: Interventricular septum; PW: Pulse wawe (mm).

IVIG can disrupt the cardiovascular system by two different mechanisms. The first of these; enlargement of plasma volume and increased oxygen demand, and second, increased plasma and blood viscosity [15]. The increase in viscosity may trigger ischemia, especially in the myocardium [16]. In a case series published by Elkayam et al. [17], acute myocardial infarction induced using high-dose IVIG was found in 4 cases. In the literature review by Lidar et al. [18], they screened thrombotic complications despite complying with the IVIG usage guidelines in all of them. They emphasized that we should be aware of this issue. Barsheshet et al. [19], on the other hand, defined ST-elevation myocardial infection during IVIG treatment in a patient with Gullian–Bare syndrome and recommended close cardiac monitoring during IVIG treatment. In our study, patients were tried to be protected from thrombotic complications by administering LMWH treatment at appropriate doses. To minimize the risk of arrhythmia and cardiac complications, ECG, cardiac enzymes, and echocardiographic follow-ups were performed before and after treatment. The patients observed no pathological rhythm, ECG changes, or enzyme elevation during the treatment.

COVID-19 pneumonia has unique coagulopathic complications. Although it causes direct endothelial damage through ACE-2 receptors, high inflammation related to the septic picture, namely, sepsis-induced coagulopathy, constitutes the main mechanism [20]. In the activity of humoral and cellular immune pathways, increased inflammatory mediators cause platelet aggregation, peripheral vasoconstriction due to increased thromboxane production, and endothelial dysfunction [21]. Thrombin formed by these mechanisms increases the risk of clotting. In addition, there are many triggers such as patients' comorbidities, immobility, and venous stasis [22]. There is an obviously increased risk of complications when we infuse an agent that increases the viscosity of patients' circulation to those who are already at risk for this type of coagulopathy. Therefore, LMWH prophylaxis should be effective, patients should be well hydrated beforehand, and diuretic use should be avoided

[23]. After their study, Cherin et al. [24] recommended hydration starting approximately 6 h before the IVIG infusion and including a few hours after the end of the infusion in diseases with a high potential to cause renal disease, such as COVID-19 infection. In addition, it has been recommended to be used with low infusion rates in high-risk patient groups to reduce the possibility of thrombotic side effects [25]. We also provided effective hydration in our patients and regularly monitored the urine output, followed creatinine, and provided renal monitoring. There was no significant increase in serum creatinine in our patients in the pre- and post-treatment period. (p=0.184). Under the recommendations, the infusion rate did not exceed 1.4 ml/kg/h in our patients.

Neutropenia is an expected side effect in patients treated with IVIG [25]. Neutropenia, one of the characteristic features of COVID-19 pneumonia, is likely to deepen during IVIG administration. As mentioned in the literature, premedication with steroid therapy is recommended for preventing neutropenia during IVIG treatment [26]. In the study, patients were premedicated with methylprednisolone at suggested doses of COVID-19 guidelines. We found no significant change in neutrophil values before and after treatment in our study (p=0.523).

Another possible side effect is commonly anaphylactoid, less commonly anaphylactic reactions. They are life-threatening if not recognized in the early period. They are a sort of IgE-mediated reactions that occur following the massive release of mediators from tissue mast cells and peripheral blood basophils in response to IVIG administration. Anaphylactoid reactions produce a clinical status similar to anaphylactic reactions, but they are not IgE-mediated. That occurs due to direct degranulation and release of mediators from mast cells and/or basophils, or direct complement activation leading to anaphylatoxin production. This reaction can be reduced by premedication with antihistamines and steroids by decreasing infusion rate [4]. We applied antihistaminic and steroid prophylaxis to our patient and thankfully did not encounter anaphylactoid reactions.

The literature has not found a study comparing echocardiographic findings before and after IVIG treatment in COVID-19 patients. In the case report of Makiello et al. [27], a mildly low ejection fraction was described in an 11-year-old patient with COVID-19-related Paediatric Inflammatory Multisystem Syndrome, and the patient was treated with acetylsalicylic acid, corticosteroid, and IVIG. The ejection fraction seemed to be improved when a control ECHO was performed 1 month later. Sawalha et al. [28], in their systematic review, 14 cases of myocarditis due to COVID-19 were examined, and 21% of them were treated with IVIG. However, this study does not include data related to ECHO follow-up. Our study suggests that IVIG therapy may be cardiovascularly safe in patients with COVID-19. In our study, no echocardiographic worsening was observed in COVID-19 patients who received IVIG treatment and were followed up by echocardiography (ECHO). Although it was not statistically significant, numerical improvement was found in sPAP values.

Limitations of the Study

Our study is a single-center study, and only COVID-19 patients given IVIG in an intensive care unit were examined. Therefore, the number of patients is inadequate.

Conclusion

Our study found out that there was no statistically worsening in the ECG, ECHO, troponin, and BNP follow-ups of COVID-19 patients who received IVIG therapy. Statistically, insignificant improvement was found in sPAP values. Close cardiac monitoring and controlled infusions can provide safe treatment during IVIG treatment by minimizing the side effect profile. This study serves as a pioneer for further large-scale studies.

Ethics Committee Approval: The Eskisehir Osmangazi University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 01.06.2021, number: 35).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – AA; Design – AA, FAA; Supervision – OTY, AU; Fundings – FAA, FM; Materials – AA, FM; Data collection and/or processing – FAA, OTY; Analysis and/or interpretation – FM, AU; Literature review – AA, OTY; Writing – AA, FAA; Critical review – AU, OTY.

REFERENCES

1. Tzilas V, Manali E, Papiris S, Bouros D. Intravenous immunoglobulin for the treatment of COVID-19: a promising tool. Respiration 2020;99:12:1087–9.
2. Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201:1430–4.

3. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934–43.
4. Azizi G, Abolhassani H, Asgardoon MH, Shaghaghi S, Negahdari B, Mohammadi J, et al. Managing patients with side effects and adverse events to immunoglobulin therapy. Expert Rev Clin Pharmacol 2016;9:91–102.
5. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343.
6. Ng KH, Wu AK, Cheng VC, Tang BS, Chan CY, Yung CY, et al. Pulmonary artery thrombosis in a patient with severe acute respiratory syndrome. Postgrad Med J 2005;81:e3.
7. Umapathi T, Kor AC, Venketasubramanian N, Lim CC, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004;251:1227–31.
8. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect 2020;81:318–56.
9. T.C. Sağlık Bakanlığı. COVID-19 (SARS-CoV2 Enfeksiyonu) Rehberi. Available at: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf. Accessed Jul 16, 2020.
10. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of ımmunoglobulin therapy. Front Immunol 2018;9:1299.
11. Galeotti C, Kaveri SV, Bayry J. Intravenous immunoglobulin immunotherapy for coronavirus disease-19 (COVID-19). Clin Transl Immunology 2020;9:e1198.
12. Shao Z, Feng Y, Zhong L, Xie Q, Lei M, Liu Z, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: a multicenter retrospective cohort study. Clin Transl Immunology 2020;9:e1192.
13. WHO. Global Surveillance for human infection with coronavirus disease (COVID-19). Available at:https://www.who.int/publications-detail/global-surveillance-for-humaninfection-with-novel-coronavirus-(2019-ncov). Accessed Apr 29, 2020.
14. Fan H, Zhang L, Huang B, Zhu M, Zhou Y, Zhang L, et al. Retrospective analysis of clinical features in 101 death cases with COVID-19. medRxiv 2020 March 17. doi: 10.1101/2020.03.09.20033068. [Epub ahead of print].
15. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology 1994;44:223–6.
16. Koenig W, Ernst E. The possible role of hemorheology in atherothrombogenesis. Atherosclerosis 1992;94:93–107.
17. Elkayam O, Paran D, Milo R, Davidovitz Y, Almoznino-Sarafian D, Zeltser D, et al. Acute myocardial infarction associated with high dose intravenous immunoglobulin infusion for autoimmune disorders. A study of four cases. Ann Rheum Dis 2000;59:77–80.
18. Lidar M, Masarwa S, Rotman P, Carmi O, Rabinowicz N, Levy Y. Intravenous immunoglobulins for rheumatic disorders and thromboembolic events-a case series and review of the literature. Immunol Res 2018;66:668–74.
19. Barsheshet A, Marai I, Appel S, Zimlichman E. Acute ST elevation myocardial infarction during intravenous immunoglobulin infusion. Ann N Y Acad Sci 2007;1110:315–8.
20. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135:2033–40.
21. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res 2020;69:1181–9.
22. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care 2020;24:360.
23. Ammann EM, Haskins CB, Fillman KM, Ritter RL, Gu X, Winiecki SK, et al. Intravenous immune globulin and thromboembolic adverse events: a systematic review and meta-analysis of RCTs. Am J Hematol 2016;91:594–605.
24. Cherin P, Marie I, Michallet M, Pelus E, Dantal J, Crave JC, et al. Management of adverse events in the treatment of patients with immunoglobulin therapy: a review of evidence. Autoimmun Rev 2016;15:71–81.
25. Bichuetti-Silva DC, Furlan FP, Nobre FA, Pereira CT, Gonçalves TR, Gouveia-Pereira M, et al. Immediate infusion-related adverse reactions to intravenous immunoglobulin in a prospective cohort of 1765 infusions. Int Immunopharmacol 2014;23:442–6.
26. Späth PJ, Granata G, La Marra F, Kuijpers TW, Quinti I. On the dark side of therapies with immunoglobulin concentrates: the adverse events. Front Immunol 2015;6:11.
27. Makiello P, Svirpliene S, Finlay L, McKnight J. Paediatric inflammatory multisystem syndrome temporally associated with COVID-19: a new virus and a new case presentation. BMJ Case Rep 2020;13:e238531.
28. Sawalha K, Abozenah M, Kadado AJ, Battisha A, Al-Akchar M, Salerno C, et al. Systematic review of COVID-19 related myocarditis: insights on management and outcome. Cardiovasc Revasc Med 2021;23:107–13.