A Retrospective Comparative Analysis of Factors Affecting the Decision and Outcome of Initial Intravenous Immunoglobulin Alone or Intravenous Immunoglobulin Plus Methylprednisolone Use in Children With the Multisystem Inflammatory Syndrome

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Research article

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Abstract

Background: Use of intravenous immunoglobulins (IVIG) with or without methylprednisolone is the most preferred therapeutic strategy for the multisystem inflammatory syndrome in children (MIS-C). This study aimed to compare the use of IVIG plus methylprednisolone vs IVIG alone in children with MIS-C.

Methods: This retrospective cohort study was conducted during the period between April 1, 2020, and November 1, 2021. All children with MIS-C were included in the study. The patients were divided in two groups according to whether they were administered IVIG alone or IVIG plus methylprednisolone as an initial treatment for MIS-C. While the patients in group I were administered IVIG with a dosage of 2 gr/kg, the patients in group II were administered IVIG (dosage of 2 gr/kg) plus methylprednisolone (2 mg/kg/day). The re-occurrence of fever, duration of hospital stay, admission to pediatric intensive care unit were compared between these two groups.

Results: A cohort of 91 patients under 18 years old and diagnosed as MIS-C was included in the study. Of these patients, 42 (46.2%) were in IVIG alone group. (group I) and 49 (53.8%) were in IVIG plus methylprednisolone (group II). The ratio of severe MIS-C was 36.7% for patients in the group II and significantly higher compared to the rate of severe MIS-C patients in the group I (9.5%) (p=0.01). The rate of hypotension was significantly higher in the group II (30.6 %) compared to the group I (9.5%) (p=0.014). Moreover, the mean serum levels of C-reactive protein were significantly higher for the patients in group II. The re-occurrence of fever was 26.5% in the group II and 33.3% in the group, however this difference was not statistically significant (p>0.05).

Conclusions: The decision of the treatment choice of patients with MIS-C should be individually evaluated. In the clinically severe MIS-C patients who were with hypotension, and/or admitted to PICU should be treated with IVIG plus methylprednisolone. However, randomized double-blind studies are required for the treatment modalities of children with MIS-C.

Background

Since April 2020, a group of children with the symptoms and laboratory findings of hyperinflammatory course was reported (1-4). These children mimicked atypical Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome, and finally described as multisystem inflammatory syndrome in children (MIS-C) (5-7). The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) described this post-infectious inflammatory response of the immune system and released their diagnostic criteria (8,9).

The treatment modalities of MIS-C are mainly based on Kawasaki disease and new experiences derived from the adults with COVID-19 (Coronavirus Disease 2019) experiencing cytokine storm. For now, intravenous immunoglobulin (IVIG) alone or in combination with corticosteroids is the most commonly used treatment modality (10-14). There are also other drugs or treatment protocols that were applied to unresponsive or severe cases, including tumor necrosis factor inhibitors or interleukin 1 inhibitors, and

plasmapheresis (5,15,16). Through the first year of the COVID-19 pandemic, the studies mostly focusing on the treatment approaches for children with MIS-C are limited and most of the treatment recommendations are derived from the institutional protocols.

This study aimed to evaluate the treatment modalities for children with MIS-C and to compare the outcome and indications for use of IVIG plus methylprednisolone vs IVIG alone in children with MIS-C.

Methods

Patients and Settings

This retrospective cohort study was conducted during the period between April 1, 2020, and November 1, 2021, at the Health of Sciences Faculty of Medicine Dr. Behçet Uz Children's Hospital. The hospital is a referral center for pediatric patients in the Aegean Region of Turkey. All children diagnosed as MIS-C according to CDC criteria was included in the study (8). In addition to the presence of persistent fever, increased inflammatory biomarkers, findings of multi-organ involvement, and exclusion of any other diagnosis, epidemiological linkage to COVID-19 were the criteria of definite diagnosis (8). All patients required proof of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposures via nasopharyngeal real-time reverse-transcription polymerase chain reaction analysis and/or SARS-CoV-2 antibody test. Exposure to a suspected or confirmed COVID-19 case within 4 weeks before the onset of clinical manifestations was also recorded. The exclusion of other diagnoses was performed using several microbiological and molecular diagnostic tests including multiplex PCR tests for common respiratory pathogens, rapid antigen tests for influenza, serological tests for Epstein–Barr virus, conventional culture tests including blood culture and throat culture in addition to peripheral smears, ultrasonography, etc.

Definitions and Treatments:

Fever was defined as a temperature of 38°C or greater by the measurement of infrared thermometers (18). The patients who had fever after the end of IVIG were noted and the time of re-occurrence of fever after the end of the IVIG therapy was recorded. Demographic data, symptoms, and medical history of the patients, and characteristic features of the patients were collected via the electronic medical record system and patient files.

The patients were divided in two groups according to whether they were administered IVIG alone or IVIG plus methylprednisolone as an initial treatment for MIS-C. While the patients in group I were administered IVIG with a dosage of 2 gr/kg, the patients in group II were administered IVIG (dosage of 2 gr/kg) plus methylprednisolone (2 mg/kg/day).

Statistics:

Statistical analysis was performed using SPSS Statistical Software (version 22; SPSS, Chicago, IL, USA). Categorical variables were compared using Pearson $\chi 2$ and Fisher's exact tests. Numerical variables were compared using the t-test or the nonparametric Mann-Whitney U test (depending on whether they show

normal distribution or not). Continuous variables were presented as means±standard deviation and categorical variables as frequencies and percentages.

Ethics approval for this study was obtained from the Institutional Review Board of Dr. Behcet Uz Children's Training and Research Hospital.

Results

A total of 91 patients with MIS-C were included in this study. Sixty-one (67.0%) patients were male and 30 (33.0%) were female. The median age of patients was 6 years 6 months (range 5 months to 17 years). Of patients, 45 (49.5%) were ≤6 years of age and 22 (24.1%) were ≥12 years of age. Among 91 patients, 84 (92.3%) were previously healthy, while 7 (77 %) had underlying disease including asthma in 3 patients and one each with prematurity, cerebral palsy, Bardet-Biedel syndrome, and osteopetrosis.

Epidemiological information:

Among 91 patients with MIS-C, 4 (4.4%) had positive real-time PCR results for SARS-CoV-2. The history of contact with a COVID-19 case was detected in 42.9% of MIS-C cases (n=39). Seventy (76.9%) patients had positive for COVID-19 immunoglobulin G and seven patients (7.7%) had positive for COVID-19 immunoglobulin M.

The rate of fever, hypotension, tachycardia, and other symptoms of the patients with MIS-C:

The fever was present in all the patients, and the median duration of fever before admission to the hospital was 5 days (minimum 1 to 12 days). Among the patients, 20.9% (n=19) had hypotension and 22.0% (n=20) of the patients had tachycardia. Eight patients (8.8%) had difficulty at breathing. The symptoms of the patients were summarized in table-1.

Echocardiographic findings:

Among 91 patients, systolic dysfunction [ejection fraction (EF) below <50%] was present in 10 (11.0%) patients and coronary artery involvement was present in 5 (5.5%) patients. One patient experienced pericardial effusion (1.0%). The mitral valve regurgitation was present in 33 (36.2%) of the patients (table-1).

Treatment modalities of the MIS-C:

Of 91 patients, 22 (24.2%) were followed up in the pediatric intensive care unit (PICU) and 69 patients (75.8%) were followed up in the pediatric infectious diseases ward (table-2). The median duration of fever after hospitalization was 1 day (range 1 to 7 days). The median duration of hospitalization in the hospital was 9 days (2 days to 55 days) and the median duration of PICU stay of 23 patients was 5 days (range 2 to 50 days).

The initial treatment was intravenous immunoglobulin alone at 42 patients (46.2%)and intravenous immunoglobulin plus steroid with a dosage of 2 gr/kg was administered at 49 patients (53.8%).

Low molecular weight heparin was initiated in 65.9% of the patients (n=60). Acetylsalicylic acid was given to 53 (71.9%) patients with low dosage after discharge (after ceasing low molecular weight heparin). Eighteen patients (19.8%) required inotropic agents and 14 patients (15.4%) required respiratory support including high-flow nasal cannula. During follow-up, no mortality was observed in our study cohort.

What effect the decision for an initial steroid to IVIG at MIS-C duration of fever and time to start IVIG:

The median age of the patients in the group II was significantly higher compared to the patients in group I (96 months, 5 to 168 months vs 51 months,16 to 204;p<0.001). The ratio of severe MIS-C patients in the group II was 36.7% (n=18) and significantly higher compared to the rate of severe MIS-C patients in the group I (n=4, 9.5%) (p=0.01). The rate of moderate and mild MIS-C in the group II was 16.3% (n=8) and 46.9% (n=23), consecutively. The rate of moderate and mild MIS-C in the group I was 66.7% (n=28) and 23.8% (n=10). The rate of admission to PICU was 34.7% in the group II and 14.3% in the group I and the difference was significantly higher in the group II (p=0.026). The rate of hypotension was significantly higher in the group II (30.6%, n=15) compared to the group I (9.5%, n=4) (p=0.014). There was no significant difference was present regarding EF between two groups (p>0.05).

The platelet count and lymphocyte count were significantly lower in the group II compared to the group I (p=0.005 and p=0.0119) (table-2). The mean serum levels of C-reactive protein (CRP) values were significantly higher in the group II, while there was no significant difference at other laboratory variables present in two groups (p>0.05).

The prognosis and the treatment of choice:

The re-occurrence of fever was 26.5% (n=13) in the group II and 33.3% (n=14) in the group I and no significant difference was present (p<0.05). The rate of respiratory support was 14.3% (n=7) in the group II and 9.5% (n=4) in the group I, and there was no significant difference between the groups (p>0.05). The mean hospitalization duration was 9.9 ±1.2 days (2 to 55 days in the group I and 10.4 ±0.6 days (4 to 20 days) in the group II and no significant difference was present between these two groups (p>0.05)

Discussion

In this study, we shared our experience with children with MIS-C and the outcome of the patients treated with IVIG alone or combination with corticosteroids. Among 91 patients, intravenous immunoglobulin alone in 42 patients (group I, 46.2%), and intravenous immunoglobulin plus steroid were administered in 49 patients (group II, 53.8%). l Corticosteroid combination therapy regime with IVIG in treatment of patients with MIS-C was significantly higher especially in children who had admitted to the PICU and/or had hypotension. When we compared the impact of two treatment strategies on the outcome, no

statistical difference was found regarding the duration of hospital stay in addition to recovery of fever. No patient died during the study period.

According to the systemic reviews at the beginning of the pandemic, IVIG was the most used treatment modality with a rate of 76.4% at 662 patients and corticosteroids followed by other drugs including corticosteroids with a rate of 52.3% (19). However, towards the end of a complete year with the COVID-19 pandemic, the combination of IVIG and steroids has been involved in leading treatment regimens (18). A recent retrospective study, including 181 MIS-C patients that compared the response of IVIG alone and in combination with steroid treatment approaches showed that the use of IVIG in combination with steroid treatment has more favorable outcome (18). While the failure to respond in terms of fever was present at 9% in the IVIG and methylprednisolone group and 51% in the IVIG alone group; and the significant failure rate was significantly higher in the IVIG group (19). Similarly, in another study, Belhadjer et al. suggested that IVIG plus steroids were associated with faster cardiac recovery in patients with MIS-C (10). The United Kingdom guidelines recommended using IVIG alone in the initial periods of the COVID-19 pandemic (13), while recent articles were more likely to favor the initial combination with IVIG and steroids (10, 18). In our study, regarding recovery fever, no significant difference was present between IVIG and IVIG plus steroid group. In a recent study, Ouldali et al. reported that among the 72 patients with MIS-C under the alone IVIG treatment group, corticosteroids were added to only a total of 13 patients (18.1%), supporting our findings(18).

The decision for adding a steroid to the IVIG at admission in patients with MIS-C is not specified by strict criteria. In two different studies from Turkey, Ozsurekci et al. and Alkan et al. reported that all patients were administered high dose IVIG and concomitant corticosteroids (20, 21). The indications for initial IVIG and steroid combination were mainly associated with the patient's clinical severity such as depressed EF, presence of hypotension, and/or respiratory insufficiencies, which were mainly included in the criteria of moderate and severe MIS-C definition (14). In our study, the rate of severe MIS-C and hypotension was significantly higher in the combination treatment, which probably led to more PICU admission. A variety of early and late reports concerning the treatment modalities were present and emerging. However, not only rapid and accurate diagnosis is important, but also determining the severity score of the MIS-C is also important for deciding treatment modalities.

In this study, the variables which are part of the outcome including the rate of hospitalization in PICU, duration of fever, and hospital durations do not differ in the steroid added group which was different from the findings of previous studies (10, 18). The current study revealed no difference regarding duration of hospitalization in the IVIG plus steroid group compared to the other groups, which may be associated with the selection bias. Since this was not a randomized controlled study, the clinicians tended to use corticosteroids and IVIG together in the critical patients which might be more likely to require longer hospitalization and rehabilitation durations. Beyond this, it must be emphasized that we did not observe any mortality during the study period and only one patient required immunomodulatory treatment, suggesting the possible efficiency of current treatment strategies for the patients with MIS-C.

This study inherits several limitations due to its design. First, it was not a randomized trial, thus possible confounding factors resulting in bias cannot be controlled. The decision to add initially steroids to IVIG was mostly subjective, for example, IVIG in combination with steroid was administered to more critical patients, which also affects some outcome-related variables such as hospital stay. However, to overcome this bias, we tried to set up, criteria for severe and moderate MIS-C definitions (14). In addition, the sample is small to generalize our findings, however, regarding the limited number of studies focusing on the treatment of MIS-C, our study gives additional useful data to help clinicians.

Conclusions

the decision of the MIS-C patients, to treat with IVIG plus methylprednisolone or IVIG alone, should be individually evaluated. In the severe MIS-C patients with hypotension and admitted to PICU, treatment with IVIG in combination with methylprednisolone should be considered. Still, randomized double-blind studies are required for the treatment modalities of children with MIS-C.

Declarations

Ethics approval and consent to participate:

approved from local committee of ethics.

Consent to participate:

Written informed consent was obtained from all individual participants included in the study.

Availability of supporting data:

The data and materials supporting the conclusions of the study are available from the corresponding author on reasonable request.

Competing interests:

Ilker Devrim had an educational grant from BD and Ilker Devrim has educational webinars for BD. However, all authors have no conflicts of interest about this manuscript

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Authors' contributions:

İD, AAK had analyzed and interpreted the data, and İD, NB, HA, TM were the contributors in writing the manuscript. EB, EK, ŞŞ, MYC, EC, MD, KOA, DB, PS, GV collected data. All authors read and approved the final manuscript.

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Tables

Table-1: The symptoms and features of the children with multisystem inflammatory syndrome in children

Presenting symptoms	**Number**	**Percentage(%)**
Fever	91	100
Cough	10	11.0
Abdominal pain	32	35.2
Chest pain	3	3.3
Vomitting	33	36.3
Diarrhea	27	29.7
Rash	28	30.8
Edema of the extremities	14	15.4
Periungal desquamation	7	7.7
Conjuctivitis	29	31.9
Headache	5	5.5
Cervical Lympadenopathy	8	8.8
Clinical evaluation	Number	Percentage(%)
Hypotension	19	20.9
Tachycardia	20	**22.0**
Tachypnea	8	**8.8**
Echo findings	Number	Percentage(%)
Systolic dysfunction	10	11.0
Coronary artery involvement	5	5.5
Pericardial effusion	1	1.1
Mitral valve regurgitation	33	36.2%
Severity score	Number	Percentage(%)
Mild	51	56.0
Moderate	18	19.8
Severe	22	24.2
The place of admission	Number	Percentage(%)
PICU	22	24.2
Pediatric Infectious Disease Unit	69	75.8

Table-2: The comparison of laboratory parameters between the groups with IVIG versus IVIG plus methylprednisolone

	IVIG alone (n=42)	IVIG plus methylprednisolone (n=49)	p value
WBC (cells/μL)	11506 (2130-23800)	10445 (1050-26170)	>0.05
ANC (cells/μL)	7737 (750-16290)	8217 (2240-23430)	>0.05
ALC (cells/μL)	2635 (510-9060)	1685 (270-7600)	0.01
PLT (cells/μL)	242238 (84000-546000)	188204 (61000-419000)	0.005
Fibrinogen (mg/dL)	616 (350-1496)	630 (320-1264)	>0.05
D-dimer (ng/mL)	957 (150-3883)	1240 (150-9924)	>0.05
CRP (mg/dL)	11.6 (0.00-32.3)	15.4 (0.00- 35.7)	0.043
ESR (mm/h)	68.27 (18-142)	72.14 (5-133)	>0.05
Ferritin (μg/L)	558.66 (54.7-2572)	778.99 (77.24-5546)	>0.05
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PLT, platelet count; WBC, white blood cell count.			