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META ANALYSIS

A systematic review and meta-analysis on the effectiveness of intravenous immunoglobulin plus corticosteroids vs immunoglobulin alone as an initial therapy of COVID-19 associated Multisystem Inflammatory Syndrome in children (MIS-C)

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) is the most severe pediatric disease associated with COVID-19 for which the optimal therapeutic strategy remains unknown. There have been studies that aim to describe treatment outcomes but have conflicting findings. Evidence is urgently needed to support treatment decisions for MIS-C.
Objective: This study aims to compare the effectiveness of intravenous immunoglobulins (IVIG) plus corticosteroids versus IVIG alone as initial therapy in MIS-C, in terms of decrease in left ventricular dysfunction, decrease in inotropic support, reduced need for adjunctive immunomodulatory treatment, favorable fever course, decrease in mechanical ventilator use, decrease in admission to the pediatric intensive care unit, and decrease in coronary artery aneurysm.
Methodology: Published articles reporting MIS-C treatment outcomes were searched through various databases. A structured data extraction was employed and risk of bias was assessed with Newcastle-Ottawa Scale. Corticosteroid effects were reported as pooled odds ratio and forest plots were generated for each outcome.
Results: The effect on the components of hemodynamic support showed no significant difference between the two treatment groups: left ventricular dysfunction (P-value= 0.86), inotrope use (P-value = 0.65), mechanical ventilator use (P-value = 0.21), and admission at the PICU (P-value = 0.87). However, initial treatment with IVIG plus corticosteroids, was associated with a more favorable fever course (P-value = < 0.02), less use of adjunctive immunomodulatory therapy (P-value = < 0.00001), and less incidence of coronary artery aneurysm (P-value = < 0.04).
Conclusion: Initial treatment with IVIG plus glucocorticoids was associated with a more favorable fever course, less use of adjunctive immunomodulatory therapy, and less incidence of coronary artery aneurysm than IVIG alone.

Introduction

Since the beginning of Coronavirus disease 2019 (COVID-19) pandemic, it has generally been thought that children have an overall milder clinical course and more favorable outcome compared to adults [1]. However, there is a subset of pediatric patients who develop an unusual pediatric syndrome called Multisystem Inflammatory Syndrome in Children (MIS-C). The exact epidemiology of this emerging disease is still not known, but geographical and temporal distribution— having a predilection to males and Hispanic or non-Hispanic Black has been described [2]. The clinical presentation of MIS-C varies from mild fever, rash or mild gastrointestinal symptoms such as diarrhea and vomiting, to life-threatening complications including vasodilatory or cardiogenic shock, and acute myocardial dysfunction. The severity of what may evolve from this syndrome calls for an urgent need to understand this disease process [3].

There have been multidisciplinary efforts that aim to form a consensus on the diagnostic criteria and immediate approach to treatment of MIS-C [4]. Therapies have included intravenous immunoglobulin (IVIG), glucocorticoids, biologic agents and a combination of one or the other. While there are no clinical practice guidelines regarding treatment of MIS-C, this current management, which was patterned from treatment plans of diseases with similar features to MIS-C, has yielded favorable outcomes [5]. Due to similar features of Kawasaki Disease and MIS-C, many children with MIS-C have received empirical treatment based on Kawasaki guidelines, with IVIG alone or combined with corticosteroids [6]. Findings of myocarditis in many patients with MIS-C also supported treatment with IVIG, given its use in clinical practice for viral myocarditis. Features of cytokine storm found in MIS-C also led to the use of dexamethasone as seen in patients with acute COVID-19. Lastly, the frequent concurrent finding of a severe shock like presentation in patients with MIS-C encouraged the use of glucocorticoids [7].

Randomized clinical trials for treatment strategies in MIS-C have been challenging because cases are sporadic after waves of COVID-19 [7]. Currently, there have been published studies confirming the use of the said immunomodulatory therapies, but only a few describe the outcomes in relation to the specific treatment modalities. *The New England Journal of Medicine* described two large observational trials – results of which have seemingly conflicting findings. In one hand, a study of Son, *et al*. including 518 patients with presumptive MIS-C showed that initial treatment with IVIG plus corticosteroid was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIG alone. In their study, they also showed that the use of adjunctive immunomodulatory therapy and risk of persistent or recurrent fever are lower with combination therapy of IVIG and corticosteroids [8]. On the other hand, a study of McArdle, *et al*., including 614 children of suspected MIS-C found no evidence of differences in outcomes between primary treatments with IVIG alone, or IVIG plus corticosteroids [9]. Another study from France by Ouldali, *et al.*, showed that combination treatment with IVIG and methylprednisolone vs IVIG alone was associated with not only a more favorable fever course, but also less severe acute complications including acute left ventricular dysfunction and hemodynamic support requirement [6]. Based on these findings, the early outcomes of these large observational studies seem to have conflicting results

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regarding the efficacy of immunomodulation with IVIG, corticosteroids or both. Currently, it remains unclear how best to carry out such a treatment strategy for MIS-C and which patient group will yield the best benefit.

This study thus aims to address the gap of the evaluation of clinical outcomes in patients with MIS-C, which could provide insight into the efficacy of various immunomodulatory therapies. Despite its rarity, MIS-C is of significant concern due to the severity of the illness, with majority of children requiring intensive care treatment [10]. Treatment strategies used in other hyperinflammatory syndromes have been employed to modulate the dysregulated hyper-inflammation apparent in MIS-C. Currently, there is still no evidence for the most effective therapeutic approach for this emerging disease.

This paper aims to review the effectiveness of IVIG combined with corticosteroids as a primary treatment in patients with MIS-C. It aims to determine whether an effect exists, based on several outcomes namely left ventricular dysfunction, use of inotropes, adjunctive immunomodulatory treatment, course of fever, use of mechanical ventilator, admission at the PICU, and coronary artery aneurysm.

Objectives of the Study

A. General Objective

This study aims to review the effectiveness of combined therapy of IVIG and corticosteroid versus IVIG alone as initial therapy of MIS-C

B. Specific Objectives

1. To determine if the use of IVIG plus corticosteroid therapy is associated with decreased incidence of cardiovascular dysfunction (LVEF <55%)
2. To determine if the use of IVIG plus corticosteroid therapy is associated with decreased use of inotropes
3. To determine if the use of IVIG plus corticosteroid therapy is associated with a reduced need for adjunctive immunomodulatory treatment after initial therapy
4. To determine if the use of IVIG plus corticosteroid therapy is associated with a more favorable course of fever in MIS-C
5. To determine if the use of IVIG plus corticosteroid therapy is associated with decreased use of mechanical ventilator
6. To determine if the use of IVIG plus corticosteroid therapy is associated with decreased admissions at the Pediatric Intensive Care Unit
7. To determine if the use of IVIG plus corticosteroid therapy is associated with decreased incidence of coronary artery aneurysm

Methodology

2.1 Search Strategy

The methods used in this study adhere to the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All observational studies and case reports with MIS-C were searched using a two-level search strategy. First, a systematic search was performed using various databases. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries.

Appropriate free-text words and Medical Subject Headings (MeSH) were used. The following free text and MeSH terms were used to search all trials registers and databases: key words ["Multisystem Inflammatory Syndrome in Children," "MIS-C," "SARS-CoV-2," "Coronavirus," "COVID-19," "children"] and ["steroid," "corticosteroid," "methylprednisone," "methylprednisolone," "immunomodulatory," "IVIG," "treatment," "outcome"]. Search dates were from August 10, 2021 to October 14, 2021.

Two independent and blinded authors (G.C. and S.V.) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria. Any discrepancies were resolved by discussion and consensus.

2.2 Study Selection

Published articles reporting treatment outcome of MIS-C cases were included. Articles were included if the studies met the criteria as follows:

1. Population including diagnosed or presumptive MIS-C ages 0-18 years old, following the established diagnostic criteria
2. Studies that included IVIG alone and combination of IVIG and corticosteroid as initial treatment
3. Studies that have an explicit treatment process
4. Studies that evidenced specific outcomes based on the given treatment modality (left ventricular ejection fraction < 55%, course of fever, use of inotropes, hemodynamic and respiratory support, coronary artery aneurysm)

The following studies were excluded:

1. Studies for which data and full text are not available
2. Studies that did not include combined IVIG and corticosteroid therapy
3. Studies that did not specify the outcome per treatment modality
4. Studies that were published before the COVID-19 pandemic (March 2020)

2.3 Risk of Bias Assessment

Risk of bias was assessed for all eligible observational cohort studies according to the Newcastle-Ottawa Scale (NOS). A 'star system' was used in which a study is judged on three broad perspectives: (1) the selection of the study groups, (2) the comparability of the groups and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. An overall risk of bias was independently assigned to each eligible study by two researchers (S.V. and K.P.), and a third reviewer (G.C.) was consulted for any disagreement.

2.4 Data Extraction

A structured data extraction form was employed to standardize the identification and retrieval of data from manuscripts. The following information was extracted: author, year of publication, type of study, country of the study, sample size, age, gender, race, co-morbidities, clinical symptoms, laboratory data, diagnostic tests, inflammatory markers, cardiac biomarkers and echocardiography, chest radiograph, therapeutic agents, and outcomes (hospitalization, intensive care unit admission, complications, or death). Data from each eligible study were extracted by two independent reviewers (G.C. and K.P.). Disagreements regarding the extracted data were resolved through discussion and consensus of a third author (S.V.).

2.5 Statistical Analysis

In the present meta-analysis, seven dichotomous outcomes namely: (1) left ventricular dysfunction, (2) inotrope use, (3) adjunctive immunomodulatory treatment, (4) course of fever, (5) mechanical ventilator use, (6) PICU admission, and (7) incidence of coronary artery aneurysm were considered in the meta-analysis. Effects of IVIG plus corticosteroid to the above-mentioned outcomes were calculated and reported as pooled odds ratio. For visual presentation, forest plots were generated for each outcome. Test for heterogeneity was carried out based on Cochran's Q and I2. Cochran Q-value with p-value less than 0.05 was considered significant. As a guide, I2 values of 25% may be considered low, 50% moderate, and 75% high. For cases with moderate to high heterogeneity, a random effects model was used to provide a conservative prevalence estimate otherwise fixed effect model was preferred. Calculations were performed using Review Manager version 5.4 software. Publication bias was also evaluated using the same software. Discrepancies regarding the studies were discussed by the authors and resolution was done after considering the disagreements.

Results

3.1 Qualitative Results

3.1.1 Study Characteristics

The baseline characteristics of the three studies included are shown in Table 1.1. Study designs are the same for all studies included— retrospective cohort. Two studies based their diagnosis of MIS-C on World Health Organization (WHO) Criteria, while one study based their diagnosis on Center for Disease Control and Prevention (CDC). Studies included both presumptive and confirmed MIS-C cases. A summary of the demographic details of the studies included is seen in Table 1.2.

Treatment

A variety of anti-inflammatory treatments were reported with majority of the population having received IVIG alone. In the studies of McArdle and Ouldali, 40% and 65% respectively of the population reported to have used IVIG alone, compared to the study of Son & Murray where majority of the population was given a combination treatment of IVIG and Glucocorticoids. The treatment regimens are summarized in Table 2.

Table 1. 1. Characteristics of each included studies at baseline

Variable	Study 1		Study 2		Study 3	
Author, Year	McArdle, 2021		Ouldali, 2021		Son & Murray, 2021	
Study Design	Retrospective Cohort		Retrospective Cohort		Retrospective Cohort	
Demographic characteristics						
Country	Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Costa Rica, Egypt, Finland, France, Germany, Greece, Honduras, Hongkong, Hungary, India, Italy, Kenya, Melta, Mexico, Norway, Panama., Paraguay, Peru, Poland, Russia, Spain, Sweden,Switzerland, Netherlands, Turkey, Ukraine, UK, USA, Zimbabwe		France		United States	
Total cases	614		181		596	
Basis of Diagnosis of MIS-C	WHO		WHO		CDC	
Treatment Group	IVIG + Cortico-steroid	IVIG	IVIG + Cortico-steroid	IVIG	IVIG + Cortico-steroid	IVIG
Number of Cases	208	246	34	72	241	89
Male/Female – no.	127/81	157/89	18/16	32/40	135/106	49/40
Age- year (Median)	8.8	7	9	8.1	8.6	5.5
	(5-12)	(3.7-11)	(5.1-12.9)	(4.6-11.9)	(4.6-12)	(2.5-10.5)
Race and ethnic group – no (%)						
White, non-Hispanic	95	124	*	*	31	12
Black, non-Hispanic	33	30	*	*	94	27
Hispanic, Latino	60	33	*	*	80	27
Asian	8	28	*	*	9	4
Other race, non-Hispanic	12	31	*	*	14	3
Comorbidities	5	5	9	14	48	21
Clinical characteristics						
Gastrointestinal Manifestations	65%	53%	97%	92%	*	*
Neurological Symptoms	30%	30%	50%	50%	*	*
Respiratory involvement	19%	17%	21%	28%	*	*
Laboratory Markers						
WBC (10^9/L)	9.9 [7-14]	9.9 [7.1-14]	11.4 [7.4–13.1]	10.8 [8.1–16.4]	*	*
D-Dimer (ng/mL)	2100 [980 – 4000]	2300 [1000 - 4400]	4000 [1661–5329]	2737 [1049–4047]	*	*
Troponin (ng/L)	50 [30 - 260]	18 [8.0 - 55]	85 [15–168]	113 [26–408]	80 [20-560]	150 [20-7500]
BNP (ng/L)	160 [65 - 820]	74 [20 - 400]	*	*	483.6 [103-1062.9]	147 [50.7-333.3]
CRP (mg/L)	150 [90 - 250]	150 [82 - 210]	*	*	*	*
Ferritin (ug/L)	560 [300 - 920]	410 [200 - 620]	400 [287–598]	409 [202–814]	*	*
Fibrinogen	5.8 [4.5 - 7.0]	5.6 [4.5 - 6.4]	5.7 [4.3–6.5]	6.5 [5.1–8.1]	*	*
LDH (U/L)	330 [250 - 480]	350 [280 - 460]	*	*	*	*

" * " - Not specified in the study
"WHO" – World Health Organization
"IVIG" – intravenous immunoglobulin
"BNP" – brain natriuretic peptide
"CRP" – c-reactive protein
"LDH" – lactate dehydrogenase test

Table 1. 2. Overall Characteristics of Included Studies

Characteristics	Results		
	Overall	IVIG + Corticosteroid	IVIG
Age, years	7.9 ± 2.1	8.7 ± 1.8	6.9 ± 2.0
Gender			
Male	518 (58.2)	280 (58.0)	238 (58.5)
Female	372 (41.8)	203 (42.0)	169 (41.5)
Ethnicity			
White, Non-hispanic	262 (33.4)	126 (28.1)	136 (40.6)
Black, Non-hispanic	184 (23.5)	127 (28.3)	57 (17.0)
Hispanic, Latino	200 (25.5)	140 (31.2)	60 (17.9)
Asian	49 (6.3)	17 (3.8)	32 (9.6)
Others	92 (11.7)	26 (5.8)	66 (19.7)
Pre-existing condition	102 (11.5)	62 (12.8)	40 (9.8)

- "IVIG" – intravenous immunoglobulin

Table 2. Characteristics of Treatment and Outcome Assessment of Included Studies

Variable	Study 1	Study 2	Study 3
	McArdle, 2021	Ouldali, 2021	Son & Murray, 2021
Treatment Modality			
IVIG alone	246 **(40%)**	72 **(65%)**	89 (17%)
IVIG + Glucocorticoids	208 (34%)	34 (31%)	241 **(46%)**
IVIG + Glucocorticoids + Biologic	*	*	107 (20.7%)
Glucocorticoids alone	99 (16%)	*	
Other Treatments	22 (3.6%)	*	81 (16.3%)
None	39 (6.4%)	5 (4%)	*
	614	**111**	**518**

- " * " - Not specified in the study

3.1.2 Risk Assessment Bias

Articles eligible for inclusion in the overall meta-analysis were independently assessed for quality by three reviewers (G.C., K.P., S.V.) using the Newcastle– Ottawa Quality Assessment Scale (NOS) for cohort studies.

3.2 Quantitative Results

Meta-analysis outcomes can be seen in Figure 1.

3.2.1 Decrease In The Incidence Of Left Ventricular Dysfunction

Based on the outcome being measured, which is decrease in the incidence of left ventricular dysfunction, McArdle favors the use of IVIG alone, while the other two studies favor the combination therapy of IVIG and corticosteroids. The I^2 Value shows moderate heterogeneity observed between the trials (P-value of Q = 0.08 and I2 = 60%). However, the P-value confirms the null hypothesis and suggests homogeneity. Hence, fixed effects model was used for calculating the summary or pooled effect. There is no statistical significant difference among the two groups with regards to decrease in the incidence of left ventricular dysfunction (pooled odds ratio = 0.96, 95% confidence interval: 0.61 to 1.52, Z = 0.17, P-value= 0.86).

3.2.2 Decrease In Inotrope Use

Data for the outcome of inotrope use were reported in all trials. There was moderate heterogeneity observed between the trials (P-value of Q = 0.01 and I2 = 77%). Random effects model was used for calculating the summary or

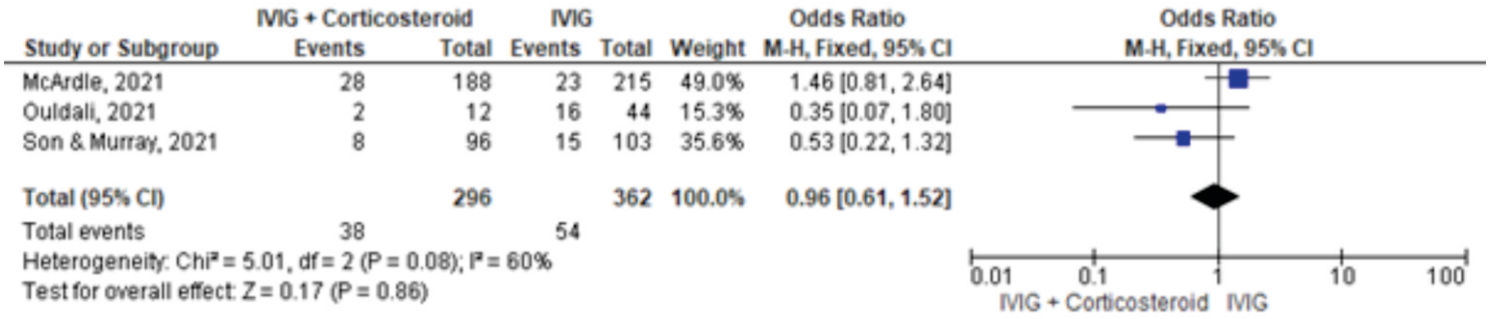

Figure 1.1. Meta-Analysis for Incidence of Left Ventricular Dysfunction between IVIG + Corticosteroid group vs IVIG alone group.

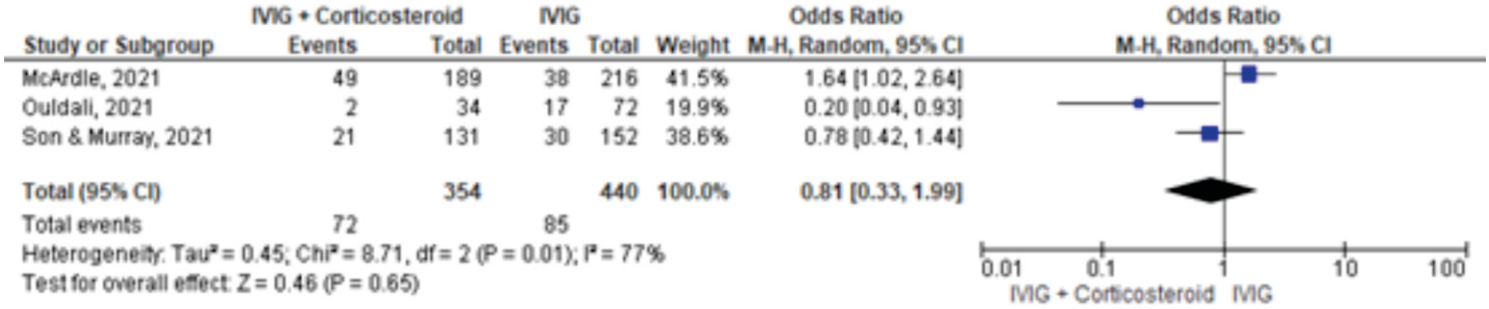

Figure 1.2. Meta-Analysis for Use of Inotropes between IVIG + Corticosteroid group vs IVIG alone group

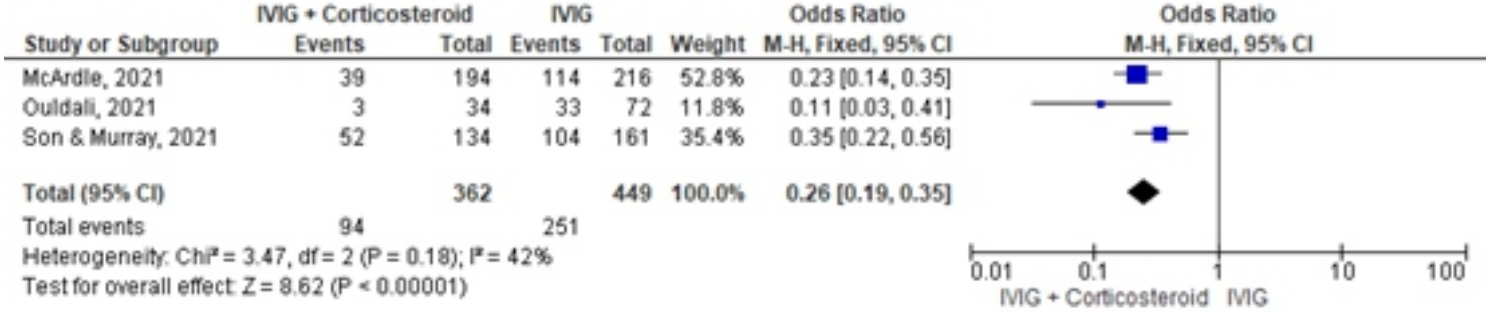

Figure 1.3. Meta-Analysis for Use Of Adjunctive Immunomodulatory Treatment between IVIG + Corticosteroid group vs IVIG alone group

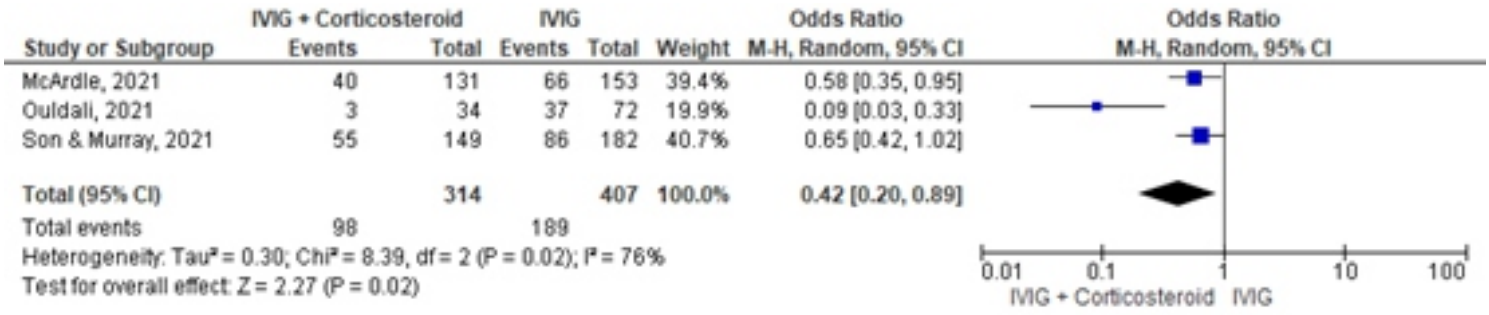

Figure 1.4. Meta-analysis for Favorable Course of Fever between IVIG + Corticosteroid group vs IVIG alone group

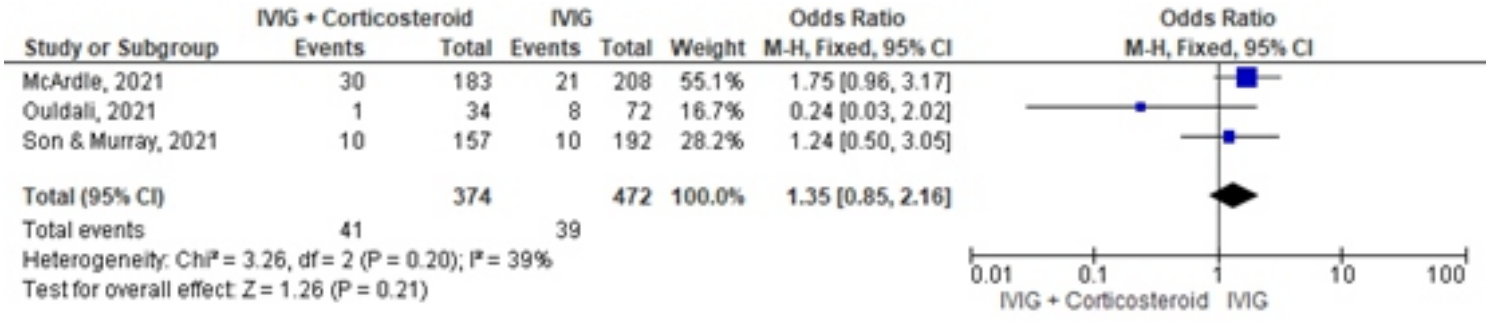

Figure 1.5. Meta-Analysis for Use Of Mechanical Ventilator Between IVIG + Corticosteroid group vs IVIG alone group

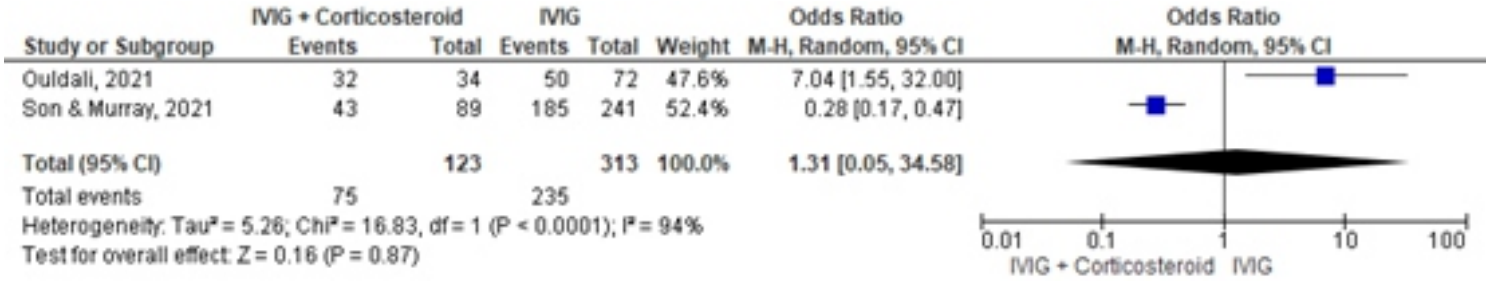

Figure 1.6. Meta-Analysis for Admission at the PICU Between IVIG + Corticosteroid group vs IVIG alone group

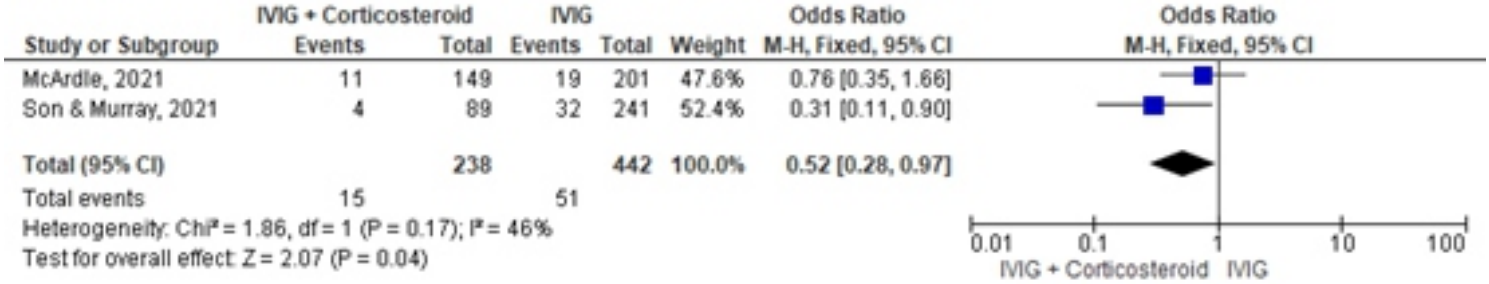

Figure 1.7. Meta-Analysis for Incidence Of Coronary Artery Aneurysm between IVIG + Corticosteroid group vs IVIG alone group

pooled effect. The likelihood of inotrope use in IVIG + corticosteroid group and IVIG group was not statistically different with an odds ratio of 0.81 (95% CI: 0.33 to 1.99, Z = 0.46, P-value = 0.65). Hence the likelihood of decreased inotrope use when IVIG alone is used versus corticoseroids + IVIG is not statistically significant.

3.2.3 Reduced Need For Adjunctive Immunomodulatory Treatment

Data for adjunctive immunomodulatory treatment between IVIG + Corticosteroid group and IVIG group were reported in all trials. There was no significant heterogeneity observed between the trials (P-value = 0.18 and I2 = 42%). Fixed effects model was used for calculating the summary or pooled effect. Adjunctive treatment of IVIG and corticosteroid was associated with a significantly decreased use of adjunctive immunomodulatory treatment with an odds ratio of 0.26 (95% CI: 0.19 to 0.35, Z = 8.62, P-value = < 0.00001) compared to IVIG alone group. Hence, the likelihood of adjunctive immunomodulatory treatment use is 74% lower if patients were given IVIG + corticosteroid as opposed to IVIG alone.

3.2.4 Favorable Course of Fever

Data for favorable fever course between IVIG + Corticosteroid group and IVIG group were reported in all trials. There was moderate heterogeneity observed between the trials (P-value= 0.02 and I2 = 76%). Random effects model was used for calculating the summary or pooled effect. Adjunctive treatment of IVIG and corticosteroid was associated with favorable fever course with an odds ratio of 0.42 (95% CI: 0.20 to 0.89, Z = 2.27, P-value = < 0.02) compared to IVIG group. Hence, the likelihood of a favorable fever course is 42% higher if patients were given IVIG + corticosteroid as opposed to IVIG alone.

3.2.5 Decreased Use Of Mechanical Ventilator

Data for the outcome of mechanical ventilator use were reported in all trials. There was no significant heterogeneity observed between the trials (P-value = 0.20 and I2 = 39%). Fixed effects model was used for calculating the summary or pooled effect. The likelihood of mechanical ventilator use in IVIG + corticosteroid group and IVIG group were not statistically different

with an odds ratio of 1.35 (95% CI: 0.85 to 2.15, Z = 1.26, P-value = 0.21). Hence the likelihood of decreased mechanical ventilator use when IVIG alone is used versus corticoseroids + IVIG is not statistically significant.

3.2.6 Decreased Admission at the Pediatric ICU

Data for the outcome of admission at the PICU were reported in two out of the three trials. There was moderate heterogeneity observed between the trials (P-value= <0.0001 2 and I2 = 94%). Random effects model was used for calculating the summary or pooled effect. The likelihood of admission at the PICU in IVIG + corticosteroid group and IVIG group were not statistically different with an odds ratio of 1.31 (95% CI: 0.05 to 34.58, Z = 0.16, P-value = 0.87). Hence the likelihood of decreased admission at the pediatric ICU when IVIG alone is used versus corticoseroids + IVIG is not statistically significant.

3.2.7 Decreased Incidence of Coronary Artery Aneurysm

Data for the incidence of coronary artery aneurysm were reported in two out of the three trials as shown in Figure VIII. There was no significant heterogeneity observed between the trials (P-value = 0.17 and I2 = 46%). Fixed effects model was used for calculating the summary or pooled effect. Adjunctive treatment of IVIG and corticosteroid was associated with decreased incidence of coronary artery aneurysm with an odds ratio of 0.52 (95% CI: 0.28 to 0.97, Z = 2.07, P-value = < 0.04) compared to IVIG group. Hence, the likelihood of coronary artery aneurysm is 48% lower if patients were given IVIG + Corticosteroid as opposed to the IVIG alone group.

Discussion

Since the beginning of COVID-19, and emergence of MIS-C in April 2020, cases of MIS-C in the Philippines have been reported [14], and many more internationally [15]. A steep learning curve for the identification, diagnosis, and treatment of this condition has been successful through global communication among multidisciplinary specialists at pediatric centers who faced the challenge of caring for MIS-C patients. With successful collaboration, experts achieved consensus about diagnostic criteria and the need to induce rapid immunomodulation, for which the primary goal is to limit the course of the illness. However, due to lack of available randomized controlled clinical trials, and consensus with regards to therapeutic management, outcomes have been elusive. Hence, treatment plan of IVIG, corticosteroids and other immunomodulators have been patterned with other diseases, fitting with their use in other vasculitic diseases.

MIS-C shares multiple features with Kawasaki Disease, and sometimes even fulfills the criteria of incomplete Kawasaki disease. However, there are some key differences identified, including age distribution, racial/ethnic predilection, and more severe clinical manifestations [3]. Based on this study, the median age of predilection for MIS-C is 7.9 +/- 2 years, compared to Kawasaki disease, which usually affects children ages 5 years old and below. Additionally, based on the summarized findings of this study, MIS-C was more commonly reported in White, Hispanic or Latinos, in comparison to Kawasaki disease, which was more commonly observed in the Asian population. Although MIS-C has overlapping features with Kawasaki disease, the inflammatory storm observed in MIS-C is much more intense. Despite these differences, the resemblance of these pro-inflammatory syndromes helped pattern the therapeutic management for this emerging disease. Hence, the journals included in this study mainly build on earlier studies of Kawasaki Disease in the use of corticosteroids with IVIG [15].

This meta-analysis comprehensively summarized the available published literature and assessed the clinical characteristics, diagnostic assessment, and management and treatment outcome of MIS-C associated with COVID- 19. The salient findings of this study can be summarized as follows: (1) there was no significant difference in the incidence of left ventricular dysfunction after the addition of corticosteroids to the primary treatment of IVIG as opposed to IVIG alone (2) there was no significant difference in terms of use of inotropes and mechanical ventilators, and admission at the PICU after primary treatment with combined IVIG and corticosteroids vs IVIG alone (3) treatment with IVIG and corticosteroids vs IVIG alone was associated with a more favorable fever course (4) the use of adjunctive immunomodulatory therapy was lower among patients who received IVIG plus corticosteroids than among those who received IVIG alone (5) there was a demonstrated reduction in the incidence of coronary artery lesions with the use of corticosteroids together with IVIG for MIS-C patients.

4.1 Decreased Incidence Cardiovascular Dysfunction- Left Ventricular Ejection Fraction < 55%

The etiology of cardiovascular involvement in MIS-C is likely multifactorial. Cardiac injury in MIS-C could have been caused by multiple hypothesized mechanisms, which include cardiomyocyte injury due to an acute and dysregulated inflammatory response related to a cytokine storm, microvascular dysfunction, and a viral invasion of cardiomyocytes resulting in cellular damage and ischemic injury [16]. Cardiovascular involvement was mainly stated in terms of cardiovascular dysfunction measured by left ventricular ejection fraction <55%. But this could also be described with the use of inotropes for hemodynamic support.

It is recommended that patients with immune-mediated myocarditis should be treated with immunosuppressive drugs, such as corticosteroids. This supports the US [8] and French [6] studies of Son & Murray and Ouldali respectively, which showed that patients who received combination therapy (IVIG + corticosteroids) were less likely to have left ventricular dysfunction in terms of LVEF <55 %, as compared to the one published by McArdle [9]. The inconsistent findings between the international studies have been analyzed and accounted for in this study. However, after analyzing these articles together, this meta-analysis shows no statistical significant difference in terms of cardiovascular dysfunction of LVEF <55% between the two treatment groups— IVIG + corticosteroids group and IVIG alone group. Hence it shows that the addition of corticosteroids do not have an additional beneficial effect to the probable immune-mediated myocarditis causing the cardiovascular dysfunction in MIS-C patients.

Some features of this emerging pediatric disease are similar to those of Kawasaki disease, and share some aspects of the physiology with each other, justifying the use of IVIG and corticosteroids. However, Kawasaki disease manifests mainly with low systolic blood pressure or clinical signs of poor perfusion [17], as compared to MIS-C where left ventricular systolic dysfunction has been present in a number of patients in association with low systolic blood pressure [18]. Therefore, in line with the study of Belhadjer et al, with heart failure as an inclusion criterion, even with the use of IVIG with or without the addition of corticosteroids, blocking or preventing the cytokine storm might not be enough. Hence, the result of this meta-analysis presumes that despite initial treatment with IVIG with or without corticosteroids, the additional determining factors for a favorable outcome in terms of left ventricular dysfunction (LVEF <55%) include proper patient stabilization, and hemodynamic support.

Although corticosteroids may improve cardiac dysfunction by mitigating the excessive immune response, its effectiveness in conjunction with IVIG will still depend on the severity of acute injury and the degree of left ventricular systolic dysfunction requiring support for hemodynamic stability. This can explain why the advantage of adding corticosteroids to IVIG therapy in MIS-C is limited, and did not demonstrate significant findings in this current meta-analysis.

4.2 Decreased Incidence Of Cardiovascular Dysfunction- Decrease In Inotrope Use, Pediatric Icu Admission, Mechanical Ventilator Use

Another indicator of the hemodynamic instability and eventually shock related to the morbidity in MIS-C patients is the use of inotrope, subsequent admission to the PICU, and need for mechanical ventilatory support. The largest French and U.S. studies included in this study found 67% and 80% of cases required ICU support, respectively. Low to moderate doses of vasoactive agents, including vasopressors and inotropes, were frequently administered to MIS-C patients admitted to the ICU due to shock resulting from myocardial involvement and severe vasoplegia. Mechanical ventilation use was also noted in substantial proportion of patients, with 10%–62% of MIS-C patients requiring invasive support in the ICU [19].

There are proposed mechanisms of action of corticosteroid for shock treatment as follows: 1) corticosteroids are required for normal cardiac function, and their cardiovascular effects are both inotropic and vascular—to enhance effects of catecholamines and provide an adrenergic blockade; 2) corticosteroids stabilize membranes, enhancing the integrity of capillaries and affecting lysosomal membrane stability; 3) they improve tissue metabolism; and 4) catecholamines may also be useful in terms of their other mechanisms of action, which include the prevention of tissue breakdown and direct detoxification of endotoxin.

Since a significant proportion of MIS-C patients are admitted at the ICU, often requiring cardiac or respiratory support, this study analyzed if the addition of corticosteroid to primary treatment of IVIG has a significant beneficial effect to these factors in MIS-C. Based on this meta-analysis, the other composites of shock aside from left ventricular dysfunction, mentioned above such as admission at the Pediatric ICU, vasopressor or inotropic use, and mechanical ventilator use showed no statistical significant difference between the two treatment groups of IVIG + corticosteroid vs IVIG alone group.

Although corticosteroids have been reported to have a favorable effect on shock resolution in other vasculitic diseases and cytokine storms, this current meta-analysis confirms that no recommendation can be made for children with MIS-C for its use in preventing ICU admission, inotrope use, and mechanical ventilator use. A detailed elaboration of diverse doses and length of corticosteroids administration for patients who suffer from hemodynamic instability and shock in MIS-C were not investigated in this meta-analysis, which is a significant variable to consider. This may have varied among the studies included, and could have caused discrepancies. Additionally, although the role of corticosteroids as immunosuppressant in cases if septic shock have been reported, severe cases in MIS-C present with vasodilated or cardiogenic shock that requires fluid resuscitation, muscular support, and even mechanical ventilation and extracorporeal membrane oxygenation (ECMO) [20]. This could explain why the benefit of adding corticosteroids to IVIG therapy in MIS-C is limited, and thus did not show significant positive findings in this current meta-analysis.

4.3 Favorable Fever Course And Decreased Incidence Of Coronary Artery Aneurysm

Significantly, in all three studies, patients who received combination therapy of IVIG and corticosteroids were less likely to have persistent or recurrent fevers. This meta-analysis also shows that the likelihood of a favorable fever course is 42% higher if patients were given IVIG + Corticosteroid as opposed to IVIG alone. Steroid treatment is already utilized in a broad range of vasculitis to great effect. Furthermore, steroids were a key part of Kawasaki Disease treatment prior to the advent of IVIG. Research into the exact pathological mechanisms is ongoing and current theories of pathogenesis implicate immunological responses to infectious agents [21]. Such reactions are thought to be controllable via steroid administration due to a reduction in inflammatory mediator transcription. In the context of Kawasaki Disease, this may mean lower levels of inflammation, and subsequently, a reduction in fever and faster normalization of temperature. This could explain the positive findings of this study, with regards to beneficial effect of combination therapy of IVIG + corticosteroids to MIS-C cases.

These findings may also prove to be an essential consideration as to why there was a beneficial effect of combination therapy of IVIG + corticosteroid to the incidence of coronary artery aneurysm. One comparative study indicates that MIS-C more frequently spares the coronary arteries compared to Kawasaki Disease [22]. Nonetheless, coronary artery dilation and aneurysms have been described with incidence of coronary artery abnormalities varying significantly among reports in MIS-C. Most of the larger series have reported coronary changes in 8-24% of patients. Although the majority of patients demonstrated small aneurysms (z-score 2.5 to 5), there have been rare cases of large/giant aneurysms (z-score $\geq$ 10) and aneurysms that developed later during the convalescent period. The pathologic mechanism of coronary artery dilation/aneurysm in MIS-C has not been elucidated. Coronary dilation in MIS-C may be related to fever and circulating inflammatory mediators, or may be due to inflammation and disruption of the arterial wall as is seen in Kawasaki Disease [23]. Hence, the addition of corticosteroids can cause lowering levels of inflammation leading to a reduction in the formation of coronary abnormalities and subsequent incidence of future cardiovascular sequelae.

4.4 Reduced Need For Adjunctive Immunomodulatory Therapy

Additionally, this current meta-analysis showed that corticosteroid used in conjunction with IVIG was significantly associated with a lower risk of use of second-line therapy. Prompt, aggressive immunomodulatory treatment for MIS-C with combined IVIG and corticosteroids help children achieve lower levels of inflammation faster, avoiding the need for additional immunomodulatory therapy. MIS-C has emerged as an important complication of COVID-19 infection among children in low- and middle-income countries [9]. IVIG and other biologic agents are costly and have limited availability in many countries, and so data on which treatment plan provides a lower risk of procuring additional agents will be beneficial. The findings in this meta-analysis then showed that likelihood of adjunctive immunomodulatory treatment use is 74% lower if patients were given IVIG + corticosteroid as opposed to IVIG alone. This finding implies that the combination therapy has a beneficial effect in preventing additional second-line immunomodulatory treatment, and subsequently lessening financial burden in MIS-C cases.

To summarize the findings, this meta-analysis reports that the combination therapy of IVIG and corticosteroids have a beneficial effect when it comes to course of fever, use of adjunctive immunomodulatory therapy, and incidence of coronary artery aneurysm. This observation suggests that IVIG and corticosteroids may act synergistically, although the exact underlying mechanism remains unclear. According to several previous studies on Kawasaki disease resistance, as mentioned in a study by Inoue, *et al*., synergistic effects between corticosteroid and immunoglobulin seem likely because their anti-inflammatory mechanisms apparently involve non-overlapping pathways [24]. A corticosteroid can potentially prevent inflammatory stimulus-induced coronary artery endothelial cell damage by inhibiting the inflammatory stimulus-induced release of damage-associated molecular patterns (DAMPs), including high-mobility group box-1 (HMGB1) and interleukin 1 alpha (IL-1α), which are not targeted by immunoglobulin. This could explain why the combination therapy had a beneficial effect in terms of incidence of coronary artery aneurysm in this meta-analysis. Furthermore, corticosteroids significantly inhibit the expression of IL-1α as well as interleukin 1 beta (IL-1β), of which both cytokines can induce and contribute to IVIG-resistant production of interleukin 6 (IL-6) and granulocyte-colony stimulating factor (G-CSF). Since such effects of a corticosteroid would probably help prevent the progression of IVIG resistance, starting the combination therapy can contribute to fever resolution, and subsequently less use of additional immunomodulators as reflected in the results of this study. However, additional studies are warranted to understand the mechanisms underlying a possible effect of combination therapy of IVIG and corticosteroids in the cardiovascular dysfunction involved in MIS-C.

Conclusion

In conclusion, among children with MIS-C, this meta-analysis found no evidence that the combination therapy of IVIG and corticosteroids have a significant positive effect on the hemodynamic stability in terms of left ventricular dysfunction, use of inotrope, use of mechanical ventilator, and admission at the PICU compared to IVIG alone. However, this study reports that IVIG combined with corticosteroids as initial treatment have a beneficial effect when it comes to course of fever, use of adjunctive immunomodulatory therapy, and incidence of coronary artery aneurysm.

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