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EFFECTIVENESS OF IVIG AND PULSE METHYLPREDNISOLONE IN TREATING MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) ASSOCIATED WITH COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has emerged as a global health concern, leading to significant morbidity and mortality. Post-COVID-19, children have exhibited an increased susceptibility to multisystem inflammatory syndrome (MIS-C). Treatment for MIS-C involved the administration of intravenous immunoglobulin (IVIG) alone or in conjunction with pulse methylprednisolone. For patients with persistent fever, a second-line treatment approach, comprising additional doses of IVIG and methylprednisolone, was considered. A systematic review and meta-analysis were conducted to assess the statistical significance of treatment outcomes. The review included five studies, demonstrating similar efficacy between the two treatment modalities for MIS-C patients. However, the determination of primary outcomes and the need for second-line treatment depended on various clinical factors. The studies exhibited a low risk of bias, and the meta-analysis showed statistical significance with a difference of 0.66 [95% CI, 0.30 to 1.44; p= <0.01] in treatment effectiveness between the two groups. This study provides clinicians with a prompt treatment option and contributes to the enhancement of treatment strategies for MIS-C patients.

Keywords: COVID-19, Multisystem inflammatory syndrome, IVIG treatment, Pulse methylprednisolone treatment, Meta-Analysis

Introduction
The emergence of COVID-19 was first identified in Wuhan, China, in December 2019. This viral pathogen rapidly disseminated globally, resulting in severe respiratory tract infections in humans and often culminating in fatal outcomes [1]. According to epidemiological studies, COVID-19 was mildly seen in children compared to adults and showed limited morbidity and mortality rates in children [2,3]. According to the national statistics, Asia, Europe, and North America showed 2.1-7.8% of pediatric COVID-19 cases [4].

The United States documented multisystem participation characterized by circulatory shock and systemic inflammation in children linked to COVID-19, termed multisystem inflammatory syndrome (MIS-C), as reported by the US Centers for Disease Control and Prevention on May 14, 2020 [5]. More than 4000 cases of MIS-C have been reported in the US alone. The median ages of affected children were 6-11 years old [3]. An increase in cases of multisystem inflammatory syndrome (MIS-C) manifested 3-6 weeks subsequent to elevated transmission of SARS-CoV-2, suggesting an association between exposure to SARS-CoV-2 and the onset of MIS-C [3]. Many recent studies suggest that the MIS-C is a post-infectious immunologically-mediated disorder which happens after exposure to SARS-CoV-2 infection. MIS-C is phenotypically similar to Kawasaki disease, a childhood inflammatory vascularity [3]. Pediatric patients with COVID-19 or MIS-C have strong IgG but weak IgM antibody responses to the trimeric S glycoprotein of SARS-CoV-2. IgG antibodies to S protein provide an important diagnostic criterion for MIS-C, whereas low IgM in MIS-C is consistent with its appearance several weeks after SARS-CoV-2 exposure [3].

MIS-C cases are typically addressed through the administration of intravenous immunoglobulin (IVIG), either with or without aspirin. This aligns with the established treatment protocol for Kawasaki disease. Notable clinical and laboratory similarities exist between MIS-C and Kawasaki disease. In certain instances, immunomodulatory agents such as infliximab, tocilizumab, and anakinra are administered to patients diagnosed with MIS-C [4]. Steroids can also be used to treat MIS-C [4]. The current treatment guidelines recommend IVIG and glucocorticoids as the first-tier agents for IMS-C cases [6,7]. Both IVIG and glucocorticoids are the most commonly used medications for MIS-C. However, the efficacy of this combined treatment is not currently available [7]. Meanwhile, the association of methylprednisolone pulse therapy with immediate and short-term favorable outcomes in MIS-C patients has also been observed in many studies. Most of the studies used IVIG alone or in combination with methylprednisolone to treat MIS-C cases [8]. However, the research centers failed to use IVIG because of the low availability and high cost.

The availability of combined treatment with IVIG and methylprednisolone leads this present study towards systematically reviewing the efficacy of IVIG alone and the combined IVIG and pulse methylprednisolone treatment on primary outcomes or second-line treatment required for persistent fever or any other symptoms like inflammation in COVID-affected MIS-C cases of various countries and statistically verified the outcome results of experimented data through meta-analysis, which is helpful for MIS-C treatment upgradation and beneficially for the patients also.

Method

Article Collection

A systematic literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research articles were searched in publicly available literature databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Science Direct (https://www.sciencedirect.com/), and JSTOR (www.jstor.org/) databases using MeSH terminologies “covid-19 AND multisystem inflammatory syndrome AND pulse methylprednisolone treatment”, “covid-19 AND multisystem inflammatory syndrome AND IV immunoglobulin treatment”, “covid-19 AND multisystem inflammatory syndrome AND IV immunoglobulin treatment AND methylprednisolone treatment”. The articles were screened by following the inclusion and exclusion criteria.

Inclusion Criteria

Articles with information on COVID-19 multisystem inflammatory syndrome treatment outcome with IV immunoglobulin and methylprednisolone. Articles should be written in the English language. Original research articles should be available in full length.

Exclusion Criteria

Review articles, letters to the editor, discussions, case reports, meta-analyses, abstracts, paid articles, other languages, and articles with unwanted data, such as other treatment methods (rather than IV immunoglobulin and methylprednisolone treatment). Articles without any information on treatment outcomes on COVID-19 multisystem inflammatory syndrome cases.

Article Screening Process

The collected articles followed by the used MeSH terms were primarily filtered as open-access research articles studied on human samples. The filtered articles were again screened based on the inclusion and exclusion criteria above. Articles with required information, especially the effect of IV immunoglobulin and pulse methylprednisolone treatment on COVID-19 multisystem inflammatory syndrome cases, were considered for further meta-analysis.

Data Retrieval

The articles underwent manual screening, and pertinent data were extracted, encompassing author information, publication year, PubMed IDs, the quantity of investigated COVID-19 multisystem inflammatory syndrome cases, population demographics, employed treatment methodology, and the impact of intravenous immunoglobulin and pulse methylprednisolone on COVID-19 multisystem inflammatory syndrome cases. The retrieved data were organized and analyzed under PICO format as follows;

P: Population- COVID-19 multisystem inflammatory syndrome cases
I: Intervention- Combined Treatment with Pulse methylprednisolone and IVIG
C: Comparator- IVIG treatment only
O: Outcome- Treatment effect on primary outcome/required second-line treatment for persistent fever or any other complications

Risk of Bias Analysis

The retrieved data were analyzed using the Cochrane risk of bias tool for randomized trials (RoB 2) through R programming. The risk of bias analysis was based on five possible domains of bias, i.e. (D1) Bias arising from the randomization process, (D2) Bias due to deviations from intended interventions, (D3) Bias due to missing outcome data, (D4) Bias in the measurement of the outcome and (D5) Bias in the selection of the reported result. The inputs under each domain lead to generating the graphical representation as “low risk of bias,” “some concerns,” or “high risk of bias” [7].

Meta-Analysis

The Meta package in R statistical programming software version 4.2.3 (https://cran.r-project.org/bin/windows/base/) was used for the binary meta-analysis using the Mantel-Haenszel method. To assess the comparative effectiveness, the binary meta-analysis was done between the intervention, i.e., treatment with combined IVIG and pulse methylprednisolone, and the control group, i.e., treated with IVIG only. The relative risk (RR) with a 95 % confidence interval was calculated for the included five studies. The test of significance (P-value) and resulting RR for each study were represented through the forest plot and generated through R programming.

Results

Study Selection

246 articles were searched through various online repositories, including PubMed (217) and ScienceDirect (29), followed by the used MeSH terminologies. Meanwhile, no results were found in JSTOR for any MeSH terminologies. Among these search results, only 110 articles were further considered after being filtered with open-access research articles studied on human species and child patients in PubMed (92) and ScienceDirect (18). The inclusion and exclusion criteria screened the

articles again, through which only 7 studies satisfied all the criteria. But among these 7 studies, only 6 were subjected to risk of bias and Meta-analysis, as those contained all the needful PICO data required.

The PRISMA flow diagram represented the study selection (Figure 1).

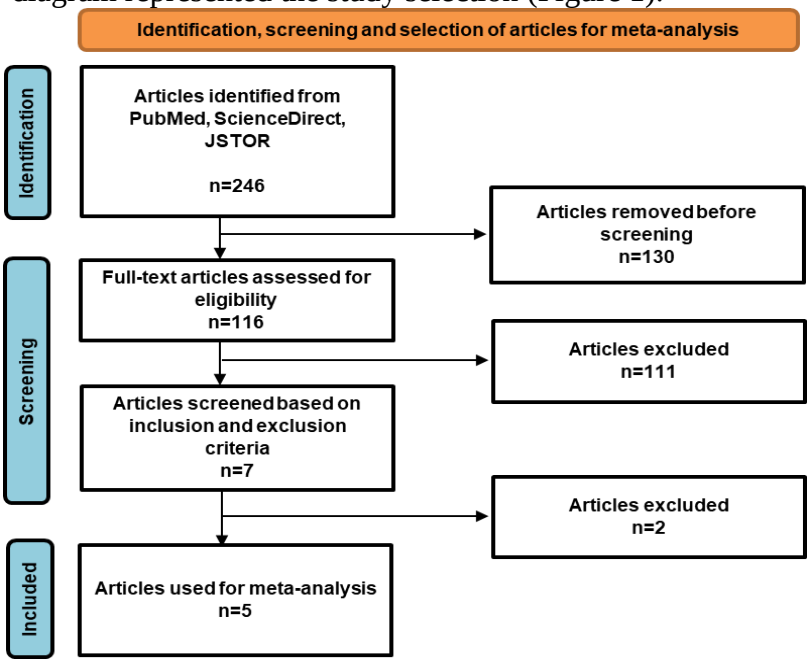

Figure 1: PRISMA flow diagram of the systematic review.

Study Characteristics

The included studies were published between 2019 to 2023. A total of 848 populations were involved in the considered studies, among which 415 cases were studied under the intervention group, i.e., treated with both IVIG and pulse methylprednisolone, and 176 cases were under the comparator group, i.e., treated with only IVIG. 2g/kg of IVIG and 2mg/kg/day doses of methylprednisolone were used for the primary treatment of the patients, whereas, for the patients who required second-line therapy, additional doses of IVIG and Methylprednisolone were used, and the hospitalization duration was increased. Among the treated cases, 256 cases (61.68%) and 101 cases (57.38%) were observed with successful outcomes in primary treatment with group 1 (both IVIG and pulse methylprednisolone treatment) and group 2 (only IVIG treatment), respectively. The remaining 159 patients (38.31%) in the intervention group and 75 (42.61%) in the control group required second-line treatment with extra IVIG and pulse methylprednisolone doses. The studied cases' ages varied between 2 months and <18 years old. The geographic locations of the studies considered were France, Vietnam, India, Turkey, and Spain.

All the patients had multisystem inflammatory syndrome and were infected with COVID-19. There were various clinical characteristics, including fever, vomiting, diarrhea, abdominal pain, altered mental status, skin rash, hypotension, hypertension, lymphopenia, thrombocytopenia, anemia, headache, bilateral conjunctival hyperemia, left ventricular dysfunction, red lips, limb edema, loose motion, tachycardia, conjunctivitis, lymphadenopathy, hypoxia, respiratory failure. Among the studied cases, the most observed clinical symptoms were fever, headache, vomiting, abdominal pain, and skin rash. According to the observed analyses in the articles, IV immunoglobulin, and pulse methylprednisolone were used mostly to treat the MIS-C children. Along with these, the implementation of some other steroids like dexamethasone, tocilizumab, and analinra was used in the treatment procedure. Both groups of the treatment procedure, i.e., (i) the combined treatment of IVIG with pulse methylprednisolone and (ii) IVIG alone, showed greater treatment outcomes in MIS-C children, but the combined treatment showed better effect during the primary treatment

outcome, whereas treatment with IVIG alone needs a second line therapy to reduce the persistent fever.

Among the considered studies, Ouldali et al. [9], Phung et al. [10], and Devrim et al. [11] have analyzed the effect of IV immunoglobulin and pulse methylprednisolone treatment on multisystem inflammatory syndrome cases with commonly seen symptoms like fever, diarrhea, abdominal pain, vomiting, loose motion, hypotension, skin rashes, They have observed the combined treatment of IV immunoglobulin and methylprednisolone showed better outcome as compared to individual treatment options i.e. IVIG alone.

Ouldali et al. [9] reported that patients treated with IVIG alone represented severe symptoms like frequent acute left ventricular dysfunction, initial PICU care, and requirement of initial hemodynamic support; thus, the 2nd line therapy was provided to the patients. Phung et al. [10] observed no persistent fever in the patients after 3 days of treatment with IVIG and methylprednisolone. In contrast, Devrim et al. [11] reported a high fever recurrence rate in patients treated with IVIG alone. Still, at the same time, the rate of respiratory support and hypertension was high in the patients treated with both IVIG and methylprednisolone. The combined treatment has been reported to be useful for the favorable short-term treatment outcome of MIS-C patients with a lower rate of treatment failure and a low rate of second-line therapy. But, according to the studies, post-discharge follow-up of MIS-C patients should be maintained for the long treatment.

Meanwhile, Bagri et al. [12] and Tagarro et al. [13] observed no significant difference between the two treatment groups, i.e., combined treatment of IVIG and pulse methylprednisolone and IVIG alone. However, Tagarro et al. [13] reported that the combined treatment of IVIG and steroids can reduce persistent fever and the escalating treatment requirement.

All the characteristics of the included studies, like study details, treatments, primary and secondary treatment outcomes, and patient information, were presented in Table 1.

Table 1: Details of considered studies.

Sl. No.	Author's Name & PubMed ID	Study Geographic Region	No. of Population	Age	Clinical Factors	Treatment, Doses	Primary Treatment Outcome	Second Line Therapy	Final Outcomes
1	Ouldali et al., 2021 [9]	France	181	4.7-12.1 years	Fever, diarrhea, vomiting, abdominal pain, ventricular dysfunction, hypotension, coronary abnormalities, rash	Methylprednisolone (0.8 to 1mg/kg) and IV immunoglobulin (2g/kg)	Persistence of fever 2 days	Hemodynamic support, acute left ventricular dysfunction after first-line therapy, and length of stay in the pediatric intensive care unit	Treatment with IVIG and methylprednisolone was associated with a more favorable fever course.
2	Phung et al., 2022 [10]	Vietnam	76	2 months-16 years	Fever, conjunctivitis, red lips, rash, limb edema, neck lymph nodes, gastrointestinal symptoms, abdominal pain, vomiting, loose stools	Methylprednisolone (2mg/kg) and IV immunoglobulin (2g/kg)	Persistent fever and increased inflammation markers	additional course of 10–30 mg/kg/day of methylprednisolone for 3 days, duration of hospital stay was increased	Anti-inflammatory treatment with IVIG and methylprednisolone had a favorable short-term outcome

3	Devrim et al., 2022 [11]	Turkey	91	<18.42 years	Fever, cough, abdominal pain, vomiting, diarrhea, rash, hypotension, tachypnea, tachycardia, conjunctivitis	Methylprednisolone (2mg/kg) and IV immunoglobulin (2g/kg)	required inotropic agents, respiratory support including high-flow nasal cannula	Respiratory support, Increased hospital duration, and follow-up patients	The combination of IVIG and methylprednisolone may be administered
4	Bagri et al., 2022 [12]	India	368	51.1(mean) months	Fever, gastrointestinal symptoms, rash, sock	Methylprednisolone and IV immunoglobulin	Requirement of vasoactive/inotropic support on day 2, need of mechanical ventilation on day 2 or beyond after initiation of immunomodulatory treatment or death during hospitalization in the treatment groups.	-	No significant difference observed between two treatment methods
5	Tagarro et al., 2023 [13]	Spain	132	109.9 months	Fever, coronary abnormalities, rash, abdominal pain, conjunctivitis, diarrhea, vomiting	Methylprednisolone (1-2mg/kg) and IV immunoglobulin (2g/kg)	Persistent fever	Additional doses of IVIG and Steroid and hospital duration were more	No significant difference was observed between the two treatment methods

Statistical Analyses

All the observed data from the considered articles were subjected to the risk of bias analysis. The risk of bias analysis was done for each study, which predicted a low risk of bias in Study 1, Study 4, and Study 5 (Figure 2A). In contrast, only study 2 and study 3 showed unclear risk of bias under domain 2 (D2) due to missing information about intended interventions. However, the overall study of biases resulted in a low risk of bias, represented in the risk of bias plot (Figure 2B), including "low risk of bias," "some concerns of biases," and "high risk of bias" represented with green, yellow and red color respectively in the graph.

Figure 2: (A) Graphical representation of risk of bias analysis of individual studies; (B) Summary of risk of bias analysis.

The statistical meta-analysis was done between the studied MIS-C cases treated with IVIG and methylprednisolone combined treatment (intervention group) and IVIG alone (control group) in all the included five studies. The analysis was done with several cases with persistent fever or other health complications that required second-line treatment after the primary treatment with the intervention group (IGIV along with methylprednisolone) and control group (IVIG alone). The meta-analysis has been graphically represented by the generated forest plot (Figure 3).

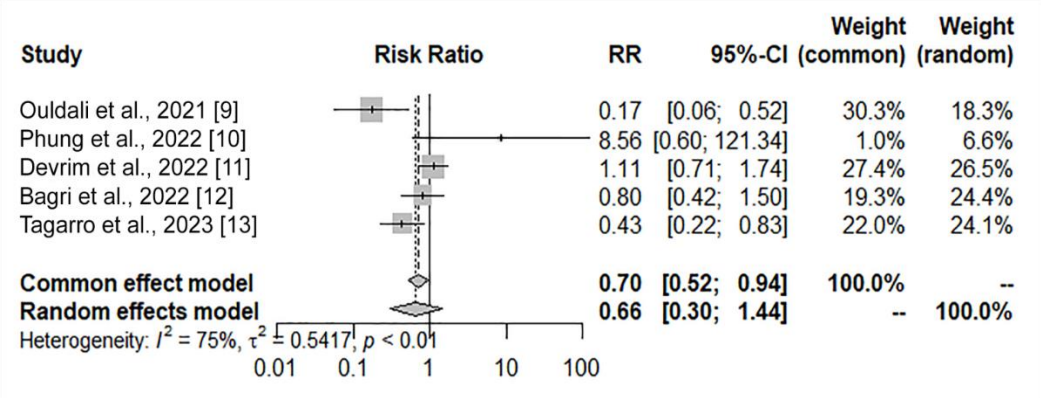

Figure 3: Meta-Analysis graphically displayed in Forest Plot.

RR for each study has been obtained with a 95% confidence interval. The generated magnitude of heterogeneity i.e., I^2 is 75%, representing the considerable heterogeneity in the studied outcomes. The meta-analysis resulted in significant differences between the treatment outcomes like the requirement of second-line treatment to reduce the persistent fever or any other complications in the COVID-19-associated MIS-C patients after the treatment with IVIG and methylprednisolone combined and IVIG alone with overall random effects 0.66 [0.30 to 1.44; p= <0.01].

Discussion

The PRISMA guideline-based systematic review has screened five research articles with all the required data on COVID-19-associated MIS-C pediatric cases treated with IVIG and pulse methylprednisolone.

According to the systematic review, along with the most used IVIG treatment, many steroids have also been combined for MIS-C treatment [12]. Glucocorticoids have also been recommended as the immunomodulatory medication used with IVIG for treating MIS-C patients. Still, the unavailability of experimental data on the combined treatment of IVIG with glucocorticoids on MIS-C cases minimizes the extensive experiments and analytical observations [7].

Meanwhile, the implementation of pulse methylprednisolone in the treatment of MIS-C with muti-organ dysfunction syndrome has shown immediate favorable outcomes. The combined treatment of pulse methylprednisolone and IVIG has mostly been used rather than individual treatments (pulse methylprednisolone alone) [8]. In all five studies, the experimental observations on methylprednisolone and IVIG combined treatment and IVIG alone on MIS-C cases showed effective outcomes immediately. Still, other clinical factors like fever, cardiac dysfunction, and respiratory complications are responsible for the early primary treatment outcomes [9-13]. At the same time, the researchers recommended long-term follow-up of patients and more experimental validations for more accurate and long-term treatment outcomes [12,13]. However, according to the studied experimental sources, IVIG with methylprednisolone showed better or more successful primary outcomes (61.68% vs. 57.38%) like a lower rate of fever and requirement of second-line therapy (higher doses of IVIG and methylprednisolone, respiratory support or increased resting

period) rather than IVIG alone. In contrast, the need for second-line therapy and persistent fever rate is high in the MIS-C patients treated with IVIG only (42.61%).

In the present study, the observed experimental effective outcomes and heterogeneity between two treatment groups, i.e., the intervention group (IVIG & methylprednisolone combined treatment) and control group (IVIG alone), have been statistically validated through the risk of bias and meta-analysis. The risk of bias analysis for each study is important to evaluate the overall strength of evidence [14]. It can assess the quality of the studies by evaluating the bias ness in study selection, population, and outcome selection, which has through ROB 2, a widely accepted and commonly used risk of bias analysis tool with innovative characteristics, and it allows analyzing the risk of bias in each randomized trial studies [15]. In the present study, the risk of bias analysis showed a lower risk of bias in overall studied outcomes.

The conducted meta-analysis has systematically assessed the results of the included five studies, analyzed the strength of evidence on treatment effects, and derived considerable heterogeneity in the studies and the statistically significant (with p-value <0.01) effect of treatment on MIS-C cases [16]. The present systematic review and meta-analysis are helpful for clinicians to get a clear idea about the treatment methods for MIS-C cases and develop novel treatment methods for long-term prognosis. Thus, more experimental validated studies with updated treatment data are required.

Conclusion

The correlation of MIS-C with COVID-19 pediatric cases has undergone development in numerous countries. Based on the findings from the encompassed studies, the concurrent administration of IVIG and methylprednisolone has demonstrated superior primary outcomes, characterized by a reduced incidence of second-line interventions prompted by persistent fever or other ailments such as respiratory support, along with increased intervals of patient rest. However, alternative treatment modalities, namely IVIG alone and the combined use of IVIG and methylprednisolone, can be considered for immediate short-term favorable outcomes as gauged by clinical symptoms. Nonetheless, for sustained long-term management, diligent post-symptomatic follow-up is imperative.

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