Original Article

An Observational Study of Clinical Profile & Short-Term Outcome with Use of Pulse Therapy of Methylprednisolone Alone Vs Methylprednisolone and Intravenous Immunoglobulin In Multisystem Inflammatory Syndrome In Children

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Abstract:

Background: Multisystem inflammatory syndrome in children (MIS-C) is a condition where different body parts can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. There is persistent fever along with inflammation, which can lead to medical emergencies and neonates and children may require critical care. **Aims and objectives:** This study evaluates use of pulse therapy of methyl prednisolone versus prednisolone and intravenous immunoglobulin (IVIG) in multisystem inflammatory syndrome in children (MISC). **Methodology:** This analytical study was carried out in 30 children with history of SARS-CoV-19 or MISC attending the PICU or NICU of the Tertiary care centre of DVVPF's Medical College, Ahmednagar. The study was carried out from January 2021 to December 2021. **Results:** Total of 30 patients were studied with male majority (60%), and mean age of 7.35 years. 28 were kept in the ICU (93.33%). GI symptoms were seen in 24 cases (80%), Mucocutaneous manifestation in 25 cases (83.33%), Multiorgan involvement (>3 organs) in 23 cases (76.67%). D Dimer was raised in 29 cases (96.67%), Thrombocytopenia was seen in 24 cases (80%). CNS involvement in 14 cases (46.67%) with headaches in 7 (23.33%), encephalopathy in 5 cases (16.67%) and seizures in 4 cases (13.33%). Respiratory system involvement was seen in 16 cases (53.33%). We observed that the outcome characteristic features were better in the Methylprednisolone pulse therapy plus IVIG group. ($p<0.05$) Out of 15 patients in the two groups, 3 patients died in Methylprednisolone pulse therapy group (20%) while there was one death in the Methylprednisolone pulse therapy plus IVIG group. Significant difference was seen in the survival of the two groups. ($p = 0.04$). **Conclusion:** There is improvement in both the groups which received the treatment with either Methylprednisolone pulse therapy or Methylprednisolone pulse therapy plus IVIG. Comparatively there was less ICU stay, less complications and better patient survival in Methylprednisolone pulse therapy plus IVIG group.

Keywords: MISC, IVIG, Methylprednisolone

Introduction:

The coronavirus pandemic has undoubtedly taken huge toll on humanity since its advent. It has casted it's repercussions indiscriminately over people of different age, gender and even socioeconomic status. It has not only instilled burden on resources in order to prevent its causation, but it also has devastating post-COVID consequences.[1-3] Multisystem inflammatory syndrome is one such serious manifestation linked to COVID-19 infection, which has affected both children and adults.[4,5] According to WHO, MISC can be stated as follows:

Children and adolescents with age between 0 and 19 years with fever more than or equal to 3 days, along with any two of the following: [5-7]

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1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

Along with any two of the above, elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin, and no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. Also, evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19 should be present.[7]

Thus, Multisystem inflammatory syndrome in children (MIS-C) is a condition where different body parts can become inflamed, which includes lungs, kidneys, brain, skin, eyes,heart or gastrointestinal system. There is persistent fever along with inflammation, which can lead to medical emergencies and neonates and children may require critical care.[8,9]

The management of MISC begins primarily with risk assessment, which helps in further dividing the cases into those with mild, moderate and severe illnesses, Further, depending upon the condition, treatment ranging from antibiotics, respiratory support, oxygen therapy, vasoactive therapy, steroids and IVIG can be given accordingly- singly or in combination. [7, 10-12]

In our hospital, due to involvement of rural population in majority, cost factors had to be taken into consideration while managing children with MISC and SARS-CoV-2. Therefore, we focussed on giving methylprednisolone alone for majority population. But for those who could afford IVIG, we also included it in our management plan. This study aims to compare the effect of both the management plans and assess efficacy of either.

Methodology:

Aims and objectives:

- To evaluate use of pulse therapy of methyl prednisolone vs prednisolone and intravenous immunoglobulin (IVIG) in multisystem inflammatory syndrome in children (MISC).
- To compare and assess the efficacy of both the management plans.

This analytical study was carried out in 30 children with history of SARS-CoV-19 or MISC attending the PICU or NICU of the Tertiary care centre of DVVPF's Medical College, Ahmednagar.

Detailed clinical history, thorough clinical examination and relevant investigations were performed. The data was compiled, tabulated and analysed with the help of Microsoft-Excel. Appropriate statistical techniques were applied for evaluation. Prior approval from institutional ethical committee was taken.

Children admitted with MIS-C aged 1 month to 12 years of age from December 2020 to May 2021 were included. Patients who fulfilled the WHO criteria for diagnosis of MIS-C during the study period were included in the study.[7] SARS-CoV-2 reverse trans-criptase polymerase chain reaction (RT-PCR) was done in patients, and SARS-CoV-2 antibody testing was done using Vitros CoV2T kit.

Echocardiography was done in all patients with MIS-C with shock at admission. All patients were subsequently referred to paediatric cardiologist to look for any cardiac or coronary dysfunction. Shock was defined when a patient required more than 20 mL/kg of intravenous (IV) fluid resuscitation or inotropic support to maintain blood pressure above the 5th centile.

Study variables collected using pre-designed pro-forma included patient demographic characteristics, initial symptoms and clinical signs, laboratory para-meters, time to defer-since, duration of ICU stay, need for inotropic support, duration of shock, duration and type of respiratory support. Patients who were treated with pulse therapy received dose of methylprednisolone 30 mg/kg once daily for 3 days followed by oral prednisolone at 2 mg/kg for 1 week or till CRP get normalized, whichever was later. Steroid was tapered and stopped over the next 2 - 3 weeks. Children who were treated with intravenous immunoglobulin received at a dose of 2 g/kg as a continuous infusion over 8-12 hours with longer duration in patients with cardiac dysfunction.

Time to fever defervescence was recorded at 12-hourly intervals. CRP and D-dimer were repeated on the third and seventh day after the start of IVIG or methylprednisolone. Treatment failure was defined as persistence of fever or worsening of clinical condition beyond 36 hours from the start of first-line therapy or recrudescence of fever within 7 days. Repeat intravenous immunoglobulin (IVIG) was considered if fever persisted beyond 36 hours of the first dose of IVIG or if there was a clinical deterioration. Children with treatment failure with IVIG first dose were treated with a second dose of IVIG with pulse methylprednisolone according to the Kerala State guidelines.[7] Children with treatment failure with pulse methylprednisolone were treated with IVIG. All patients were followed up at two weeks after discharge.

All patients with shock were started on prophylactic dose of low molecular heparin(LMWH). Children on LMWH were transitioned to low dose aspirin once liver enzymes normalized and platelet count increased to more than 80×109/L. Children with coronary thrombus on echocardiography were put on LMWH and anti-platelet dose of aspirin. Anti-inflammatory dose of aspirin (50 mg/kg) was given in refractory cases of MIS-C with Kawasaki disease like presentation. Children also received IV pantoprazole at prophylactic dose.

Results:

A total of 30 patients with 18 males (60%) and 12 females (40%) were studied. Patients aged between newborn to 12 years were enrolled, mean age of the patients was 7.35 years. Twenty patients were antibody positive (66.67%) and 10 patients were PCR positive (33.33%). The clinical characteristics are given below.

All children presented with fever with a median duration of 4-5 days. Of the total 30 patients admitted 28 were kept in the ICU (93.33%). GI symptoms were seen in 24 cases (80%), Mucocutaneous manifestation in 25 cases (83.33%), Multiorgan involvement (>3 organs) in 23 cases (76.67%). D Dimer was raised in 29 cases (96.67%), Thrombocytopenia was seen in 24 cases (80%). CNS involvement in 14 cases (46.67%) with headaches in 7 (23.33%), encephalopathy in 5 cases (16.67%) and seizures in 4 cases (13.33%). Respiratory system involvement was seen in 16 cases (53.33%). [table1]

Table 1: Characteristic of the patients

Characteristics	No	(%)
ICU Admission	28	93.33
RTPCR positive	10	33.33
Serology positive	20	66.67
GI symptoms	24	80.00
Mucocutaneous manifestation	25	83.33
Multiorgan involvement (>3 organs)	23	76.67
Coagulopathy:		
D Dimer >0.5 µg/dl	29	96.67
Thrombocytopenia	24	80.0
INR >1.5	5	16.67
CNS involvement	14	46.67
Seizures	4	13.33
Headache	7	23.33
Encephalopathy	5	16.67
Respiratory system:	16	53.33
Abnormal x ray findings	13	43.33
Cough	4	13.33

We divided the patients in two groups with 15 cases each, one who received Pulse therapy with Methylprednisolone and another Methylprednisolone pulse therapy plus IVIG group.

We observed that the outcome characteristic features were better in the Methylprednisolone pulse therapy plus IVIG group. ($p<0.05$)

ICU stay was seen 6.5 ± 2.6 days in Methylprednisolone pulse therapy and 4.5 ± 2.1 days in Methylprednisolone pulse therapy plus IVIG group. ($p<0.001$) Total hospital stay was seen 13.56 ± 4.27 days in Methylprednisolone pulse therapy and 9.65 ± 3.64 days in Methylprednisolone pulse therapy plus IVIG group. ($p<0.001$) Shock cases were more in Methylprednisolone pulse therapy group (11 – 73.33%) as compared to 4 cases (26.67%) in Methylprednisolone pulse therapy plus IVIG group. ($p<0.001$) Similarly Cardiac dysfunction and ≥ 5 Organ Involvement was seen more in Methylprednisolone pulse therapy group. ($p<0.05$)

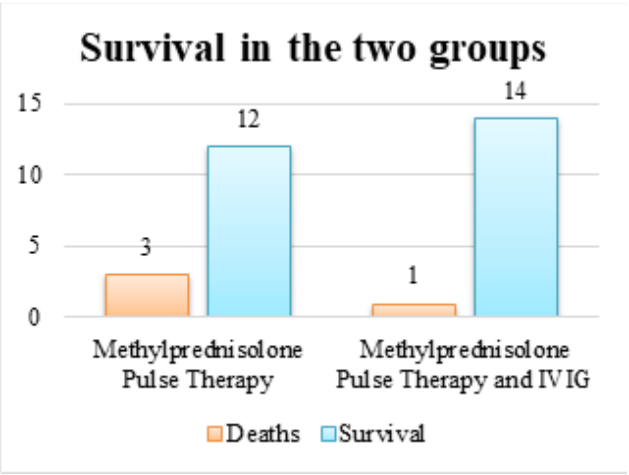
Repeat Immunomodulation was required in 10 cases (66.67%) in Methylprednisolone pulse therapy group and in 4 cases (26.67%) in Methylprednisolone pulse therapy plus IVIG group. ($p<0.001$) Significant decrease in CRP and D-Dimer on day 3 was seen more in Methylprednisolone pulse therapy plus IVIG group ($p<0.05$). [table 2]

Table 2: Characteristic features in the two groups

Characteristic features	Pulse therapy (15 Patients) Number (%) Mean ± SD	Pulse therapy with IVIG (15 Patients) Number (%) Mean ± SD	P Value
ICU stay (Days)	6.5 ± 2.6	4.5 ± 2.1	<0.001*
Total Hospital Stay (Days)	13.56 ± 4.27	9.65 ± 3.64	<0.001*
Shock	11 (73.33%)	4 (26.67%)	<0.001*
Cardiac Dysfunction	6 (40.0%)	2 (13.33%)	<0.001*
= 5 Organ Involvement	7 (46.67%)	3 (20%)	0.014*
Repeat Immunomodulation	10 (66.67%)	4 (26.67%)	<0.001*
CRP <60 on Day 3	8 (53.33%)	2 (13.33%)	<0.001*
D-Dimer Decrease by day 3	6 (40%)	3 (20%)	0.011*

Out of 15 patients in the two groups, 3 patients died in Methylprednisolone pulse therapy group (20%) while there was one death in the Methylprednisolone pulse therapy plus IVIG group. Significant difference was seen in the survival of the two groups. (p = 0.04) [Fig 1]

Figure 1: Outcome in the two groups



Discussion:

The present study reports favourable outcomes in MIS-C with pulse methylprednisolone therapy and Methylprednisolone pulse therapy plus IVIG treatment modalities.

A total of 30 with 18 males (60%) and 12 females (40%). Patients aged between newborn to 12 years were enrolled, mean age of the patients was 7.35 years. Twenty patients were antibody positive (66.67%) and 10 patients were PCR positive (33.33%). The clinical characteristics are given below.

S Sugunan *et al* [13] observed 63% males in their study with mean age of 7.5 years. 31% were RTPCR positive and 69% were serologically positive for Covid-19.

Bhat CS *et al*[14] observed similar patients characteristics with 62% males and mean age of 6.2 years.

All children presented with fever with a median duration of 4-5 days. Of the total 30 patients admitted 28 were kept in the ICU (93.33%). GI symptoms were seen in 24 cases (80%), Mucocutaneous manifestation in 25 cases (83.33%), Multiorgan involvement (>3 organs) in 23 cases (76.67%). D Dimer was raised in 29 cases (96.67%), Thrombocytopenia was seen in 24 cases (80%). CNS involvement in 14 cases (46.67%) with headaches in 7 (23.33%), encephalopathy in 5 cases (16.67%) and seizures in 4 cases (13.33%). Respiratory system involvement was seen in 16 cases (53.33%).

S Sugunan *et al* [13] observed that ICU admission was required in 94%, GI symptoms in 84% cases, Multiorgan involvement in 69%, Mucocutaneous manifestation in 91% of the cases. They observed thrombocytopenia in 59% cases, raised D-Dimer in 100% cases and CNS involvement in 40% cases. Respiratory involvement in 43% of the cases.

Bhat CS *et al*[14] observed that the Multiorgan involvement was present in 72% cases while CNS involvement in 43% and Respiratory involvement in 51% of the cases. Raised D-Dimer was seen in 96% of their cases.

We divided the patients in two groups with 15 cases each, one who received Pulse therapy with Methylprednisolone and another Methylprednisolone pulse therapy plus IVIG group.

We observed that the outcome characteristic features were better in the Methylprednisolone pulse therapy plus IVIG group. (p<0.05)

S Sugunan *et al* [13] also had similar findings with significant better patient outcome characteristics in Methylprednisolone pulse therapy plus IVIG group. (p<0.05)

ICU stay was seen 6.5 ± 2.6 days in Methylprednisolone pulse therapy and 4.5 ± 2.1 days in Methylprednisolone pulse therapy plus IVIG group. (p<0.001)

Nakra NA *et al*[15] observed that ICU stay was significantly less in Methylprednisolone pulse therapy plus IVIG group similar to our study.

Shock cases were more in Methylprednisolone pulse therapy group (11 – 73.33%) as compared to 4 cases (26.67%) in Methylprednisolone pulse therapy plus IVIG group. ($p<0.001$)

Repeat Immunomodulation was required in 10 cases (66.67%) in Methylprednisolone pulse therapy group and in 4 cases (26.67%) in Methylprednisolone pulse therapy plus IVIG group. ($p<0.001$)

S Sugunan *et al* [13] observed that Repeat Immunomodulation was required less in Methylprednisolone pulse therapy plus IVIG group.

Nakra NA *et al*[15] observed that Repeat Immunomodulation was required less in pulse therapy plus IVIG group but there was no any significant difference.

Significant decrease in CRP and D-Dimer on day 3 was seen more in Methylprednisolone pulse therapy plus IVIG group ($p<0.05$).

Out of 15 patients in the two groups, 3 patients died in Methylprednisolone pulse therapy group (20%) while there was one death in the Methylprednisolone pulse therapy plus IVIG group. Significant difference was seen in the survival of the two groups. ($p = 0.04$)

S Sugunan *et al* [13] observed better survival in Methylprednisolone pulse therapy plus IVIG group similar to our study.

Nakra NA *et al* [15] observed that there were 10% deaths in their study with significantly more deaths in Methylprednisolone pulse therapy group as compared to Methylprednisolone pulse therapy plus IVIG group, similar to our study findings.

Conclusion:

We conclude that the multisystem inflammatory syndrome is one of the most serious complications of Covid-19 infections in children. We observed improvement in both the groups which received the treatment with either Methylprednisolone pulse therapy or Methylprednisolone pulse therapy plus IVIG. Comparatively there was less ICU stay, less complications and better patient survival in Methylprednisolone pulse therapy plus IVIG group. Cost of therapy needs to be considered in the treatment with IVIG as it may not be affordable in all the patients, however considering the benefits it has in combination with Methylprednisolone pulse therapy, patients can be counselled for the combination therapy.

Conflict of interest – None

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References:

1. Ciotti M, Ciccozzi M, Terrinoni A, Jiang WC, Wang CB, Bernardini S. The COVID-19 pandemic. Critical reviews in clinical laboratory sciences. 2020 Aug 17;57(6):365-88.
2. Kaushal V, Srivastava S. Hospitality and tourism industry amid COVID-19 pandemic: Perspectives on challenges and learnings from India. International journal of hospitality management. 2021 Jan 1;92:102707.
3. Unni JC. Social effects of Covid-19 pandemic on children in India. Indian Journal of Practical Pediatrics. 2020;22(2):102-4.
4. Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S, Shobhavat L, Andankar P, Karande T, Kulkarni S. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. Indian pediatrics. 2020 Nov;57(11):1015-9.
5. Gupta Dch S, Chopra Md N, Singh Md A, Gera R, Chellani Md H, Pandey PhD R, Arora Md BS. Unusual clinical manifestations and outcome of multisystem inflammatory syndrome in children (MIS-C) in a tertiary care hospital of North India. Journal of Tropical Pediatrics. 2021 Feb;67(1):fmaa127.
6. Shah SK, Munoz AC. Multisystem inflammatory syndrome in children in COVID-19 pandemic. The Indian Journal of Pediatrics. 2020 Sep;87(9):671-3.
7. Mirrahimi AS, Tabatabaei SR. An Algorithmic Approach to Management of COVID-19 Associated Multisystem Inflammatory Syndrome in Children. Arch Pediatr. 2021 Jan;9(1):e110479.
8. Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: Multisystem inflammatory syndrome in children (MIS-C). The American journal of emergency medicine. 2020 Nov 1;38(11):2492-e5.

9. Tiwari A, Balan S, Rauf A, Kappanayil M, Kesavan S, Raj M, Sivadas S, Vasudevan AK, Chickermane P, Vijayan A, John ST. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a hospital-based prospective cohort study from Kerala, India. BMJ paediatrics open. 2021;5(1).
10. Sai BV, Kumar H, Arun Babu T, Chaitra R, Satapathy D, Kalidoss VK. Clinical Spectrum of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 Infection. Indian Journal of Pediatrics. 2022 Jan 30:1-.
11. Aslan N, Yildizdas D, Sinanoglu MS. A pediatric COVID19 case with suspected acute abdomen, hyperferritinemic sepsis and developing MIS-C and pancreatitis. The Indian Journal of Pediatrics. 2021 Mar;88(3):288-.
12. Sarkar M, Pal P, Raychaudhuri D, Sen B, Roychowdhoury S, Chattopadhyay A, Hazra A, Mondal R. PIMS-TS vs. MIS-C: Diagnostic Criteria in COVID-19–Associated Hyperinflammation in Children. Indian Journal of Pediatrics. 2021 Nov;88(11):1149-50.
13. Sugunan S, Bindusha S, Geetha S, Niyas HR, Kumar AS. Clinical profile and short-term outcome of children with SARS-CoV-2 related multisystem inflammatory syndrome (MIS-C) treated with pulse methylprednisolone. Indian Pediatrics. 2021 Aug;58(8):718-22.
14. Bhat CS, Gupta L, Balasubramanian S, et al. Hyperinflammatory syndrome in children associated with COVID-19: Need for awareness. Indian Pediatr. 2020;57:929-35.
15. Nakra NA, Blumberg DA, Herrera-Guerra A, et al. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: Review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel). 2020;7:E69.