Research Paper

Clinical Profile and Short-Term Outcome of Children with SARS-CoV-2 Related Multisystem Inflammatory Syndrome (MIS-C) Treated with Pulse Methylprednisolone

***SHEEJA SUGUNAN, S BINDUSHA, S GEETHA, HR NIYAS AND A SANTHOSH KUMAR**

From Department of Pediatrics, SAT Hospital, Government Medical College Thiruvananthapuram, Kerala, India.

Correspondence to: *Dr Sheeja Sugunan, Associate Professor, Department of Pediatrics, SAT hospital, Government Medical College Thiruvananthapuram, Kerala. sheejavimalk@gmail.com*

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ABSTRACT

Background: Multi system inflammatory syndrome in children (MIS-C) is a rare, but life-threatening complication of SARS-CoV-2 infection. **Objective:** To study the clinical profile and outcome of children with MIS-C treated with methylprednisolone pulse therapy and /or IVIG. **Study design** Observational study. **Participants:** Children satisfying CDC MIS-C criteria admitted during the study period. **Outcome measures:** Primary outcome was persistence of fever beyond 36 hours after start of immunomodulation therapy. Secondary outcomes included duration of ICU stay, mortality, need for repeat immunomodulation, time to normalization of CRP and persistence of coronary abnormalities at 2 weeks. **Results:** Study population included 32 patients with MIS-C with median (IQR) age of 7.5 (5-9.5) years. The proportion of children with gastrointestinal symptoms was 27 (84%), cardiac was 29 (91%) and coronary artery dilatation was 11 (34%). Pulse methylprednisolone and intravenous immunoglobulin were used as first line therapy in 26 (81%), and 6 (19%) patients, respectively. Treatment failure was observed in 2/26 patients in methylprednisolone group and 2/6 patients in IVIG group. C-reactive protein levels less than 60mg/L by day 3 was seen in 17(74%) in methylprednisolone group and 2 (25%) in IVIG group (P=0.014). There was no mortality. At 2 weeks follow-up coronary artery dilatation persisted in 4 in methylprednisolone group and 1 in IVIG group. **Conclusion:** In patients with SARS-CoV-2 related MIS-C, methylprednisolone pulse therapy was associated with favorable short-term outcomes.

Keywords: *Coronary artery, COVID-19, IVIG, Kawasaki disease, Methyl prednisolone, Vascular thromboembolic event*.

SARS- COV- 2 related multi system inflammatory syndrome in children (MIS-C) is a dreaded complication which is seen more often in children than in adults [1]. Intravenous immunoglobulin (IVIG) is considered as the treatment of choice for Kawasaki disease (KD) [2]. MIS-C has many dissimilarities with KD like occurrence in older children (median age 10 years), presence of multi-organ involvement, commonly gastrointestinal tract, myocardial dysfunction and shock [3]. MIS-C has been treated empirically with IVIG and steroids [2]. Some studies have used biologicals like tumor necrosis factor inhibitor, interleukin 1 inhibitor, interleukin 6 receptor antibody etc. Most studies have used IVIG alone or in combination with methylprednisolone than methylprednisolone alone in the treatment of MIS-C [1,4]. Availability and high cost of IVIG precludes its use in many centers. Hence, this observational study was conducted to assess the clinical profile and treatment outcome of patients treated with pulse methylprednisolone.

METHODS

This observational study was conducted in a tertiary care teaching hospital in southern India. This was the preliminary analysis of an ongoing prospective observational study at the institute. Ethical Committee clearance was obtained for the study and informed consent was taken from patient care

takers. Children admitted with MIS-C aged 1 month to 12 years of age from September to November 2020 were included.

Patients who fulfilled the CDC criteria for diagnosis of MIS-C during the study period were included in the study [5]. Infective causes like Dengue, Leptospirosis, Scrub and bacterial sepsis were excluded by appropriate investigations. COVID-19 RT PCR was done in all patients. COVID 19 antibody testing was done using Vitros CoV2T kit [6].

Choice of immunomodulation was decided by the treating unit based on patient demographics and Kerala State guidelines for treatment of children with MIS-C [7]. Bedside echocardiography was done in all patients with MIS-C with shock at admission. All patients were subsequently seen by pediatric cardiologist to look for coronary artery status and cardiac dysfunction. Z-score of coronary artery diameter with value more than 2 were considered to have coronary artery dilatation / aneurysm [8]. Coronary artery changes like increased echogenicity and non-tapering in the absence of Z- score more than 2 were taken as nonspecific coronary artery changes. Shock was defined when a patient required more than 20 mL/kg of IV fluid resuscitation or inotropic support to maintain blood pressure above the 5th centile.

Study variables collected using pre designed proforma included patient demographic characteristics, initial symptoms and clinical signs, laboratory parameters, type of immunomodulator used, time to defervescence, duration of ICU stay, need for inotropic support, duration of shock, duration and type of respiratory support, coronary artery changes at admission and 2 weeks follow-up and mortality. Patients who were treated with methylprednisolone received pulse dose of 30 mg per kg once daily for 3 days followed by oral prednisolone at 2 mg/ per kg for 1 week or till CRP normalized, whichever was later. Steroid was tapered and stopped over the next 2 to 3 weeks. Children who were treated with IVIG received 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 start of first line therapy or recrudescence of fever within 7 days. Repeat immunomodulation was considered if fever persisted beyond 36 hours of first dose of immunomodulatory therapy or if there was a clinical deterioration, irrespective of time since finish of first therapy. 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 low molecular weight heparin (LMWH) at prophylactic dose which was changed to treatment dose if thrombus was detected. Children on LMWH were transitioned to low dose aspirin once liver enzymes normalized and platelet count

increased to more than 80,000 cells/mm^3. Children with thrombus were put on LMWH and anti-platelet dose of aspirin. Anti-inflammatory dose of aspirin (50 mg/kg) was given in refractory MIS-C with KD like presentation. Children receiving methylprednisolone were prophylactically put on IV pantoprazole.

*Statistical analysis***:** Data was entered in MS Excel and analyzed using SPSS 20. The results were expressed as mean (SD) for parametric data and median (IQR) for non-parameteric data. Independent sample *t*-test was used for comparison of means. Categorical variables were compared using nonparametric tests. Logistic regression was done to assess the relationship between clinical variables and treatment outcome.

RESULTS

A total of 32 (males 21) patients with a median (IQR) age of 7.5 (5-9.5) years were enrolled. Seventeen patients were antibody positive, 8 patients were both PCR and antibody positive and two were only PCR positive. Five patients were negative for PCR and antibody, but were epidemiologically related to COVID 19 positive cases.

All children presented with fever with a median (IQR) duration of 5 (3-6) days. The clinical characteristics are shown in **Table I**. The mean (SD) CRP was 141(72) mg/L and ESR 41(33.1) mm in first hour.

The mean (SD) age of children with shock was significantly higher than those without shock [7.93 (2.27) vs 5.67 (3.39) years; *P*=0.02]. Children with shock also had statistically significant higher D dimer [4.75 (3.3) vs 1.59 (0.982) mcg/mL; *P*=0.007] , lower albumin [2.8 (0.40) vs 3.32 (0.5) gm/dL, *P*=0.008*]*, higher CRP [152 (62.7) vs 120 (98.9) mg/L; *P*=0.049], higher lactate [2.35 (1.27) Vs 1.01(0.212) mmol/L; *P*=0.012] and lower ejection fraction [53.5 (13.09) vs 65.1(6.29)%; *P*=0.015]. Eighteen patients (56%) had transaminitis but hepatic failure was seen in only one child. Of the four patients with vascular thromboembolic events (VTE), three had thrombus in left ventricle and one in right popliteal vein. Even though 10 (31%) patients were PCR positive, antiviral therapy with Remedisivir was offered only to one child in our series.

Table II shows comparative clinical features in children who received pulse methylprednisolone (*n*=26) or IVIG (*n*=6). Treatment failure was observed in 2/26 patients in methylprednisolone group and 2/6 patients in IVIG group. No child required additional immunomodulation with immuno biologicals or succumbed during the study period.

Logistic regression was done to assess the effect of clinical variables which were significantly different between the two treatment groups, on the likelihood of occurrence of treatment failure. Logistic regression did not show any effect of age (P=0.7), respiratory support (*P*=0.7) and five or more organ involvement (*P*=0.2) on the likelihood of occurrence of treatment failure.

Out of 11 patients with coronary artery dilatation at admission, four had persistent dilatation at two weeks. Six patients (21%) had echogenic non tapering coronaries but coronary artery diameter

was less than 2 Z score. One patient in this group developed coronary dilatation with Z score more than 2.5 at 2 weeks. LV thrombus had resolved in two patients at 2 weeks follow up while one patient continued to have thrombus at 2 weeks follow up even though the ejection fraction had normalized at 2 weeks. Of the 13 patients with LV dysfunction, 11 (85%) had normal ejection fraction at 2 weeks follow up. LV systolic function normalized for the remaining 2 patients, at 6 weeks follow up.One child had developed mononeuritis of right peroneal nerve after one week, which improved with continuation of steroids and aspirin at antiplatelet dose.

DISCUSSION

The present study reports favourable outcomes in MIS-C with pulse methylprednisolone therapy. MIS-C had dissimilarities to classical KD like higher age at presentation and higher incidence of GI symptoms and shock, as seen earlier [3,9,10].

Only 6% of children were referred with a suspected diagnosis of MIS-C, highlighting the fact that MIS-C continues to be a great masquerader.

Clinical features in children with acute SARS-CoV-2 infection included fever in 49%, cough in 45% and GI symptoms in a few [11]. In contrast, all children with MIS-C, had fever with a higher proportion of GI symptoms, while cough was rare [12,14], as also seen in the present study.

As previously reported more children in our study had conjunctival congestion than oral mucosal changes[12,13]. 31% of children also had conjunctival haemorrhage which has not been reported in other studies. Breathlessness was also observed in a higher proportion of patients compared to cough [14]. Unilateral lung infiltrates are more frequently reported in acute Covid-19 infection in children [15]. While, bilateral lung infiltrates were seen in a higher proportion of patients with MIS-C.

A higher seropositivity rate with or without SARS-CoV-2 RT PCR positivity is reported in patients with MIS-C with shock and multiorgan involvement [14]. Presence of positive COVID-19 antibody in patients with positive SARS-CoV-2 PCR at admission probably indicates a greater role of immune mediated inflammatory response than acute SARS-CoV-2 viremia in the pathogenesis of MIS-C. As many children with MIS-C have hepatic derangement, use of antiviral therapy in these patients may be counterproductive [13].

Cardiac involvement is the most frequently reported organ dysfunction in MIS-C as also seen in the present study [1,10,12,6] Occurrence of coronary artery aneurysm at follow up in a patient with nonspecific coronary artery changes without dilatation in the initial echo, highlights the need for meticulous follow up with echocardiogram. Thrombosis has not been reported in similar studies from India [16,17], but seen in studies from US and UK [12,13].

Earlier studies [12,14], have shown the need for repeat IVIG and immunomodulators in almost 20% of those who received IVIG. In our study only 2 patients who had received steroids subsequently needed IVIG. Logistic regression did not show any relationship between clinical variables like age, shock or multiorgan involvement with initial treatment failure. None of the

children required any other alternative immunomodulators. There were no deaths or need of ECMO in our study. Earlier studies have reported a mortality of 1.2-2% [13,14] and need for additional cardiac support with ECMO in 4% of patients [12,13].

Studies have reported favourable short-term response to IVIG and steroid [3,14]. Currently proposed treatment modalities are derived from its similarity with KD and are based on expert opinion. Treatment with IVIG in resource limited settings is a challenge. In our study children who received methylprednisolone were significantly older and had higher number of organ involvement. Outcome measures showed similar duration of ICU stay, lesser requirement of repeat immunomodulation, absence of need for other biological agents, absence of mortality, absence of need for ECMO and similar coronary artery profile at follow up, suggesting a favourable role for pulse methylprednisolone in the treatment of MIS-C. A recent study [18], also found a more favourable outcome in those treated with IVIG and methylprednisolone than those treated with IVIG alone. Small sample size, observational nature and absence of matching cohorts are the main limitations of the study.

In patients with MIS-C with shock and MODS, IV methylprednisolone pulse therapy was associated with favorable immediate and short term follow-up outcomes. Patients with nonspecific coronary changes like absence of tapering and increased echogenicity need to be meticulously followed up for occurrence of coronary artery dilatation even with low initial *Z*-score.

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WHAT IS ALREADY KNOWN?

- MIS-C is a life threatening complication of SARS-CoV-2 infection which has similarities with Kawasaki disease and can be treated with high dose IVIG.

WHAT THIS STUDY ADDS?

- Use of pulse methylprednisolone therapy as the first line treatment for MIS-C was associated with favorable immediate and short term follow up outcomes.

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Table I Demographic and Clinical Characteristics of Patients with MIS-C (*N*=32)

	n (%)
Underlying medical condition (rhabdomyoma 1, obesity2, hypothyroidism2)	4 (12.5)
ICU admission	30 (94)
RT PCR Positive	10 (31)
Serology positive	22 (69)
Multiorgan involvement (>5 organs)	22 (69)
GI symptoms	27 (84)
Mucocutaneous manifestations	29 (90.6)
Conjunctival congestion	22(69)
Conjunctival Haemorrhage	10(31)
Oral mucosal changes	3(9)
Rash	21(66)
Coagulopathy	32 (100)
INR > 1.5	4 (12.5)
D dimer > 0.5mcg/ml	32 (100)
Thrombocytopenia < 1.5lakhs/mm3	19 (59.3)
CNS involvement	13 (40.6)
Seizure	3 (9.3)
Headache	4 (12.5)
Encephalopathy	6 (18.7)
Respiratory	14 (43.7)
Cough	2 (6%)
Abnormal chest X-ray	7 (21.8)
Bilateral lung infiltrates	6(18.7%)
Liver	18 (56)
AST > 40IU/L	18 (56)
ALT > 40IU/L	16 (50)
Renal	8 (25)
Urea > 40mg/dl	8 (25)

AKI stage 2	2 (6.2)
AKI stage 3	2 (6.2)
Cardiac involvement	29 (90.6)
Myocardial dysfunction (EF < 55%)	13 (40.6)
Elevated NT Pro BNP	28 (87.5)
Coronary artery dilatation / aneurysm	11 (34.4)
Arrhythmia	3 (9.3)
Clinical Thrombosis	4 (12.5)
Serositis	8 (25)
CRP >60 mg/L	30 (94)
Elevated ESR	15 (47)

MIS-C: Multisystem inflammatory syndrome in children temporally associated with SARS CoV2 infection. ICU: Intensive care unit; GI: Gastrointestinal; CNS: Central Nervous System; AST: Aspartate aminotransferase; ALT : Alanine aminotransferase; EF: Ejection fraction; AKI: Acute kidney injury AKI stage 2: Doubling of serum creatinine from baseline. AKI stage 3: Tripling of serum creatinine from baseline or need for renal replacement therapy.

Table II Comparison of Clinical and Outcome Measures in Two Treatment Groups

	Methyl prednisolone group n = 26	*IVIG group n = 6*
Age, [a]	8 (6-10.25)	3.5 (2.38-4.5)
Duration of ICU stay[d] Days	4.5 (3-6.25)	4 .5 (2-10)
[a]Duration of hospital stay days	11 (10-14)	8.5 (2.7-21)
Shock[a]	20 (77)	2 (33)
Cardiac dysfunction	11 (42)	2 (33)
Coronary artery dilatation / Aneurysm	8 (30.8)	3 (50)
Coronary artery non- specific changes	6 (23)	0
≥5 organ involvement[d]	20 (77)	2 (33)
Inotropic support	18 (69)	2 (33)
≥2 inotropes	14 (52)	1 (17)
Respiratory support	19 (72)	1(17)
Invasive ventilation	4 (16)	0
CPAP	14 (52)	1 (17)
NIV	1 (4)	0
CRP < 60 mg/L on day 3	17 (68)	2 (33)
D dimer decrease by day 3 , *n* (%)	19 (68)	4 (83)
Need for repeat immunomodulation	2 (7.7)	2 (33.3)
Persistent coronary artery dilatation /aneurysm at 2 wks	3 (12)[b]	1 (25)[c]
Persistent nonspecific coronary changes	4 (16) [b]	1 (25) [c]
Normal ejection fraction at 2 weeks	23 (92) [b]	4 (100) [a]

Data expressed as n (%) or [a] median (IQR). [b] n=25; [c] n=4.
MIS-C: Multisystem inflammatory syndrome in children temporally associated with SARS CoV2
Infection; cardiac dysfunction: Ejection fraction < 55%; NIV: non invasive ventilation; CRP: C Reactive Protein;CPAP: Continuous positive airway pressure.
[d]*P<0.05;* [e]*P=0.01.*