Original Research Paper

Volume - 13 | Issue - 04 | April - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Paediatrics

METHYLPREDNISOLONE - THE SAVIOR IN CHILDREN WITH MULTISYSTEM INFLAMMATORY SYNDROME (MIS-C)

Dr. Anand*	Senior Resident, Department of Pediatrics, JJM Medical College, Davanagere. *Corresponding Author
Dr. Spoorthi S M	Assistant Professor, Department of Pediatrics, JJM Medical College, Davanagere.
Dr. Chethan K B	Associate Professor, Department of Pediatrics, JJM Medical College, Davanagere.
Dr Mugunagowda Patil	Professor And HOD, Department of Pediatrics, JJM Medical College, Davanagere.

ABSTRACT **Background:** Multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome is a new entity and is fatal disease that is temporally associated with SARS-COV 2 (PIMS-TS) [1]. We aimed at studying varied clinical presentation, management and outcome in children with MIS-C associated with covid-19 treated with IvIg and methylprednisolone at tertiary care centre, Davangere. **Methods:** This is a retrospective observational study conducted at two tertiary care hospitals at Davangere from October 2020 to August 2021 (11 months.). All cases who fulfilled WHO criteria for MIS-C were included in the study. Institutional ethics committee approval was taken. Data was obtained from hospital records .Parameters studied were demographics, symptomatology, laboratory markers, medications and immediate outcome. All children were then grouped into 2. Group 1- those who presented with shock and group 2- those who presented without shock . Data were entered and analyzed using SPSS software version 22.0. For interpretation of results significance was adopted at p-value less than 0.005 and at 95% confidence interval. **Results:** A total of 182 patients with MIS-C were treated during the study period. The median age of presentation was 6.8±4.5 years. We had 14 cases of infants. M:F ratio 1.35:1 showing no sex predilection. Children who presented with shock had significant symptoms of pain abdomen, tachypnoea, Lower GCS and lower saturation levels and had significantly higher CRP, LDH, ferritin, D-dimer levels and had lower albumin levels which is statistically significant . Also requirement of IVIg was significantly more in children with shock (TABLE 2). Out of 182 children with MIS-C, only 21 received IVIg and rest all received only steroids - methylprednisolone (due to financial constraints). However the outcome did not vary much with IVIg or steroids. IV methylprednisolone pulse therapy was associated with favorable immediate outcome which is comparable with IVIg in our study. Mortality in our series was 6.04% which is comparable to international studies [11,12]. **Conclusion** In our study most of our children with MIS-C recovered with timely use of pulse methylprednisolone therapy alone with favourable short term outcomes. Thus in resource limited settings methylprednisolone pulse therapy can help in saving lot of young children with MIS-C.

KEYWORDS :

INTRODUCTION:

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, [1,2] also called as Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [3] , is a hyper inflammatory syndrome occurring in close temporal association with a severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection in children. The initial cases from India were reported in May, 2020 and as the number of COVID-19 cases has grown exponentially across the country, clinicians have started identifying this new entity more frequently[4]. This rare syndrome shares common features with other pediatric inflammatory conditions including: Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. It can also present with unusual abdominal symptoms with excessive inflammatory markers[5].

Due to high cost and non availability of IVIg , its use is difficult in most centers. Hence we conducted this observational study to compare IVIg vs steroids . Most studies have used IVig alone or in combination with Methylprednisolone than Methylprednisolone alone in treatment of MIS-C [1,4].

OBJECTIVES:

- To study the clinical presentation , management and outcome of children with multisystem inflammatory syndrome in children (MIS-C) associaed with COVID-19 in PICU, Bapuji Child Health Institute (BCHI) and Chigateri General Hospital (CGH), JJM Medical College, Davanagere, Karnataka in India.
- To compare the IVIg and steroids in terms of overall outcome

METHODS:

Source of Data: BCHI and CGH PICU, JJM Medical College, Davanagere

Sample size : 182
Study period: October 2020 to August 2021 (11 months)
Type of Study : Observational Study

Inclusion criteria:

- Children who met WHO criteria for MIS-C.

Exclusion criteria:

- Patient with dengue shock syndrome and bacterial sepsis.

Methodology:

This is a Retrospective Observational study conducted in JJM medical College, a Tertiary care centre, which is attached to Bapuji Child Health Institute (BCHI) and Chigateri General Hospital (CGH), Davanagere. This is a preliminary analysis of an ongoing observational study from the Division of pediatric ICU, BCHI and CGH, JJMMC, Davangere.

All children less than 18 years of age admitted to PICU with MIS-C who fulfilled the WHO criteria [2] and treated at the participating centers between October 2020 to August 2021 were included in this study. Other infective causes with similar presentation like dengue shock syndrome and bacterial sepsis were excluded from the study. Institutional ethics committee approval was taken. Data were extracted from hospital records and were entered on a Microsoft Excel spreadsheet. Variables studied included Demographics, Clinical features , laboratory parameters, treatment given and the outcome in terms of recovery or death. The cases were categorized into two groups based on their clinical presentation. Group 1 - MIS-C with shock (Those patients requiring inotrope use and/or fluid resuscitation >20 ml/kg to maintain BP more than 5th centile for age) and Group 2- MIS-C without shock..

Specific laboratory markers described for MIS-C were measured as per the treating pediatrician's discretion and institutional protocols. This included total and differential white blood cell

count, platelet count, acute phase reactants (C-reactive protein, ferritin, D-dimer), renal and liver function tests. Laboratory parameters were labeled as elevated or depressed in relation to the age-specific normal ranges.Clinical Myocarditis was defined as Clinical features of cardiac dysfunction with left ventricular ejection fraction (LVEF) <50% on echocardiography. Patients presenting with shock with left ventricular (LV) dysfunction on echocardiography were classified primarily as cardiogenic shock. Meningo-encephalitis was defined as GCS<13, with or without clinical signs of meningeal irritation with a Positive Lumbar puncture report.

SARS-CoV-2 infection was diagnosed by rapid antibody test for SARS-CoV-2 (Vitros Anti SarsCovIgG antibody kit, Ortho Clinical Diagnostics) as recommended by Indian Council for Medical Research. Additionally, history of contact with a COVID19 positive patient was also considered positive as per the WHO criteria. Outcome was classified as recovery or death. Long term follow-up of these patients is ongoing.

Statistical analysis

Data were entered and analysed using SPSS software version 22.0 (statistical package for the social science, IBM Inc. New york). For interpretation of results significance was adopted at p-value less than 0.005 and at 95% confidence interval. For comparing categorical variables Chi-square test and fisher exact test were applied. Student-t test was used to compare normally distributed data and Mann Whitney U test was used to compare data which was not normally distributed.

RESULTS

A total of 182 patients with MIS-C were treated during the study period. Demographics and clinical presentation are detailed in Table 1 And lab findings and treatment are shown in Table 2.

Table-1 Demographic And Clinical Parameters In Children With Mis-c With Covid19 (n-182)

CHARACTERS	GROUP-1 SHOCK (N-65)	GROUP-2 NO SHOCK (N-117)	P-VALUE
AGE (MEAN)	7.76±4.93	6.27±4.23	0.034
SEX(M:F)	39:26	63:54	0.423
FEVER	64/65(98%)	117/117(100%)	0.357
PAIN ABDOMEN	31/65(47%)	32/117(27%)	0.006
DIAHROHEA	27/65(41%)	23/117(19%)	0.002
VOMITING	32/65(49%)	43/117(36%)	0.101
TACHYPNOEA	35/65(53%)	44/117(337%)	0.013
RASH	33/65(50.7%)	35/117(29.9%)	0.005
JOINT PAIN	9/65(13%)	7/117(5%)	0.073
MENIGITIS	20/65(30.7%)	18/117(15.3%)	0.040
GCS	12.40±1.68	13.91±2.13	0.000
SATURATION	95.7±2.77	90.91±6.82	0.000

Table-2 Laboratory Findings And Management In Children With Mis-c (n-182)

CHARACTERS	GROUP-1 SHOCK (N-65)	GROUP-2 NO SHOCK N-(117)	P-VALUE
HB	10.30±2.20	10.46±1.974	0.626
PLATELETS	1.62±1.63	2.611±3.42	0.031
TLC	12.12±8.82	10.46±5.764	0.174
LYPHOCYTES	24.24±15.761	30.71±16.583	0.011
CRP	179.31±118.31	122.564±103.41	0.001
LDH	740.53±547.006	476.7880±296.96	0.000
FERRITIN	699.72±502.776	467.78±399.6	0.001
D-DIMER	1331.53±1258.006	821.40±634.5061	0.000
ALBUMIN	2.57±0.708	2.944±0.47090	0.000
STEROIDS	64/65(98.2%)	112/117(95.7%)	0.302
IVIG	16/65(23%)	5/117(4.27%)	0.000
INOTOPES	53/65(81.5%)	13/117(11.1%)	0.000
NIV	40/65(61.5%)	29/117(24.7%)	0.000
MV	17/65(21.2%)	0/117(0%)	0.000
CARDIAC DYSFUNCTION	26/65(40%)	29/117(24.7%)	0.032
DURATION OF PICU STAY	3.7077±2.28	2.273±1.489	0.000
DEATH	11/65(16.92%)	0/117(0%)	0.000

There was no sex predilection for children presenting with shock in MIS-C. Median age of presentation was 6.8±4.5 years.. Out of total 182 children 14 of them were infants (less than 1 year age group) and they responded promptly to treatment and recovered.

Most common presentation was symptoms of gastrointestinal system involvement (56%) ,other system involved are Respiratory system (43%), Cardiovascular system (21%),Central nervous system (20%),Musculoskeletal system (8.2%),Renal system (4.2%) we also had 2 cases of pancreatitis who fulfilled WHO criteria for MIS-C. Median age of presentation in group 1 was 7.76±4.93 years and in group 2 was 6.27±4.23years, with p value of 0.034 which is statistically significant this shows that older aged children were more prone to present in shock group. The children presented in shock group had significant symptoms pain abdomen (p value 0.002),vomiting(p value- 0.004) shock group.0.004), Diarrhea (p value-0.002) and had elevated levels of CRP (P value 0.001), LDH (p value 0.000),serum ferritin (p value-0.001) D-dimer (p value -0.001) and had significant lymphopenia (p value-0.011) and hypoalbuminia (p value-0.00) in our study.

Table-3 : Ivig Vs Steroids Group In Terms Of Outcome.

CHARACTERISTICS	IVIG N-21	STEROIDS N-161	P-VALUE
INOTROPES	15/21(71.4%)	51/161(31.67%)	0.000
DURATION OF PICU STAY	4.714±2.47	2.534±1.706	0.000
NIV	16/21(76.19%)	53/161(32.9%)	0.000
MV	7/21(33.3%)	10/161(6.2%)	0.001
CARDIAC DYSFUNCTION	9/21(42.8%)	46/161 (28.57%)	0.180
OUTCOME RECOVERED DEATHS	17/21(80.5%) 4/21 (19.0%)	154/161 (95.6%) 7/161(4.34%)	0.026

Out of 182 children only 21 received IVIg (11.2%) while major junk of patients i.e.161(96%) received methyl prednisolone. Interms of overall duration of PICU stay (p value 0.00), requirement of inotropes (p value 0.001), requirement Mechanical ventilator (0.000) and death/recovery (p value 0.000) were more in IVIg group than steroid group. This finding is explained by the fact that more sick children received IVIg due to clinical discretion of treating pediatrician . Few children with severe MIS-C could not get IVIg due to financial constraints and received only Methyl prednisolon. Thus overall it is evident that mild to moderate MIS-C the outcome does not vary much with IVIg or steroids. Only in cases of severe MIS-C IVIg may be required. Hence larger randomized controlled studies are required to conclude regarding the efficacy of IVIg v/s steroids.

Overall outcome with methyl prednisolone is comparable with IVIg. IV methyl prednisolone pulse therapy was associated with favorable immediate outcome which is comparable with IVIg in our study. Mortality in our series was 6.04% which is comparable to international studies [11,12]

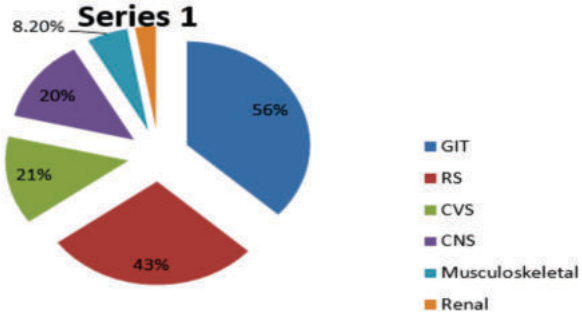

Figure 1: Organ System Involvement In Mis-c

Various systemic complications were noted during study period in figure 2. Out of 182 cases we had 40 cases with cardiac involvement(Myocarditis, Pancarditis, LV dysfunction, PAH, Pericardial effusion, endocarditis, and coronary involvement) and 18 cases with CNS involvement (Menigoencephalitis /cerebellar ataxia) and one case with new onset type1 DM with DKA with AKI and child recovered well and we also had 2 children with MIS-C who presented with pancreatitis.

DISCUSSION

Dr Sheeja Sugunanet al [8] Study population included 32 patients with MIS-C with median 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, respec-tively. In patients with SARS-CoV-2 related MIS-C, methylprednisolone pulse therapy was associated with favorable short-term outcomes .which was comparable with our study

Dhanalakshmi, et al [9] reported hypotension requiring vasoactive medications in 57% of patients presenting with PIMS-TS Previous authors have observed coronary involvement in all clinical groups of MIS-C, regardless of laboratory markers. This observation is consistent with the present series that requiring vasoactive medications and in shock group it was 81% with statistically significant .As coronary involvement was 7.6%(14cases)in our study. This implies that all patients with MIS-C would need serial echocardiographic surveillance for coronary and myocardial involvement in the acute and convalescent phase of illness, even if the initial echocardiogram was normal at least until definite guidelines for long term.

Feldstein et al,[10] report on 186 patients with MIS-C in 26 states. The median age was 8.3 years, 115 patients (62%) were male, 135 (73%) had previously been healthy, 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing, and 164 (88%) were hospitalized after April 16, 2020. Organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), hematologic in142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%). The median duration of hospitalization was 7 days. Also reported KD/ KD like illness in 36%, Myocarditis in 53%, shock in 10% and coronary aneurysms in 9% of their cohort of children with MIS-C from New York. With mortality was 4.7% [11]. Mortality in our series was 6.04% which is comparable to international studies.]

In our study out of 182 cases the median age of presentation was in shock group was 7.76±4.93 and in non shock group was 6.8±4.5 years, male were 102 (56%) ,females were 80(44%) in shock and non shock group there was no sex predilection for children who presented with shock had significant symptoms of gastrointestinal system with statistically significance (p valve –less than 0.05). And 21% with cardiac involvement Myocarditis 50%, coronary involvement 8.24% , LV dysfunction 27% and pericardial effusion 2.3% and 75% of cases in shock group .depicted in figure 2.

Dufort et al[11] a similar systematic review was published in August. similar to our study, had significant gastrointestinal symptoms as abdominal pain in severe cases, which implied an active inflammatory reaction had occurred in the digestive system cardiovascular involvement 40cases (21%) were 75% cardiac involvement was seen shock group other systems involvement included in study group were respiratory involvement CNS manifestations(9.8%) and arthritis 16 (8.7%) Lower GCS and lower saturation levels. have observed 50% MIS-C patients presenting with cardiovascular shock leading to vasopressor or inotropic support as compared to only 5% of children with KD in the United States.

Whitaker, *et al.* [3] have proposed three clinical patterns of PIMS-TS presentation those with shock and cardiac involvement, those with fever and elevated inflammatory markers without features of KD, and those who fulfilled diagnostic criteria for KD. In our series, while only 2 patient fulfilled diagnostic criteria for classical KD and 2 for unclassical KD

With raised inflammatory markers, and 2 cases with classic KD presenting with shock, and all 4 children recovered .The most important clinical factor in our patients affecting treatment and outcomes was shock inotropic and ventilatory requirements were more in children with shock. Additionally, neutrophilia, lymphopenia, elevated serum ferritin and liver enzymes were significant laboratory parameters observed in patients with shock. Use of IV immuno globulin(IVIg) was significantly more in this group of our patients, possibly because they were sicker at admission.Shock, myocarditis and LV dysfunction were all more common in older children[6] .

In our series , elevated levels , of CRP(P value 0.001), LDH (p value 0.000),serum ferritin (0.001) D-dimer (p value -0.001) and had significant lymphopenia (p value-0.011) and hypoalbumineia (0.000) were comparable with this study .

In the US MIS-C series, [11,12] IVIg (77%) and systemic steroids (49%) were used in most patients [12]. In the UK series, 71% received IVIg and 64% corticosteroids. Three patients received anakinra and eight received infliximab inotropic support was required in 47% [10,13]. In our series, 96% of the patients received steroids and 11.2% IVIG, and 35% required inotropic support. Biologicals such astocilizumab/infliximab were not used The relatively lower usage of IVIg can be attributed to the high cost of this treatment, , thus overall it is evident that mild to moderate MIS-C the outcome does not vary much with IVIg or steroids. Only in cases of severe MIS-C may be required .we can believe that at present, levels of acute phase reactants can reliably predict the subsequent clinical course of the child. The cardiac biomarkers (NT pro BNP, Troponin and CPK-MB) are of course indicative of Myocarditis and can be used to predict clinical deterioration and shock.

Generally, the short-term outcomes of MIS-C have been promising. Studies have reported favorable short-term response to IVIg and steroid.

Currently proposed treatment modalities are derived from its similarity with KD and are based on expert opinion.

Rosanova, et al [13] recent study also found a more favorable outcome in those treated with IVIg and methyl prednisolone than those treated with IVIG alone In patients with MIS-C with shock and multi-organ dysfunction syndrome, IV methyl prednisolone pulse therapy was associated with favorable immediate outcome, which is comparable with our study.

Steroids are a low-cost therapy that are easily available and understanding their potential benefits as a primary treatment for MIS-C. Is vital from a global health perspective.The cost of diffrence between Methylprednisolone and IVig is substantial.for a 25kg child. 10mg/kg methylprednisolone cost 250 rupees,where as 2gram/kg IVig cost 10,000 rupees in india.As a blood product it poses additional challenges in term of availability,cost and acceptability. The risk effects of corticosteroids are mild and transient in children.IVIg can cause hypersensitivity reactions in children and risk of overload in cardiac compromise.

Treatment with IVIg in resource limited settings is a challenge. In our study, children who received methyl prednisolone were significantly older and had a higher number of organ involvement. Outcome measures showed a favorable role for pulse methyl prednisolone in the treatment of MIS-C.

The present study reports favorable outcomes in MIS-C with pulse methyl prednisolone therapy.

CONCLUSION

Multisystem inflammatory syndrome in children is a new pediatric entity which is serious and potentially lethal with high intensive care admissions if not detected early. Diagnosis, management in MIS-C is a challenge. And with prompt early recognition and medical attention, if treatment initiated early with methyl prednisolone has got good outcome. Our results suggest that favorable outcomes in MIS-C could be achieved by sparing IVig infusion in the earliest phase of disease in resource limited settings.

REFERENCES:

1. Multisystem Inflammatory Syndrome in Children (MISC) Associated with Coronavirus Disease 2019. Centers for Disease Control and Prevention. Emergency preparedness and response: Health alert network. May 14, 2020. Available from: https://emergency.cdc.gov/han/2020/ han00432.asp. Accessed July 15, 2020.
2. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief: World Health Organisation. 15 May 2020. Available from: *https://www.who.int/publications-detail/multisysteminflammatory-syndrome-in-children-andadolescents-with-covid-19*. Accessed July 15, 2020.
3. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, *et al*. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020; e2010369.
4. Balasubramanian S, Nagendran TM, Ramachandran B, Ramanan AV. Hyper-inflammatory syndrome in a child with COVID-19 treated successfully with Intravenous immunoglobulin and tocilizumab. Indian Pediatr. 2020; S0974 75591600180
5 RCPCH. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with Covid-19. Royal College of Paediatric and Child Health (RCPCH). COVID-19. 2020 .pp.1-6.
6 Shreepal Jain, SupratimSen, SrinivasLakshmivenkateshiah, PrashantBobhate,

SumitraVenkatesh, et al. Multisystem inflammatory syndrome in children with Covid-19 in Mumbi, India. Indian Pediatrics 2020 Nov.15;57:1015-1019.
7 McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, Treatment, and Long-term Management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association. Circulation. 2017;135: e927-99.
8. Sugunan, et al. Clinical Profile and Short-Term Outcome of Children With SARS-CoV-2 related Multisystem Inflammatory Syndrome (MIS-C) Treated With Pulse Methylprednisolone indian pediatrics April 20, 2021; ***PII:*** S097475591600319
9. Dhanalakshmi K, Venkataraman A, Balasubramanian S,Madhusudan M, Amperayani S, Putilibai S *et al*. Epidemiologicaland clinical profile of pediatric inflammatorymultisystem syndrome - temporally associated with SARSCoV-2 (PIMS-TS) in Indian children. Indian Pediatr. 2020;
10. Feldstein LR, Rose EB, Horwitz SM, Collins JP,Newhams MM, Son MBF, *et al*. Multisystem inflammatory syndrome in U.S. children and adolescents.N Engl J Med. 2020; 383:334-6.
11. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM Muse A, Rowlands J, *et al* . Multisystem inflammatory syndrome in children in New York State. N Eng Med. 2020;383: 347-58
12. New York State Department of Health. Health advisory: pediatric multi-system inflammatory syndrome temporally associated with COVID-19 interim case definition in New York State. May 13, 2020 (https://health .ny .gov/ press/ releases/ 2020/ docs/ 2020 -05-13_health_advisory .pdf)
13. Maria teresa rosanova,1 guadalupe perez,1 maria martha katsicas,2 ana paula ariaspediatric inflammatory multisystem syndrome associated with sars-cov-2: a retrospective cohort Study from Argentina Indian Pediatr. 2020
14. Shobhavat L, Solomon R, Rao S, et al. Multisystem inflammatory syndrome in children: Clinical features and management-intensive care experience from a pediatric public hospital in Western India. Indian J Crit Care Med. 2020;24:1089-1094
15. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of childrenwith paediatric inflammatory multisystem syndrome temporally associated with SARSCoV-2 (PIMS-TS) in the UK: A multicentre observational study. Lancet Child AdolescHealth. 2020;4:669-77
16. Chandrika S. Bhat, Latika Gupta, S. Balasubramanian, Surjit Singh, et al. Hyperinflammatory syndrome in children associated with COVID-19: Need for Awareness. Indian Pediatrics 2020 July 15;1-12. [E-Pub Ahead of Print]
17. S. Balasankar, NandiniKuppusamy, D. Rajkumar, M. Balasubramanian, et al. Practical guide to management of MIS-C. ICH & RC, Madurai Medical College, 2020.