Multisystem Inflammatory Syndrome in Children (MIS-C): Comparison of the First and the Second Waves

This study comparing the different parameters of children suffering from multisystem inflammatory syndrome in children (MIS-C) in Kolkata, India, during the two waves (July, 2020-January, 2021 and April-July, 2021) showed that the second wave had a higher propensity of Kawasaki disease (KD)-like presentation, cardiac affection and pediatric intensive care unit admission, and increased incidence of use of steroids for treatment.

Keywords: *Delta variant, Kawasaki disease, Steroids*.

Multisystem inflammatory syndrome in children (MIS-C) is a well described hyperinflammatory syndrome occurring 2-8 weeks after symptomatic/asymptomatic severe acute respiratory syndrome 2 (SARS-CoV-2) infection [1,2]. The first MIS-C wave hit eastern India around July, 2020 and lasted till January, 2021. The second wave of MIS-C started in April, 2021 and went on till July, 2021. The second coronavirus disease 2019 (COVID-19) wave in India was mainly of the Delta variant, and resulted in higher number of hospital admissions in adults and increased mortality [3]. The second wave of MIS-C that occurred in the aftermath of this COVID wave was shorter lasting, but like the adult Delta wave, was more intense, affecting a higher number of children younger than 5 years.

This is a single-center study of MIS-C patients diagnosed by the World Health Organization (WHO) criteria admitted at Institute of Child Health, Kolkata, a tertiary care pediatric hospital in eastern India. Hospital records of the clinical presentations, laboratory data, echocardiographic features, treatment protocols and outcomes of these patients were retrieved from hospital records and analyzed.

The comparative data between the two waves of MIS-C are summarized in **Table I**. There was an appreciable change in the clinical picture with increased incidence of patients presenting with only fever without organ involve- ment, and Kawasaki disease (KD)-like presentations. Majority of children during the first wave had abdominal symptoms and rashes, the numbers were much less during the second wave; but there was a higher propensity of cardiac affection and need for pediatric intensive care unit (PICU) admission. Statistical analysis of the results by the assumptions of the two sample *z*-proportion hypothesis test showed that history of SARS-CoV-2 positivity was statistically significant during the second wave, presence of rashes and abdominal symptoms were significant during the first wave.

Table I Characteristics of Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) Following the First and the Second Wave of Coronavirus Disease 2019 (COVID-19), Kolkata

Clinical presentations	*First wave (n=75)*	*Second wave (n=48)*
Age (y)[a]	5.66 (3,8)	4.62 (1.7,7)
History of SARS-CoV-2 positivity	32 (42.5)	33 (68.75)
Rash	64 (86)	19 (39.5)
Abdominal symptoms	53 (70.6)	20 (41.6)
Only febrile phenotype	3 (4)	13 (27.1)
Myocarditis	21 (28)	19 (39.5)
Coronary artery dilatations	22 (29.3)	23 (47.9)
PICU admission	34 (45.3)	28 (58.3)
Death	0	3 (6.3)
Treatment		
Intravenous immunoglobulin (IVIG)	29 (38.7)	0
IVIG + steroids	43 (57.3)	32 (66.6)
Only steroids	4 (5.3)	14 (29.1)
Biologics (infliximab)	0	3 (6.3)

Data presented as no. (%) or [a]median (IQR). SARS-CoV-2-severe acute respiratory syndrome coronavirus 2; PICU-pediatric intensive care unit.

The second wave also saw a paradigm shift in management, with an increased early use of steroids. During the first wave, especially in the earlier months, there was a predominance of intravenous immuno-globulin (IVIG) use. However, with passage of time and experience, use of methylprednisolone increased with the result that none of the patients were treated by only IVIG during the second wave. On the contrary, many patients without myocarditis responded only to methylpre-dnisolone and did not require IVIG. Use of early steroids increased, and only patients with myocarditis and KD-like presentation received IVIG. Infliximab was used by us in three IVIG and steroid resistant KD-like patients, who also had coronary artery dilatations.

We had previously done a retrospective analysis on the use of steroids in treating MIS-C [5]. We found that more severe cases of myocarditis with reduced ejection fraction required steroids in addition to IVIG for treatment. During the second wave, we initiated treatment with methylprednisolone in all and IVIG was added in patients with severe myocarditis presenting with shock. Patients presenting with features of myocarditis and shock were

started on pulse methylprednisolone (10 to 30 mg/kg/day), sicker children received higher doses, usually resulting in clinical improvement by the next 2 to 3 days.

There was no mortality during the first wave, whereas there were three deaths during the second wave; one due to refractory macrophage activation syndrome (MAS) and two with late referral, who succumbed to severe myocarditis and refractory hypotension.

The antigenic shift of the virus led to differences in severity and outcome between the two COVID waves. This difference was also evident amongst the MIS-C patients with change in clinical presentations, the Delta variant leading to a disease of increased severity and poorer outcome.

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MIMI GANGULY, PURBASHA GUPTA, DEBOPAMA BISWAS, SUBHAJIT DEY SARKAR, PRIYANKAR PAL*
Pediatric Rheumatology Unit, Institute of Child Health, Kolkata, West Bengal.
**mailme.priyankar@gmail.com*

REFERENCES

1. Dhanalakshmi K, Venkataraman A, Balasubramanian S, et al. Epidemiological and clinical profile of pediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS) in Indian children. Indian Pediatr. 2020;57: 1010-1014.
2. World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents Temporally Related to COVID-19. WHO; 15 May, 2020. Accessed on Nov 31, 2022. Available from: *https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19*
3. Kumar S. Second wave of COVID-19: emergency situation in India. J Travel Med. 2021;28:aab082.
4. Ganguly M, Nandi A, Banerjee P, et al. A comparative study of IL 6, CRP and NT proBNP levels in post COVID multisystem inflammatory syndrome in children (MISC) and Kawasaki disease patients. Int J Rheumat Dis. 2022;25:27-31.
5. Pal P, Bathia JN, De H, et al. A retrospective analysis of the need for methylprednisolone in addition to IVIG for treating multisystem inflammatory syndrome in children. Rheumatology. 2022;61:e141-2.

Neonatologist-Performed Ultrasound-Guided Internal Jugular Vein Cannulation

We retrieved data of ultrasound-guided neonatal internal jugular vein (IJV) cannulations done between November, 2020 and March, 2021. Of the 33 ultrasound-guided IJV cannulation in neonates, 32 were successful with overall success rate of 97%. Median (IQR) number of attempts per insertion was 2 (1,3.5). There were no major complications observed during the insertion of the catheter. In one instance, inadvertent carotid artery puncture was encountered, without significant bleeding.

Key words: *Central line, Percutaneous, Simulation, Training*.

Trial registration: CTRI/2021/07/034944

Traditionally, cannulation of internal jugular vein (IJV) is performed by a 'blind' technique based on anatomical landmarks [1]. This technique; however, has a high failure rate and may be associated with several complications such as inadvertent carotid artery puncture, pneumothorax or hemothorax, and formation of hematoma, particularly in young infants [1,2]. Ultrasound (USG)-guided IJV cannulation is a standard technique in pediatric population and is reported to have reduced risk of cannulation failure as compared to conventional approach [3]. Literature on neonatal USG-guided IJV cannulation is limited, and has been mainly described by anesthesiologists or pediatric surgeons [2,4-6].

We describe the success rate and complications of neonatologist-performed USG-guided IJV cannulation

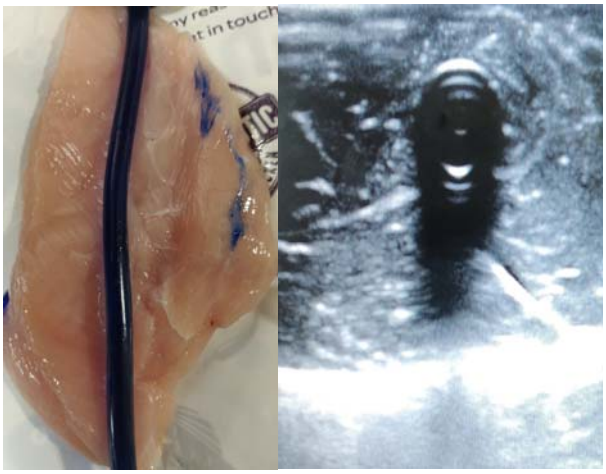

Fig. 1 Chicken breast simulator and its ultrasound image. Left side shows one chicken breast with dye filled tube. It is covered with another breast on top and wrapped with a plastic cover. Right side shows ultrasound image of model casting an acoustic shadow resembling a large vein.

from a tertiary care unit. The unit is a 32-bedded level 3B accredited neonatal intensive care unit. The unit has more than 1200 admissions per year, of which approximately 60% are extramural neonates; most being referred in critical condition such as hypoxic respiratory failure or shock, without any reliable venous access. In this retrospective study, demographic and clinical details of neonates who underwent IJV cannulation between November, 2020 and March, 2021 were retrieved. Outcome measures were success of cannulation, number of attempts per cannulation, catheter dwell time, and complications such as carotid artery puncture, pneumothorax, hematoma formation, cardiac tamponade, arrhythmia and central line-associated blood stream infection. The study was approved by institutional ethics committee and registered with the Clinical Trial Registry of India. The neonatologists acquired necessary training and expertise by first observing the cannulation performed by interventional radiologists, and then practicing puncturing at artificial targets in phantom models. This was followed by training on a simulation model, prepared by placing a rubber tubing filled with fluid, tunnelled in between chicken breast pieces, tightly wrapped in a plastic cover (**Fig. 1**) [7].

All IJV cannulations were performed by one of the two neonatologists, using Sonosite M Turbo machine with 13-6 MHz linear probe. Informed consent was obtained from the parents before the procedure. Neonates were positioned in the Trendelenburg position by placing a shoulder roll and head was tilted to the opposite side. We used short-axis, out-of-plane method, in which, USG probe was kept in a perpendicular manner, approximately at the base of Sedilot triangle to visualize IJV and surrounding structures in cross section. Internal jugular vein was differentiated from carotid artery based on its ellipsoid shape, larger size, presence of compressibility and absence of pulsatility. Venepuncture was performed under real time USG visualization with a 22-gauge cannula, introduced just behind the mid-point of the probe, at an angle 45-60% and directing it towards the ipsilateral nipple. Non-dominant hand was used to hold the probe and dominant hand was used for needle puncture. Successful puncture was ascertained by free flow of blood through the cannula, following which a guide-wire of calibre 0.46 mm was introduced through it. Subsequently, cannula was removed, while keeping guide wire in place and a catheter of 22-gauge, 4 cm length (leaderflex, Vygon) was threaded over the guide wire using Seldinger technique. Following this, guide-wire was removed and line was secured, after ensuring free flow of blood. Radiograph was done to confirm tip position and to evaluate for complications such as pneumothorax or hemothorax. Number of attempts and complications were routinely recorded on the patient's case record. Maximum five attempts were made, following which the procedure was abandoned. Cardiac tamponade was identified by sudden onset hypotension, muffled heart sounds and enlarged cardiac silhouette on radiograph. Cardiac arrhythmia was defined as any change in the normal sequence of heart rhythms during or after catheterization and confirmed on electrocardiogram. Central line-associated blood stream infection was defined as positive blood culture not related to an infection at another site, when the jugular line was in place at the time of or within 48 hours before the onset of infection.

During the study period, a total of 33 IJV cannulations were performed on 29 neonates. Of these, 32 (97%) were successful. Median (IQR) number of attempts per insertion was 2 (1, 3.5). All IJV cannulation were performed on extra-mural neonates, who had no access for umbilical or peripherally inserted central venous catheters. Majority (68.2%) of cannulations were performed on right IJV. The mean (SD) birth weight and gestation of neonates were 2405 (860) g and 35.17 (4.2) weeks, respectively. Nineteen neonates were mechanically ventilated at the time of line insertion. Cumulative success rate with first, second and third attempt was 39%, 51.5% and 75.8%, respec-tively. Median (IQR) catheter dwell time was 13.5 (7.0, 17.5) days. There were no major complications observed during insertion of catheter. In one neonate, who was extremely preterm, inadvertent carotid artery puncture occurred without significant bleeding. Attempt to cannulate was unsuccessful in another neonate, who was born at term gestation. In this patient, cannulation was attempted without use of sedation, as there was no IV access available prior to procedure. Central line associated blood stream infection was reported in three cases. All except three catheters were removed once not required. One catheter was removed on day 8 of insertion due to local extravasation, while two were removed on day 15 and day 22 due to catheter occlusion.

Literature regarding feasibility and success rate of neonatologist-performed USG-guided IJV insertion is limited. Goldstein, et al. [5] reported feasibility of USG-guided IJV cannulations in 20 neonates, which were performed by pediatric surgeons or anesthesiologists [5]. Cannulations were performed successfully in all neonates without any complication related to the procedure. Similarly, Tapia, et al. [2], in a case series of USG-guided IJV cannulation performed on neonates by pediatric surgeons, observed a high success rate (94%) with median (IQR) number of attempts 2 (1,8). Authors reported procedure related complications in none of the

neonates [2]. Oh C, et al. [4] reported serious complication in one out of 12 IJV cannulations performed by pediatric surgeons, in the form of hemoericardium [4].

USG-guided cannulation of peripheral veins in neonates is technically challenging as these vessels have a narrow lumen and small diameter. We performed IJV cannulation in extramural neonates, in whom the umbilical and peripheral veins were exhausted. Internal jugular vein was preferred over femoral veins as it is a larger and more easily accessible vein with a diameter that exceeds femoral vein by at least 50% [8]. We used single tube, chicken breast simulation model for training. Further improvement of this model can be done by inserting another fluid-filled tube to simulate carotid artery and therefore enhancing skills to avoid carotid artery puncture.

To the best of our knowledge, this is the first feasibility report of neonatologist-performed USG-guided IJV cannulation. Our findings suggest that neonatologist-performed USG-guided IJV cannulation is feasible, with success and complication rates comparable to those reported with other interventional operators [2,4-6]. Before contemplating the procedure on neonates, intensivists should acquire adequate skills by undergoing systematic training on simulation models.

Ethics clearance: EIC, Sir Ganga Ram Hospital, No. EC/04/21/1875, dated June 08, 2021.
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ANUP THAKUR,* MANOJ MODI, NEELAM KLER, PANKAJ GARG
Department of Neonatology, Institute of Child Health, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi
**dr.thakuranup@gmail.com*

REFERENCES

1. Troianos CA, Hartman GS, Glas KE, et al. Councils on Intraoperative Echocardiography and Vascular Ultrasound of the American Society of Echocardiography. Guidelines for Performing Ultrasound Guided Vascular Cannulation: Reco-mmendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr. 2011;24:1291-318.
2. Montes-Tapia F, Rodríguez-Taméz A, Cura-Esquivel I, et al. Efficacy and safety of ultrasound-guided internal jugular vein catheterization in low birth weight newborn. J Pediatr Surg. 2016;51:1700-3.
3. de Souza I, Brandao, MB, Nadal JH, Nogueira RJ. Ultrasound guidance for pediatric central venous catheterization: A meta-analysis. Pediatrics. 2018;142: e20181719.
4. Oh C, Lee S, Seo JM, Lee SK. Ultrasound guided percutaneous internal jugular vein access in neonatal intensive care unit patients. J Pediatr Surg. 2016;51:570-2.
5. Goldstein SD, Pryor H, Salazar JH, et al. Ultrasound-guided percutaneous central venous access in low birth weight infants: Feasibility in the smallest of patients. J Laparoendosc Adv Surg Tech A. 2015;25:767-9.
6. Uzumcugil F, Yilbas AA, Akca B. Ultrasound-guided anatomical evaluation and percutaneous cannulation of the right internal jugular vein in infants <4000 g. J Vasc Access. 2020; 21:92-7.
7. Fürst RV, Polimanti C, Galego SJ, et al. Ultrasound-guided vascular access simulator for medical training: Proposal of a simple, economic and effective model. World J Surg. 2017; 41:681-6.
8. Tailounie M, Mcadams LA, Frost KC, et al. Dimension and overlap of femoral and neck blood vessels in neonates. Pediatr Crit Care Med. 2012;13:312-7.