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Dear Esteemed Members,

Greetings from NNF Delhi!

It gives me a feeling of immense pleasure to see the success of our Monthly Bulletin **NeoClips** (Neonatal Clinical Practice). This idea has emerged as a unique proposition from the minds of experienced neonatologists teaming up with young budding counterparts.

This section covers a few important topics like a review article on Delivery room management of neonates born through Meconium-stained Amniotic Fluid. An interesting case of aortic thrombosis has been mentioned in case section.

My sincere congratulations to the NeoClips team for their continuing efforts in publishing this monthly bulletin.

With Best Regard

L Bharti

Dr. Lalan Bharti
President, NNF Delhi

From Secretary's Pen

DR KUMAR ANKUR

Secretary, NNF Delhi

Dear friends,

Warm greetings from National Neonatology Forum, Delhi!

It gives me immense happiness to see the success of NNF Delhi monthly E- Bulletin, launched in February 2022 with the name of '***NeoClips' (Neonatal Clinical Practice)***. Every month it's getting better & better. And credit goes to the Chief editor Dr Naveen Gupta & his exceptional team. OSCE as system wise which would be very helpful for Neonatal fellow/Residents/Postgraduates. This month we have included some interesting topics like delivery room management of babies born through meconium-stained liquor. An interesting Xray of a wandering umbilical line has been discussed in the image section.

We are requesting all the esteemed members to contribute to these E-bulletins. We shall be giving the due credits to all the contributors.

We eagerly look forward to your feedback and hope to give you an experience that you will cherish forever!

Dr. Kumar Ankur
Secretary, NNF Delhi

Editor's Desk

DR NAVEEN PARKASH GUPTA

Chief Editor, Neo Clips

Dear Friends,

Greetings from the NeoClips team.

As Editor I would like to start by thanking the editorial team for the effort and the authors for their contribution to this and previous issues.

I would like to thank all the readers for giving positive inputs in every edition.

In the present issue, we have covered some interesting topics.

An interesting case of aortic thrombosis has been covered in case report section.

Delivery room practices for babies born to meconium-stained liquor have changed recently. The same has been covered in review article.

An interesting case of Giant congenital melanocytic naevi has been covered in the picture of the month.

The image section describes an interesting Xray of umbilical venous line.

The OSCE section covers the Central Nervous System.

We hope that you will enjoy reading this issue. Please share your feedback with us. It will help us improve the journal.

Dr Naveen Parkash Gupta

A rare condition mimicking coarctation of the aorta in the neonate

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A male neonate was born at 38 weeks gestation weighing 2500 gms to a primigravida mother through a vaginal route with an uneventful antepartum and intrapartum period. At 96 hrs of life, the baby was admitted with poor feeding, lethargy and jaundice. His vitals were stable at admission but he had excessive weight loss (20%) with admission weight but he had excessive weight loss being 2000gms and was in moderate bilirubin encephalopathy. The baby was started with fluid rehydration, intensive phototherapy and an urgent double volume exchange transfusion (DVET)was planned. Blood investigations revealed: Serum urea- 131 mg%, S creatinine 0.9 mg%, Na- 161 meq/l, K- 4.5 meq/l, S. Bil 38.6 mg%(Total), 8.1 (D), mother and baby blood group –O positive, Retic count- 2%, Peripheral smear- no hemolysis. Double volume exchange transfusion (DVET) was performed with umbilical arterial (UAC) and umbilical venous catheter with UAC tip at T8 level. Blood was pulled out from the UAC and pushed back through UVC. Bilirubin levels decreased and phototherapy was discontinued after 48 hrs. serum sodium normalized in the next 36 hrs. However, urine output started decreasing after 48 hours of admission. The baby was also noted to have cold lower limbs, feeble pulses and unrecordable blood pressure in legs with high blood pressure (>99th centile) in upper limbs. Urgent echocardiography was done which showed a peculiar finding – The arch of the aorta with the beginning of descending aorta was normal with adequate flow. Near the region of T7-T8, there was a rounded echogenic shadow s/o thrombus causing obstruction to the aortic flow. The baby was planned for thrombolytic therapy through the UAC, however parents took the baby against medical advice in view of poor long-term prognosis due to bilirubin encephalopathy.

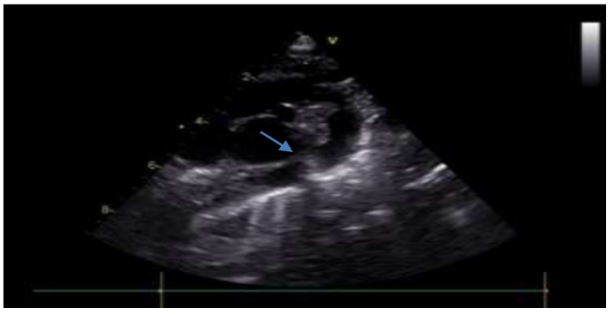

Fig 1 Shows thrombus in the descending aorta

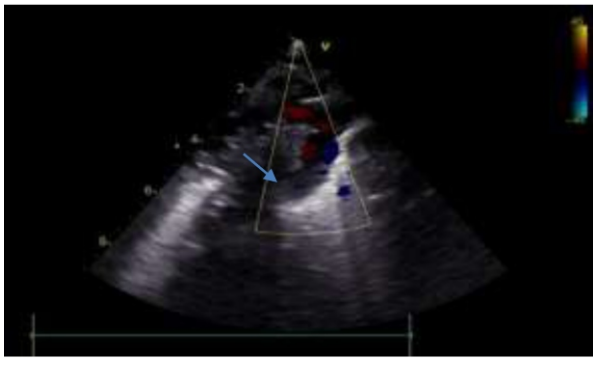

Fig 2 showing adequate flow in arch and isthmus with thrombus in the descending aorta (T7-8 level

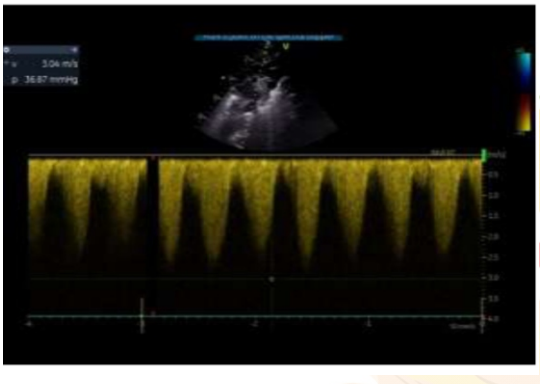

Fig 3 showing Continous wave Doppler with diastolic tailing and obstruction(pressure difference of 36 mmhg)

Discussion

Neonatal aortic thrombosis is an uncommon entity. The incidence of symptomatic thromboembolism is around 1 case per 400 admissions to NICU or 1 case per 20,000 births with arterial thrombosis being half as common compared with venous thrombosis. (1,2)

Aortic thrombosis can manifest as decreased lower limb pulses, discolouration of lower limbs, congestive heart failure or acute kidney injury.

UAC is the commonest risk factor for aortic thrombosis with nearly 78 % patients having an indwelling catheter.(3) 20-30% of neonates with UAC have ultrasonographic evidence of aortic thrombosis with the commonest complication being hypertension.(4,5) Only 5 cases of hypernatremic dehydration-associated thrombosis have been reported so far. Other identified risk factors include sepsis, polycythemia, asphyxia and the presence of prothrombotic conditions. Recommendations on screening for thrombophilia in the neonatal period for thrombosis are controversial. Prothrombotic disorders including deficiencies of antithrombin, protein C, protein S, Factor V Leiden mutation and prothrombin G20210A, methylene tetrahydrofolatereductase C677T and elevated fasting homocytseine have been associated with thrombosis in neonates and children. (6) The investigation of choice is ultrasonography because it is non invasive and available at the bedside. Contrast angiography considered as gold standard by few, is rarely feasible in this population. (7). Limited data exist to guide the best treatment modality with options being heparin, Low molecular weight heparin, tissue plasminogen activator (tpa) and surgical removal. Thrombolytic therapy with tPa should be considered when aortic thrombosis is organ or life-threatening. tpa infusion is recommended at a rate of 0.1-0.5 mg/kg/hr for 6 hours and the second dose can be considered if there is no improvement clinically or radiologically. Measuring the fibrin degradation products and D dimer can be useful in determining whether the fibrinolytic effect is evident. Repeated courses have not been shown to increase bleeding rates. Repeated courses of systemic tPA may provide resolution of thrombus in patients showing no initial response.(8) Anti-coagulation with LMWH or unfractionated heparin should be used if thrombosis is non-organ/ limb or life-threatening or contraindications to thrombolytic therapy exists.

Nearly 82% of neonates have survived to hospital discharge with hypertension and limb length discrepancy being commonest complications.

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Delivery room management of neonates born through Meconium-stained Amniotic Fluid

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Introduction

'Meconium', a nomenclature derived from the Greek word '*mekoni*' which means poppy juice or opium because of its black tarry appearance. Passage of in-utero meconium complicates nearly 10-26% of all deliveries with one-quarter of them being depressed at birth and about 4-10 % developing meconium aspiration syndrome (MAS).(1-4) Infants with MAS are at increased risk of mortality, and both short- and long-term morbidities, therefore, antenatal and postnatal interventions aimed at prevention as well as treatment of MAS have intrigued many researchers. Delivery room management of neonates born through the meconium-stained amniotic fluid (MSAF) has significantly evolved over the last four decades with a trend toward less aggressive management.(5) However, some questions still remained unanswered in this aspect of management and require well-conducted multicentric trials.

Pathophysiology of MAS

MAS is a clinical diagnosis that involves the delivery of a neonate born through MSAF with respiratory distress, a characteristic appearance of chest radiograph and a lack of an alternative diagnosis to explain.(5)

Major mechanisms contributing to the pathophysiology are

(i) Physical Obstruction of airways, which can either be partial, producing ball valve effect and air trapping in the airways, or complete, leading to atelectasis and V/Q mismatch in the lungs.

(ii) Inflammatory response due to various cytokines, chemokines, activation of the complement cascade, arachidonic metabolites and reactive oxygen species. These inflammatory mediators not only produce chemical pneumonitis but also ignites a systemic inflammatory response.

(iii) Surfactant inactivation and/ or decreased synthesis (

iv) Fetal compromise and hypoxia, leading to remodelling of the pulmonary vasculature, which in turn results in pulmonary hypertension and subsequent postnatal hypoxia, hypercarbia and acidosis.(6) Hence the interaction of meconium with bronchial and alveolar epithelium and the host immune system plays a major role in the pathophysiology of MAS.(7,8) Asphyxia being commonly associated with MAS additionally contributes to ventricular dysfunction and hence may further complicate pulmonary hypertension.(9,10)

Delivery room management: Historical aspect

Neonates born through MSAF may require resuscitation at birth and are at risk of certain morbidities such as hypoxic-ischemic encephalopathy (HIE), respiratory difficulty varying from mild respiratory distress to life-threatening respiratory failure, persistent pulmonary hypertension of the newborn (PPHN), air leaks, bronchopulmonary dysplasia (BPD), prolonged hospital stay, post-discharge re-admissions for recurrent respiratory tract infections, reactive airway disease, poor growth, hearing loss and poor long-term neurodevelopmental outcome.(11-15)

Certain evidence-based changes have evolved over the last few decades in the delivery room management of such neonates. In the early 1960s, airway obstruction by meconium was assumed to be the primary cause of MAS. Hence, intrapartum

oropharyngeal suctioning (IP-OP) after the delivery of the neonatal head followed by endotracheal (ET) suctioning was performed routinely for all neonates born through MSAF until the International Liaison Committee on Resuscitation (ILCOR) Consensus on Science with Treatment Recommendations (CoSTR) 2000 recommended performing ET suction only in neonates who were non-vigorous (NV) at birth (defined as a heart rate less than 100 beats, decreased tone and poor breathing efforts). ILCOR in 2005 recommended that routine oropharyngeal suctioning before delivery of shoulders was not necessary in babies born through meconium-stained amniotic fluid.(16) This was largely based on the well-designed prospective multicentric trial by Wiswell et al and was further affirmed in the metanalysis by Halliday et al.(17,18) In fact, amnioinfusion was another modality, considered to reduce the incidence and severity of MAS by diluting meconium and decreasing cord compression.(19) However, the publication of one of the largest multicentric randomized controlled trial in 2005, showed no reduction in MAS and mortality by the practice of amnioinfusion for MSAF.(20) Following this the American College of Obstetrics and Gynaecology (ACOG) released a committee opinion that 'routine prophylactic amnioinfusion for the dilution of MSAF' is not recommended. (21)

Following these two major changes in the immediate postnatal management of infants born through MSAF, concerns were being raised regarding routine ET suction of NV MSAF neonates.(22) ET suctioning is supposed to benefit if performed before the meconium is aspirated into distal airways and lungs. However, given the possibility that significant meconium may have been aspirated into fluid-filled lungs in-utero, routine postnatal ET suction may not be beneficial in most NV MSAF infants.(23) In addition, tracheal intubation using direct laryngoscopy is known to be associated with bradycardia and hypoxia; and might delay the timely initiation of positive pressure ventilation (PPV).(24) Three RCTs (Nangia et al, Chettri et al, Kumar et al) did not show any significant benefits with routine ET suctioning in NV MSAF neonates.(25-27) Accordingly, ILCOR CoSTR 2015, gave a weak recommendation based on low CoE against routine immediate laryngoscopy for ET suctioning in NV MSAF neonates and suggested for initiating immediate resuscitation without direct laryngoscopy.(22)

NRP-based recommendation of neonates born through meconium-stained amniotic fluid

Neonatal resuscitation Textbook	Guidelines for approach to an infant born through MSAF
1st Edition, 1987	Meconium thin, watery: No special management Meconium thick, particulate (pea soup): 1. **Intrapartum Oropharyngeal Suctioning (IP-OP):** Suction mouth, oropharynx & hypopharynx at perineum as soon as the head is delivered 2. **Endotracheal Intubation & Tracheal Suctioning:** Clear hypopharynx, intubate & suction trachea under **direct visualization**
2nd Edition, 1990	Same as above
3rd Edition, 1994	1. **Intrapartum Oropharyngeal Suctioning (IP-OP)** 2. Thin meconium with depressed infant or thick particulate meconium: **ET Suctioning**

4th Edition, 2000	1. **Intrapartum Oropharyngeal Suctioning (IP-OP)** 2. **Vigorous: NO ET Suctioning; Clear** mouth & nose of secretion. 3. **Non-Vigorous: ET Suctioning** under direct visualization
5th Edition, 2006	**Intrapartum Oropharyngeal Suctioning (IP-OP) NOT Recommended** 1. **Vigorous: NO ET Suctioning; Clear** mouth & nose of secretion. 2. **Non-Vigorous: ET Suctioning** under direct visualization
6th Edition, 2011	Same as above
7th Edition, 2016	1. **Vigorous: NO ET Suctioning;** Clear mouth & nose of secretion if required 2. **Non-Vigorous: Routine ET Suctioning NOT recommended. Initiate PPV if infant is not breathing or HR <100/min after the initial steps of resuscitation.**

Lacunae in the current literature

Unlike other recommendations by ILCOR which were based on multicentric and multinational RCTs conducted in both high-income countries (HICs) and low-and-middle-income countries (LMICs) settings, the current recommendation was based on evidence generated by single-centre RCTs from LMICs enrolling a relatively smaller number of babies. Since the CoE was low, the outcomes of NV MSAF neonates who are resuscitated according to the new recommendations need to be scrutinized.

With the burden of mortality and morbidity related to MAS being much higher in LMICs when compared to HICs where high-cost interventions such as inhaled nitric oxide (iNO) and extracorporeal membranous oxygenation (ECMO) have significantly reduced mortality, it is important that the policy change to no routine ET suction in NV MSAF neonates cared for in HICs and LMICs be evaluated differently.

Recent evidence

Recently, eight observational studies have evaluated the outcomes of infants born through MSAF post-policy change to no routine ET suction.(28-35) The results from these studies are largely inconclusive. Further, the generalizability of evidence from HICs to LMICs and vice-versa is contentious.

Author	Population	Result
Chiruvolu et al(28) 2018	2 epochs of non-vigorous neonates born through MSAF: • Oct'15- Sept'16 Retrospective cohort (n=130) • Oct'16-Sept'17 Prospective cohort (n=101)	• A significantly higher proportion of newborns were admitted to the NICU for respiratory issues in the prospective group compared with the retrospective group (40% vs 22%; OR 2.2; 95% CI:1.2-3.9). • Significantly higher proportion of infants needed oxygen therapy (37% vs 19%; OR 2.5; 95% CI: 1.2-4.5), mechanical ventilation (19% vs 9%; OR 2.6; 95% CI: 1.1-5.8), and surfactant therapy (10% vs 2%; OR 5.8; 95% CI: 1.5-21.8) in prospective group. • No differences in the incidence of other outcomes, including MAS

Edwards et al(29) 2019	2 epochs: • Epoch 1: 2013-15 (n=222438) • Epoch 2: 2017 (n=78712)	• NICU admissions for MAS infants decreased from 1.8% to 1.5% (RR: 0.82; 95%CI: 0.68-0.97) • Treatment with conventional or high-frequency ventilation, iNO, or ECMO remained unchanged. • Increased use of surfactant (24.6% to 30%, 1.22; 1.02-1.48), Mortality (2.6 to 2.9%, 1.12; 0.74, 1.69) and moderate/severe hypoxic-ischemic encephalopathy (5.4 to 6.8%, 1.24; 0.91, 1.69) in no ET suction cohort.
Aldhaferri et al(30) 2019	2 Epochs of neonates born through MSAF: • Period 1- Jan'16- Dec'16 (n=261) • Period 2- Jan'17-Dec'17 (n=159)	• A nonsignificant lower rate of intubation at birth (2.3% vs 0.6%), admission to neonatal intensive care unit (3.8% vs 3.1%), and meconium aspiration syndrome (1.5% vs 0.6%) in period 2 compared to period 1
Kalra et al(31) 2020	2 epochs of infants with MAS: • Epoch 1: 2013-15 (n=375) • Epoch 2: 2017 (n=282)	• Among infants with MAS, delivery room intubations decreased (44.3 vs. 35.1%; p = 0.005) • Similar proportion of infants required invasive respiratory support, inhaled nitric oxide or extracorporeal membrane oxygenation
Meyer et al(32) 2020	2 epochs of term infants born through MSAF: • Phase A: 2014-2015 (n=364) • Phase B: 2016-1017 (n=208)	• 1-minute Apgar scores were significantly improved in Phase B. • Need for continued respiratory support after the first day of life also decreased. • Admission rates to the NICU, length of stay, and the need for respiratory support on admission were unchanged.
Oommen et al(33) 2021	2 epochs of NV MSAF infants • Retrospective group: Aug'15- July'16 (n=72) • Prospective group: Oct'16-Sept'17 (n=157)	• No differences in the incidence of MAS, the requirement of mechanical ventilation, inhaled nitric oxide or surfactant therapy • Less NICU admissions in prospective cohort compared with the retrospective group (19.1% vs 55.6%, respectively; p<0.05).
Kalra et al(34), 2021	2epoch of NV MSAF neonates • ET suction era: 2013-2014 (n = 280) • No ET suction era: 2017-2018 (n=282)	Admissions for meconium aspiration syndrome (15% vs 53%) and respiratory distress (18% vs 57%) were significantly higher among non-vigorous infants in the no-suction era.
Kumar et al(35), 2021	2epoch of NV MSAF neonates • Routine ET suction group: 2015-2016 – 271 • No ET suction group: 2018-2019- 276	• There was no significant difference in the incidence MAS • NV MSAF neonates with hypoxic ischemic encephalopathy (HIE) was significantly lesser in the prospective cohort (No ET group: 19.2% vs ET group: 27.3%; p=0.03). • Incidence of air leaks and need for any respiratory support significantly increased after policy change. • In NV MSAF neonates with MAS, need for mechanical ventilation (MV) (No ET group: 24 % vs ET group: 39.7 %; p=0.04). and mortality (No ET group: 18.7% vs ET group: 33.8%; p=0.04) were significantly lesser.

Routine tracheal suctioning in NV-MSAF might possibly be associated with decreased risk of MAS. Due to the availability of low CoE, the results of most of the studies remain uncertain. Observational studies with a before and after design evaluating the impact of the policy change to 'no routine tracheal suctioning and immediate positive pressure ventilation (PPV) when needed' should enrol a homogenous population of NV-MSAF for better evaluation of the results and conclude accordingly.

Limitation of the current evidence:

One of the major drawbacks associated with Before and After studies is the increased risk of bias due to historical controls. The differences could be real or due to changes in NICU practices over the timeframe. Moreover, the exact date of implementation of revised guidelines is highly variable across various centres. Also, most of the studies did not provide information on the timing of ET suctioning or the skill of the provider. These findings call for large RCTs evaluating 'routine tracheal suctioning' versus 'no routine tracheal suctioning and immediate PPV when needed' in NV-MSAF neonates separately in HIC and LMIC.

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A Large birth mark on back and trunk of a neonate: A rare diagnosis

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Clinical presentation

A 39 weeks 5 days female infant was born to a 26 year old primigravida mother with O positive blood group by elective caesarean in view of breech presentation with a weight of 3.479 Kilograms. Uneventful postnatal transit.

Baby was born with a large lesion on the lower back extending from thorax to lower trunk just above the buttocks with a flat black skin (size 11 cm x 17 cm) of smooth velvety appearance (Fig.1), non- hairy and a small satellite lesion of size 1cm x 2cm (Fig. 2) present on the medial aspect of the right upper arm. The main lesion had a pronounced thickening and wrinkling. There was no bruit on auscultation and other systemic examination was normal. There were no other associated congenital anomalies or dysmorphism.

Diagnosis- Giant Congenital Melanocytic Nevi

Course – No neurological abnormality was noted during the 3 days hospital stay. All other routine blood investigations were normal. The baby was discharged and kept on follow up (after 48 hours and 1,3,6,12 months of age). Parents were counselled regarding possible available treatment options and future course. They were also advised to seek the opinion of a dermatologist, plastic surgeon and paediatric neurologist. Presently baby is 3 months old, doing well and the skin lesion is of the same size currently.

REVIEW OF LITERATURE-

Giant congenital melanocytic nevus is usually defined as a melanocytic lesion present at birth that will reach a diameter > 20 cm in adulthood. Its incidence is estimated in <1:20,000 newborns. CMN are benign, tumour-like abnormalities resulting from defective maturation of pigment cells i.e. melanocyte precursors in the embryo. They are composed of a mixture of skin elements.(1) Kopf et al classified the lesions according to the surface diameter as small lesions being <1.5 cm, intermediate lesions between 1.5 to 20.0 cm and giant lesions >20.0 cm. 75% of such lesion are associated with small, multiple lesions known as "satellites".(2)

Although their occurrence is rare, the diagnosis is critical, as they may develop into dermal or extra-dermal melanoma and may also be associated with neurocutaneous melanosis (NCM).(3) The prognosis is poor in nevus where melanoma develops. Patients with large nevus have a risk of developing melanoma between 1.25 -10%.(4,5) Thus, the management of each case must be individualized and should consist of a multidisciplinary approach including neonatologists, paediatric neurologists, dermatologists, plastic surgeons and psychologists. Early surgical removal is often desired for large CMN because of their cosmetic and psychosocial sequelae and concern for possible malignant transformation. Decision and timing of surgery depend on size, location of large CMN and anaesthesia options.

Key messages

1. Congenital melanocytic nevi (CMN) occur in 1 to 3 percent of newborn infants; large or giant CMN occur in approximately 1 of 20,000 births.
2. Giant CMNs are sometimes referred to as "garment" or "bathing trunk" nevi and are frequently accompanied by multiple smaller, widely disseminated "satellite" nevi

3. These babies are at risk of developing melanoma or neurocutaneous melanosis (NCM). NCM may be asymptomatic or may present with neurologic signs like hydrocephalus and seizures
4. Large CMN may need surgery depending upon size, location and anaesthesia options.
5. MRI brain should be done in first 6 months of life in babies at risk of NCM (especially if nevus overlies the posterior axis or spine)

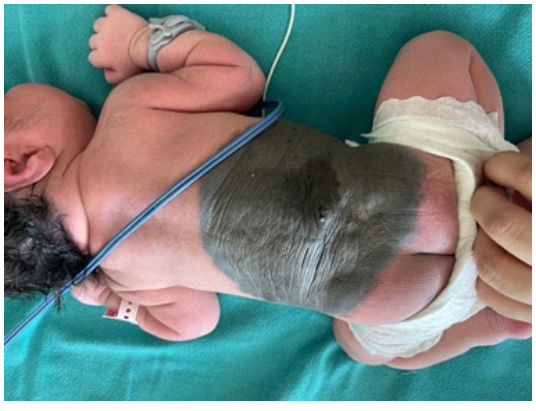

Fig. 1

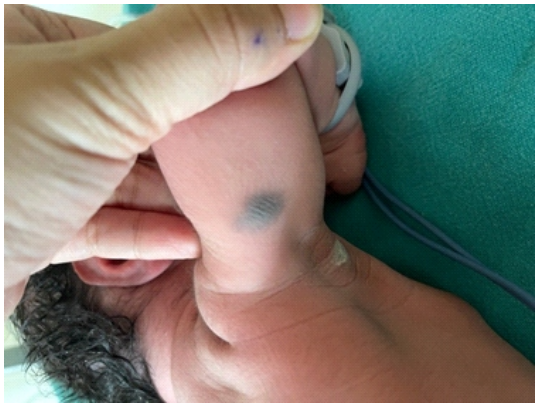

Fig. 2

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Wandering Umbilical venous line

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Presentation:

A 38-week gestation early-term baby was delivered by emergency LSCS in view of fetal distress. The baby required positive pressure ventilation for 1 minute. The baby was found to have an absent anal opening on examination. Further, it was not possible to put an orogastric tube suggesting the possibility of associated trachea-esophageal fistula. An umbilical venous line (UVC) was put in for intravenous access. The X-ray revealed the unusual course of the umbilical venous line (Figure 1).

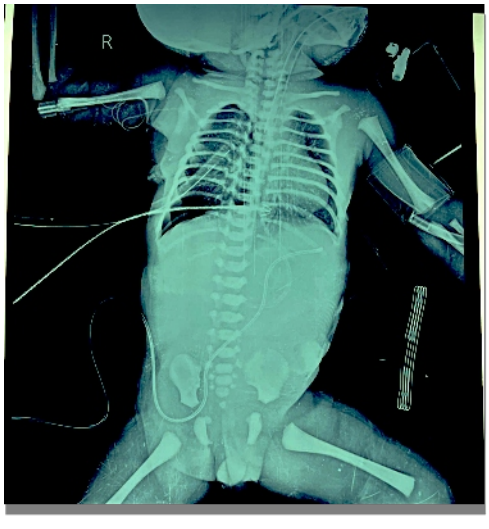

Fig. 1 : The malpositoned UVC in left sub-diaphragmatic region.

Suspicion: The umbilical lines are notorious to go to anomalous positions i.e. too high, too low, left portal vein, right portal vein, crossing the patent foramen ovale to the left atrium. The UVC in the present case was pointing towards the left sub-diaphragmatic area. Such position could be explained by two possibilities of malposition either splenic vein or superior mesenteric vein.

Course: We planned to look for the course and position of the umbilical venous catheter. However, the line got accidentally out before that. In the present case, the UVC was pointing towards left sub-diaphragmatic area which led to the possibility of it being positioned in the splenic vein (Figure 2). It the tip of UVC points further in a downward direction after pointing towards the left sub-diaphragmatic area then it is possibly positioned in the superior mesenteric vein (Figure 2). In the present case, the catheter was positioned in splenic vein.

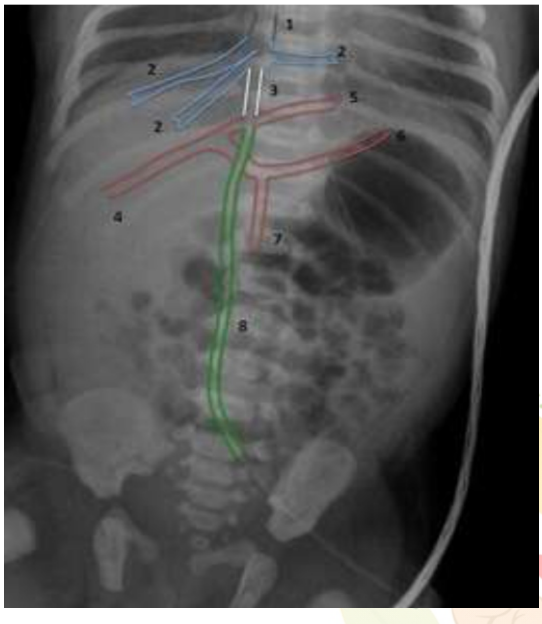

Fig. 2: The various possibility of abnormal positioning of UVC (From Salreno S et al.[3]) Inferior vena cava (1), hepatic veins (2), ductus venosus (3), right portal vein (4), left portal vein (5), splenic vein (6), superior mesenteric vein (7), umbilical vein (8)

Discussion

The umbilical cord contains two umbilical arteries and one vein. The umbilical vein is larger in calibre but has thinner walls as compared to the umbilical arteries. A UVC catheter placed in the umbilical vein should course travel from the umbilical vein into the ductus venosus and its tip should be positioned in the inferior vena cava just below the right atrium.(1)

The various abnormal position of UVC has been described and reported (Figure 2).(2,3) Various complications have been reported associated with abnormal position of tip of umbilical venous catheter like hepatic abscess or necrosis, portal venous thrombosis, infection, haemorrhage etc. Tip of malpositioned UVC is usually seen in right or left portal veins or portal sinus. The Umbilical venous tip in the splenic vein hasn't been described much in literature. A case of splenic abscess was described by Aslam A et al, due to malpositioned UVC with tip in splenic vein in an extremely preterm neonate.(4) It is important to document the curse and position of UVC after its insertion.

Key points:

1. The UVC can be mal-positioned at various anatomical sites.
2. The understanding of anatomical consideration is important for understanding abnormal positions.
3. An abnormally placed UVC should be removed immediately to avoid complications.
4. Point of care USG is very important to document and confirm the position of UVC.

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Journal Scan

Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh

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Lancet Global Health. 2021 Sep;9(9):e1273-e1285.

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Research Question Whether therapeutic hypothermia alongside optimal supportive intensive care reduces death or moderate or severe disability after neonatal encephalopathy in South Asia.

Hypothesis

Population	**Infants born at or after 36 weeks of gestation with moderate or severe neonatal encephalopathy and a need for continued resuscitation at 5 min of age or an APGAR score of less than 6 at 5 min of age (for babies born in a hospital), or both, or an absence of crying by 5 min of age (for babies born at home).**
Intervention	**Controlled reduction of rectal temperature to 33·5°C for 72 h, followed by automated re-warming at 0·5°C per h with the use of a servo controlled whole-body cooling device (Tecotherm Neo; Inspiration Health Care, Crawley, UK)**
Control	**Usual neonatal intensive care including invasive ventilation and inotropic support, avoidance of iatrogenic hyperthermia**
Outcome	**The primary outcome was death or a moderate or severe disability assessed between 18–22 months.**

METHODS

- **Design: M**ulticountry open-label, Randomised Controlled trial
- **Allocation/ Randomization:** Neonates were randomly assigned using web-based randomisation system to either intervention or control group.
- **Blinding:** Neither clinicians nor parents could be blinded to study but those involved in the magnetic resonance biomarker analysis and Neurodevelopmental outcome assessments were masked to the allocation.
- **Setting:** recruited newborn infants from seven large public sector tertiary neonatal intensive care units in South Asia
- **Patients:** 408

Inclusion criteria: Infants born at or after 36 weeks of gestation with a birth weight of more than 1800 grams

and admitted within 6 hours of birth having moderate or severe neonatal encephalopathy and a need for continued resuscitation at 5 min of age or an Apgar score of less than 6 at 5 min of age, or both (for babies born in a hospital), or an absence of crying by 5 min of age (for babies born at home).

Exclusion criteria: Infants who had no heart rate at 10 min of age despite adequate resuscitation, those with major life-threatening congenital malformations, or if the parents were unable to attend follow-up assessments.

Sample size Researchers calculated the sample size required to detect a 30% relative risk reduction in the primary outcome from 50% in the control group to 35% in the intervention group with an 80% power and two-sided 5% significance level. Allowing for a 10% loss to follow-up, the required sample size was 204 infants per group.

Intervention- Using a web-based randomisation system, they allocated infants into a group receiving whole body hypothermia (33·5°C) for 72 h using a servo-controlled cooling device, or to usual care (control group), within 6 h of birth. All recruiting sites had facilities for invasive ventilation, cardiovascular support, and access to 3 Tesla MRI scanners and spectroscopy. Masking of the intervention was not possible, but those involved in the magnetic resonance biomarker analysis and neurodevelopmental outcome assessments were masked to the allocation. The primary outcome was a combined endpoint of death or moderate or severe disability at 18–22 months, assessed by the Bayley Scales of Infant and Toddler Development (third edition) and a detailed neurological examination. Analysis was by intention to treat.

RESULTS

98 (50%) infants in the hypothermia group and 94 (47%) infants in the control group died or had a moderate or severe disability (risk ratio 1·06; 95% CI 0·87–1·30; p=0·55). 84 infants (42%) in the hypothermia group and 63 (31%; p=0·022) infants in the control group died, of whom 72 (36%) and 49 (24%; p=0·0087) died during neonatal hospitalisation. Five serious adverse events were reported: three in the hypothermia group (one hospital readmission relating to pneumonia, one septic arthritis, and one suspected venous thrombosis), and two in the control group (one related to desaturations during MRI and other because of endotracheal tube displacement during transport for MRI). No adverse events were considered causally related to the study intervention.

Conclusion: Therapeutic hypothermia did not reduce the combined outcome of death or disability at 18 months after neonatal encephalopathy in low-income and middle-income countries, but significantly increased death alone. Therapeutic hypothermia should not be offered as treatment for neonatal encephalopathy in low-income and middle-income countries, even when tertiary neonatal intensive care facilities are available.

Reviewer's Comments-

Neonatal encephalopathy is the most common cause of death and serious brain injury in term infants affecting at least 1.2 million infants globally every year; over 96% occurs in low- and middle-income countries (LMICs)[1] In the HELIX study researchers suggested that all low-income and middle-income countries (LMICs) should immediately suspend use of cooling in neonates. The reported absence of benefit and increased mortality in neonates who were cooled are in contrast to the earlier experience and the findings in meta-analyses in LMICs.[2,3] The findings of this trial has created a controversy regarding the use of therapeutic hypothermia as a modality for management of neonates with asphyxia.

Strengths of the trial include it's a RCT from LMICs with a large sample size. The HELIX trial has set a new benchmark for conducting high quality randomized controlled trials in terms of research governance, consent, ethics, follow-up rates, and involvement of parents. The implementation of therapeutic hypothermia in LMICs before this trial was based largely upon the recommendations from the studies conducted in more developed world and/or observational studies[4-6] from the LMICs so much so that therapeutic hypothermia was taken as a standard of care for neonates with perinatal asphyxia and was incorporated in the ILCOR recommendations for neonatal resuscitation.[7] The HELIX trial provided a strong evidence from a RCT against the use of cooling in low cost settings.

Limitations - Several differences in the HELIX study

preclude the generalisation of their findings to all LMICs. First, the HELIX cohort showed increased illness severity compared with a South African cohort; more infants required ventilation (60% *vs* 34%), inotropes (80% *vs* 17%), and treatment for coagulopathy (39% *vs* 14%).[5] Second, intrapartum hypoxia was not adequately defined: 11% of neonates had cord pH measurements; 67% of neonates had 5 min Apgar scores; and fetal heart rate decelerations were documented in 6% of neonates. Third, encephalopathy and seizures were not robustly defined. Seizure onset before cooling is associated with reduced treatment effect. 73% of infants in the HELIX study had seizures before recruitment. Seizures are underdiagnosed in the absence of amplitude integrated electroencephalography (aEEG) as clinical scores lack specificity compared with aEEG.[8] Fourth, the inclusion of infants with anthropometry 2 SD below the mean and the use of low temperature targets in the control group (36·0°C *vs* 36·5°C) might have mitigated the benefits of cooling. Lastly, sepsis limits the benefit of cooling and might have had a role in increased mortality.[9] Despite these limitations, the HELIX study found an important benefit of decreased disabling cerebral palsy in cooled infants (11% *vs* 21%; risk ratio 0·53 [95% CI 0·28–0·98]), which is particularly relevant in resource-constrained settings.

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QUESTIONS

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Question1.

Term neonate born thorough emergency LSCS (done in view of abruptio placentae). Baby was born limp, needed intubation and chest compressions in delivery room. Apgars were 0 and 3 at 1,5 minutes respectively. Baby was shifted to NICU. Cord gas revealed pH of 6.8 with BE -22. Baby was ventilated in NICU, IV fluids were started, central lines were put. Doctor on duty started therapeutic whole body hypothermia with servo controlled machine.

a. What are the indications of starting therapeutic hypothermia?

b. Hypothermia improves outcomes by preventing which kind of brain injury?

c. What should be the duration of therapeutic hypothermia?

d. What is supportive care needed in child with HIE when baby is receiving therapeutic hypothermia?

e. What is current evidence regarding impact of therapeutic hypothermia on improving outcomes in developed and low middle income countries?

Question 2.

Baby in question 1 had focal clonic seizures at 4 hours of life. His RBS is 64 mg/dl. Ionized calcium is normal in blood gas. What should be next step in management?

a. Which drug should be given to control seizures

b. What is a EEG (amplitude integrated EEG)

c. Which form of EEG is best for picking up seizures (conventional vs a EEG)

d. What are electrographic criteria for neonatal seizures

Question 3.

The baby in question 1 improved after 48 hours. The baby was extubated on 4th day of life. Was started on direct feeds on his 5th day of life which he accepted well.

a. Name few scoring systems used in babies with HIE

b. What is neuroimaging of choice to diagnose injury related to Hypoxic ischemic encephalopathy

c. What should be the timing of MRI in a baby who had HIE

d. What is the role of EEG in prognostication

Question 4.

The term appropriate for gestation age baby presented to OPD on day 5 of life with seizures. Seizures are myoclonic in nature. On history taking, parents informed that these episodes are happening only during sleep

a. What is most probable etiology?

b. How do you differentiate benign sleep myoclonus from pathological myoclonus?

c. In which part of sleep benign myoclonic jerks happen more frequently?

d. How is neurological outcome in benign sleep myoclonus.

Question 5.

a. Phenytoin shouldn't be diluted in which solution?

b. What is the dose relationship of fosphenytoin to phenytoin?

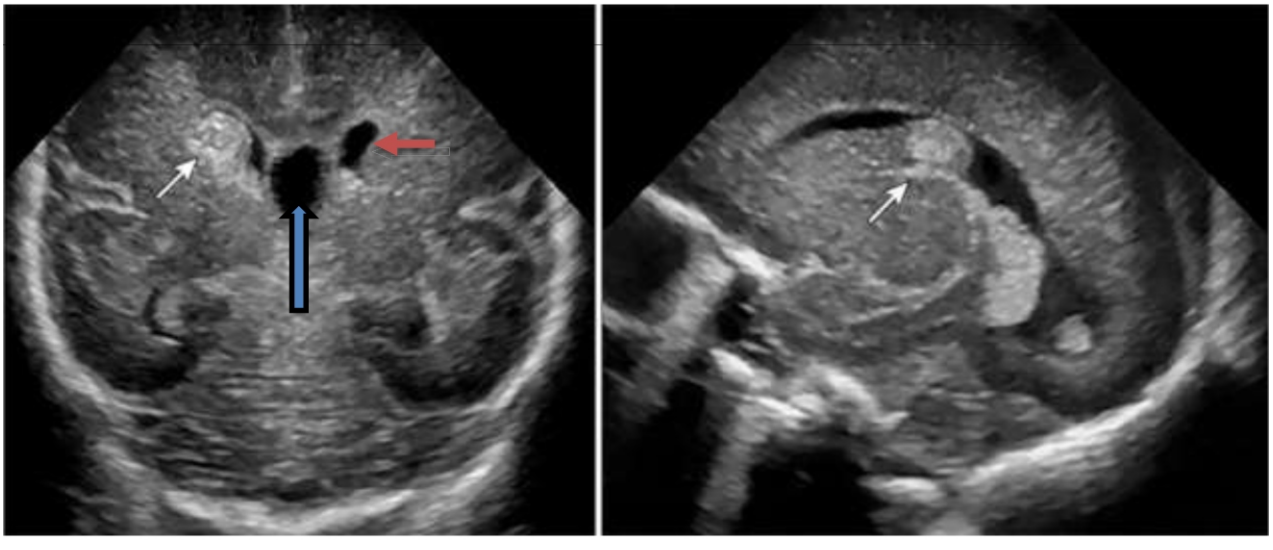
c. How much blood level of phenobarbitone is expected after giving a bolus dose of 20 mg/kg?

d. Maintenance dose of phenobarbitone should be started after how many hours of a loading dose?

e. Name 2 etiologies leading to neonatal seizures that carry a very good prognosis

Question 6.

Prterm (27 weeks) AGA born to primigravida mother thorugh LSCS (done in view of abruptio placentae). Mother didn't receive antenatal steroids. Baby was intubated at birth and received 1 dose of surfactant along with other preterm care. On 3rd day of life baby developed sign of poor perfusion ,ECHO done showed hemodynamically significant PDA which was managed with oral ibuprofen and inotropes (Milrinone and Adrenaline).On 4th day of life baby looked "PALE" and had sudden increase in Fi02 requirement on ventilator. Blood investigation done showed Hb:8g/dl. You did a bed side USG cranium which is shown below.



a. What is your provisional diagnosis? Mention its incidence in preterm born <32weeks?

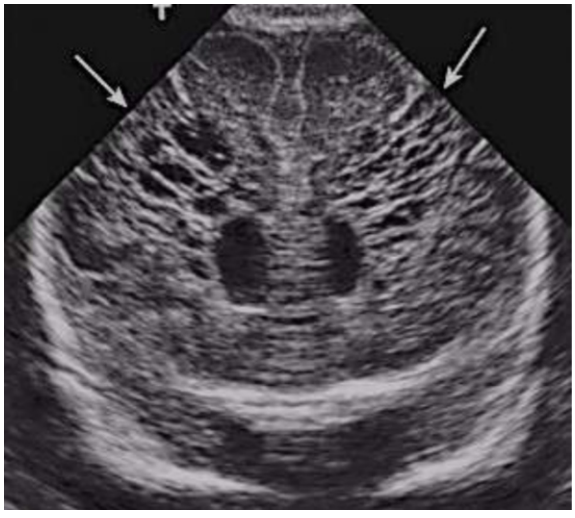
b. Identify the structures mentioned in the above-mentioned USG cranium (white, blue, red arrows).

c. What are the recommended guidelines for the timing of cranial ultrasonography in NICU to screen for intraventricular hemorrhage (IVH)?

d. What could be the contributory factors in this baby which resulted in the present condition?

Question 7.

Preterm (31 weeks) SGA born to primigravida thorugh LSCS (Reversal of end diastolic blood flow in umbilical artery). Baby required intubation and surfactant at birth and was extubated after 24hours of life to CPAP support.The baby was started on feeds by 2nd day of life and was on full feeds by 6th day of life. Baby had late onset Staphylococcus aureus sepsis on day 20th of life which was managed with appropriate antibiotics. He received PRBC transfusion twice for anemia during hospital stay. Presently at 36weeks gestation baby continues to be on CPAP support (Fi02:21% and PEEP:5) .USG cranium done at 36 weeks is shown below.



a. What is your diagnosis?

b. Which modality is best for diagnosis of diffuse white matter injury?

c. Which cells are most susceptible to injury in this condition?

d. What is the pathogenesis of this condition in a newborn? How do you grade this condition?

e. What are the long-term complications associated with this condition?

Question 8.

Preterm 26 weeks AGA born to primigravida mother thourgh LSCS (Abruptio Placentae) developed grade 3 intraventricular hemorrhage on day 3 screening ultrasound cranium.

a. What are the preventive strategies to decrease the incidence of intraventricular hemorrhage in a preterm newborn?

b. What are the two systems widely used for grading IVH/GMH in neonates?

c. What are the two most common complications associated with GMH/IVH?

d. How will you manage this baby?

Question 9.

A preterm 28week male baby with birth weight 800 grams is admitted in your NICU for prematurity care. Baby is now 3 weeks old and had a stormy NICU course, resulting in grade 3 intraventricular hemorrhage. During serial cranial USG monitoring you have noticed dilated lateral ventricles. On clinical examination head cirucumference has increased by 3 cm over last one week and anterior fontanelle is bulging.

a. What is the most probable diagnosis?

b. Which are the parameters we measure on head ultrasound to monitor progress of post hemorrhagic hydrocephalus

c. What percentage of babies will have rapid progression of ventricular dilatation?

d. How will you monitor this baby?

Answer 1.

a. Indications of starting therapeutic hypothermia

All of the following should be present

- Gestational age ≥ 36 weeks and ≤ 6 hours of age
- Any of the following:
  - Metabolic or mixed acidosis with a pH of ≤ 7.0 or a base deficit ≥ 16 mmol/L in an umbilical cord blood sample or any blood obtained within first hour after birth
  - 10-minute Apgar score of ≤5
  - Ongoing resuscitation (eg, assisted ventilation, chest compressions, or cardiac medications) initiated at birth and continued for ≥10 minutes
- Moderate to severe encephalopathy on clinical examination

b. Reduction in brain metabolic rate, effects on cerebral blood flow, reduction of the critical threshold for oxygen delivery, blockade of excitotoxic mechanisms, calcium antagonism, preservation of protein synthesis, reduction of brain thermopooling, a decrease in edema formation, modulation of the inflammatory response, neuroprotection of the white matter and modulation of apoptotic cell death. It reduces secondary energy failure (thereby reducing apoptotic injury).

c. During therapeutic hypothermia a rectal temperature between 33-33.5 degrees C is maintained for 72 hrs followed by gradual rewarming over a period of 6-12 hours.

d. Maintain adequate ventilation and avoid hyperoxia and hypocapnia

Maintain sufficient brain and organ perfusion (avoid systemic hypotension and hypertension; avoid hyperviscosity)

Maintain normal metabolic status (normoglycemia, normal pH)

Treat seizures with anticonvulsants (phenobarbital, levetiracetam, fosphenytoin or levetiracetam)

For persistent pulmonary hypertension, use high frequency ventilation, nitric oxide, or extracorporeal membrane oxygenation to maintain oxygenation

e. In a meta-analysis of 7 randomized controlled trials involving 1214 newborns of high methodology published in 2012 (Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA Arch Pediatr Adolesc Med. 2012;166(6):558), therapeutic hypothermia started within 6 hours of birth was associated with a significant reduction in the composite primary outcome of death or major neurodevelopmental disability (48 versus 63 per cent, risk ratio [RR] 0.76, 95% CI 0.69-0.84). The number needed to treat (NNT) was 6 for moderate encephalopathy and 7 for severe encephalopathy.

Therapeutic hypothermia increased survival with a normal neurologic outcome at 18 months (40 versus 24 per cent, RR 1.63, 95% CI 1.36-1.95).

A recent randomized controlled trial done in low and middle income countries involved 408 babies. The trial (HELIX trial) found no difference in death or severe disability among treatment and control group (risk ratio 1·06; 95% CI 0·87–1·30; p=0·55). (Lancet Glob Health. 2021 Sep;9(9):e1273-e1285)

Answer 2.

a. Phenobarbitone

Existing evidence supports phenobarbital as the first-line agent for neonatal seizure treatment. The initial dose of phenobarbital is typically 20 mg/kg by intravenous [IV] infusion, followed by a maintenance dose of 4 to 6 mg/kg per day in two divided doses. If seizures do not resolve after the first loading dose, repeat boluses of 10 to 20 mg/kg should be given with a goal phenobarbital

level of approximately 50 micrograms/mL or a total 24-hour dose of 50 mg/kg

b. aEEG is created from a single channel EEG. The main features that transform the recorded EEG activity to the aEEG trend include

(i) asymmetric filter that slightly amplifies EEG activity within the main frequencies (2–15 Hz) and attenuates most low- and high-frequency activity, rectifying of the signal

(ii) a semilogarithmic output with a linear display of low-voltage activity (0–10 µV), and a logarithmic display of activity between 10 and 100 µV.

The aEEG is displayed as a time-compressed trend, usually at 6 cm/h. This makes it easy to follow long-term trends in cerebral activity, but the time-compression also makes it impossible to see brief, transient changes in activity.

We should assess the trace for 3 parameters:-

1. Amplitude

Normal – Lower margin of trace above 5uV, Upper margin of trace above 10uV and EEG shows continuous activity

Moderately abnormal – Lower margin of trace below 5uV, Upper margin of trace above 10uV and EEG shows moderately discontinuous activity

Severely abnormal – Lower margin of trace below 5uV, Upper margin of trace below 10uV except during bursts and discontinuous EEG.

2. Seizures – Sudden change in amplitude of the EEG trace (sudden rise and narrowing of trace)
3. Artifact – Amplitude may change artificially due to electric or mechanical artifacts. Eg. ECG artifact may artificially raise the lower margin of the EEG trace.

c. Conventional EEG

d. Following are the criterias on EEG to label pattern as electrographic seizures (Volpe, Joseph, J. et al. Volpe's Neurology of the Newborn. 6th Edition. Chapter 12, page no 284.)

- Sudden change in EEG
- Repetitive waveforms that evolve in morphology, frequency, and/or location
- Amplitude: At least 2 µV
- Duration: at least 10 s
- Seizures must be separated by at least 10 s to be considered separate
- Clinical signs may or may not be present

Answer 3.

a. Modified Sarnat and Sarnat, Thompson, Siben.

b. MRI (Diffusion-weighted MRI more sensitive than conventional MRI, especially in first days after birth, when former shows decreased diffusion (increased signal) in injured areas)

c. The optimal time for detection of DWI abnormality in the most common varieties of hypoxic-ischemic disease in the term newborn is approximately 2 to 3 days (Volpe 6th edition). For conventional MRI optimal time is between 5-14 days after insult.

d. EEG patterns associated with favorable outcome in babies with HIE (Volpe 6th edition, chapter 20, page 541)

(i) Mild depression or less on day 1

(ii) Normal background by day 7

EEG patterns associated with unfavorable outcome in babies with HIE

(i) Predominant interburst interval > 20s on any day

(ii) Burst suppression pattern on any day

(iii) Isoelectric tracing on any day

(iv) Mild (or greater) depression after day 12

Answer 4.

a. Benign Sleep Myoclonus

b. Benign myoclonus can be stopped by rousing the infant and typically does not involve the face

c. Quiet sleep (REM sleep)

d. Normal

Answer 5

a. Normal Saline

b. 1.5 mg of fosphenytoin yields approximately 1 mg of phenytoin

c. The 20 mg/kg loading dose of phenytoin results in a therapeutic blood level of approximately 15 to 20 µg/kg

d. 12 hours
e. Late onset hypocalcemia (100% normal development), Primary Subarachnoid hemorrhage (90% normal development)

Answer 6.

a. Intraventricular hemorrhage. Incidence of IVH/GMH in preterm born at <32weeks gestation is between 15%to 20%.

b. Strutures : White – IVH

Blue – Cavum septum pellucidum

Red – Body of lateral ventricle

c. According to **AAP guidelines**

Routine USG screening should be performed on all infants with GA< 30 weeks by 7-10days of age. Screening before 7 days is indicated for infants with sign and symptoms of brain injury.Repeat screening is recommended at 4-6weeks of age, term equivalent, or before discharge.

d. Factors contributing to development of IVH/GMH in this baby includes:

(i) Prematurity

(ii) Lack on antenatal steroids

(iii) hsPDA

(iv) Hypotension and shock

Answer 7.

a. Cystic Periventricular leukomalacia.

b. MRI brain

c. Oligodendrocytes

d. PVL/WMI results from the interaction of multiple pathogenetic factors including Hypoxic-ischemic injury, Intrinsic vulnerability of cerebral white matter of preterm newborn , Infection/ inflammation

Grading of PVL

Grade I: Transient periventricular echodensities persisting for >7 days

Grade II: Transient periventricular echodensities evolving into small, localized frontoparietal cysts

Grade III: Periventricular echodensities evolving into extensive periventricular cystic lesions

Grade IV: Densities extending into the deep white matter evolving into extensive cystic lesions.

e. PVL/WMI is associated with increased risk of sensory, motor, cognitive impairement and cortical visual impairment in preterm newborn.T here is 10% increased risk of cerebral palsy in preterm with PVL and 20 % risk in those with cystic PVL. Spastic diaparesis being the most common type of CP seen in such baby's.They are also at increased risk for developing epilepsy which also influence scholastic performance. Visual disturbances like strabismus, nystagmus, visual field deficits are common in such babies.

Answer 8.

a. Antenatal preventive strategies:

i. Antenatal corticosteroids (Dexamethasone/ Betamethasone)

ii. In-utero transport of at risk babies.

Postnatal preventive strategies:

i. Prevention of hypothermia.

ii. Prevention of sudden fluctuation in cerebral blood flow/cerebral venous pressure.

iii. Avoiding Umbilical cord milking (UCM) as it is shown to be associated with increased risk of severe IVH.

iv. Early treatment of HsPDA

v. Minimal handing/Bundle care/Gentle handing by trained staff also helps in minimizing IVH in preterm neonates.

b. Grading of GMH/IVH

GRADING SYSTEM	SEVERITY OF GMH/IVH	FINDING
PAPILE (based on CT)	I	Isolated GMH(No IVH)
	II	IVH without ventricular dilatation
	III	IVH with ventricular dilatation
	IV	IVH with parenchymal hemorrhage.

GRADING SYSTEM	SEVERITY OF GMH/IVH	FINDING
VOLPE (based on ultrasound)	I	GMH with no or minimal IVH(<10% ventricular volume)
	II	IVH occupying 10-50% of ventricular area on parasagittal view
	III	IVH occupying >50% of ventricular area on parasagittal view

In Volpe Classification, parenchymal hemorrhage needs separate notation

c. Periventricular hemorrhagic infarction(PVHI) and Posthemorrhagic ventricular dilation(PVD).

d. Treatment mainly includes supportive care i.e maintaince of arterial blood pressure and avoiding sudden fluctuation in BP, providing adequate oxygenation, ventilation, and appropriate fluids, metabolic, nutritional support to the baby to minimize any further brain injury and also early identification of complications .

Answer 9.

a. Post hemorrhagic ventricular dilatation or Post hemorrhagic Hydrocephalus

b. Diagnosis is based on serial monitoring (twice weekly monitoring up to 4weeks) by cranial ultrasound. There are 3 most used indices (Figure 1A, 1B).

(i) **Ventricular index** (VI): Distance between the falx and lateral wall of the anterior horn in coronal plane at the level of foramen of Monro.

(ii) **Anterior horn width** (AHW): Defined as the diagonal width of anterior horn measured at widest point in coronal plane at the level of Monro.

(iii) **Thalamo-Occipital distance** (TOD): Distance between the outermost point of the thalamus at its junction with choroid plexus and the outermost part of the occipital horn in parasagittal plane.

c. PHH can have 3 kind of courses

I. 40% of newborns will have spontaneous arrest without a need for intervention.

ii. **10% will have rapid progression**

iii. 50% will have slow progression.

d. PHVD usually develops 1-3 weeks after the onset of IVH grade 3/4.Serial monitoring by cranial USG helps in early identification and prompt management. VI, AWH are monitored and plotted on the Levene and Davies charts respectively (Figure 2). When newborn meet a threshold where VI >97th +4mm and AHW reaches > 10mm, then intervention should be considered.

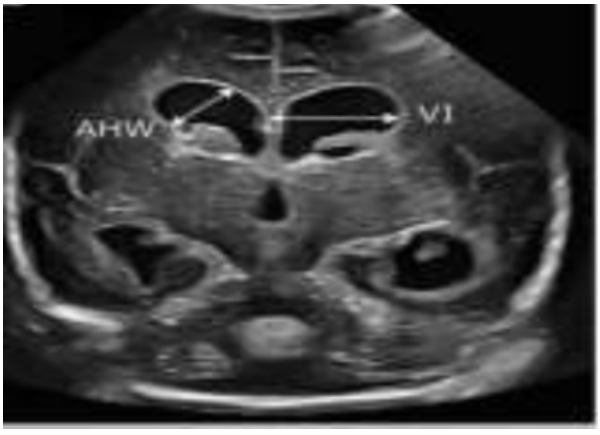

AHW
VI

Fig. 1A

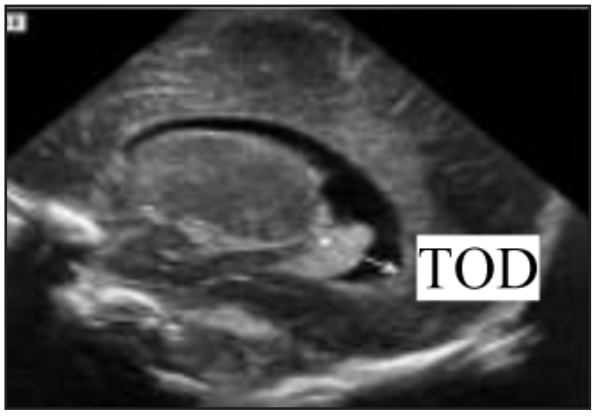
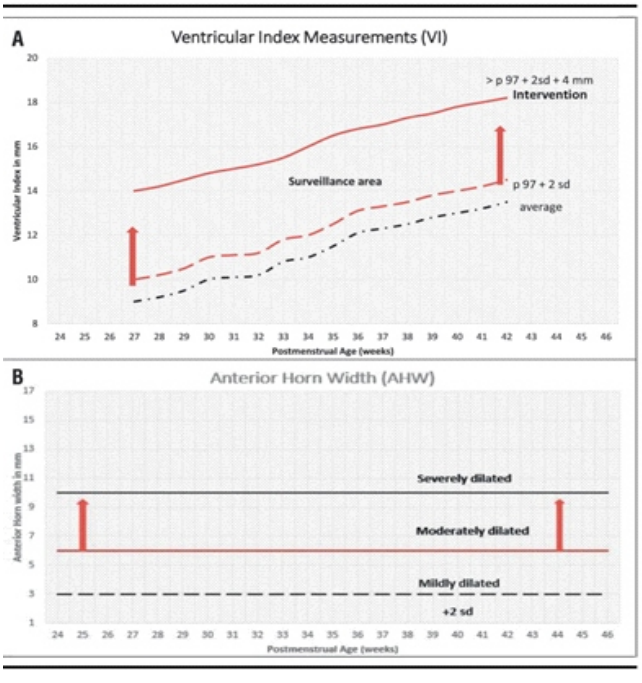

TOD

Fig. 1B


A
Ventricular Index Measurements (VI)
> p 97 + 2sd + 4 mm
Intervention
Surveillance area
p 97 + 2 sd
average
Ventricular Index in mm
Postmenstrual Age (weeks)
B
Anterior Horn Width (AHW)
Severely dilated
Moderately dilated
Mildly dilated
+2 sd
Anterior Horn width in mm
Postmenstrual Age (weeks)

Instructions for Authors

Review Article	**The article should be approximately 2-3 pages long with a word count of 2000-2500 words. Author should summarize key practice points at the end. Please include 5-6 references as suggested reading.**
Case Report	**This would be a summary of the case discussed in that months clinical meeting. Interesting cases even if not presented may also be submitted. It should include the clinical presentation and a brief discussion about the condition. Word count should be 1000-1500. Please include 2-3 references at the end.**
Journal Scan	**Some recent research paper of interest to pediatricians and neonatologists. The structure should include Introduction, Research question, Hypothesis, Methods, Results, Limitations and strengths of study, Reviewers comments. Word count should be approximately 1000 words. Please include 2-3 references if needed at the end.**
Picture of Month	**An interesting case related to neonatal practice. It should have a brief case history and a commentary, all fitting on one page along with the pictures.**
Image section	**Any interesting Xray, Ultrasound, CT or MRI of clinical interest. Brief clinical presentation and about the condition should be summarized on one page along with image.**
OSCE	**About 10-12 questions would be included in this section along with answers.**

Contact Us

On behalf of committee, I request all members of NNF, Delhi to actively contribute to various sections of the newsletter.

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