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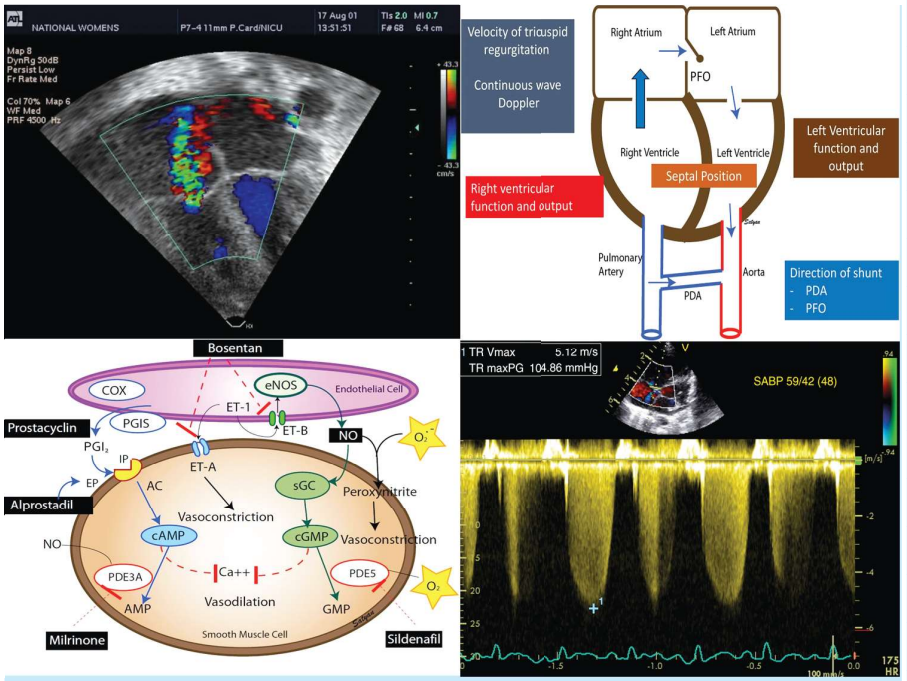

Editorial

"Persistent Pulmonary Hypertension of Newborn"

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EDITORIAL

Persistent Pulmonary Hypertension of Newborn (PPHN)

Manzoor Hussain

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) can occur due to failure of the normal cardiopulmonary transition. Incidence is 2 per 1000 live born term infants, and some degree of pulmonary hypertension complicates the course of more than 10% of all neonates with respiratory failure.[1] It is associated with high mortality and morbidity.

Pulmonary hypertension is a normal and necessary state for the fetus. At birth, with air entering the lungs and the umbilical cord being clamped, the situation is reversed with the Pulmonary vascular resistance (PVR) falling due to vasodilatation of vessels with oxygenation and systemic vascular resistance (SVR) rising due to the elimination of the low-resistance placental circuit. In PPHN this transition is disturbed, resulting in sustained elevation of PVR. PVR exceeds SVR resulting in the right-to-left haemodynamic shunting through the patent foramen ovale and/or ductus arteriosus leading to the vicious cycle of hypoxaemia, further resulting in pulmonary vasoconstriction leading to diminishing pulmonary perfusion and systemic hypoxaemia.[2] The main hallmarks of PPHN include sustained elevation of PVR, abnormal vasoreactivity and structural remodeling of the pulmonary vascular bed.[3] Idiopathic PH is found in 10-20% of all infants with PPHN.[4]

A high index of clinical suspicion is warranted to diagnose PPHN in a baby. The presence of any of the risk factors like Birth asphyxia, Meconium aspiration, Early-onset Sepsis/Pneumonia, Pulmonary hypoplasia due to causes like Congenital diaphragmatic hernia, amniotic fluid leak, oligohydramnios, pleural effusion, maternal drug intake like NSAIDs (Ibuprofen, aspirin, naproxen, indomethacin) and selective serotonin-reuptack (SSRI), especially fluoxetine, other factors like RDS, hypothermia, hypoglycaemia, polycythaemia, familial occurrence should prompt the diagnosis.[5,6]

Diagnosis

Affected infants are usually full-term or post-term and are frequently born through meconium-stained amniotic fluid. The infant is either ill in the delivery room itself or illness manifests within the first 12 hours of life. Infants with PPHN may manifest with severe cyanosis, tachypnoea, grunting, nasal flaring, chest retractions, tachycardia, and shock although signs of respiratory distress may be minimal initially.[7] Cardiac examination may reveal prominent precordial impulse, single or narrowly split and accentuated second heart sound and/or a systolic murmur consistent with tricuspid valve regurgitation. Heart failure is usually not seen though hypotension is encountered.[7] Difference in pre and post ductal saturation of >10% in the absence of structural heart disease suggests PPHN.[8] When hyperventilated for 10 minutes, infants with PPHN may show an increase in PaO_2 by >30 mmHg when pH is raised to 7.55.[9] The chest radiograph usually appears normal in asphyxia associated and idiopathic PPHN. Echocardiography remains the gold standard for diagnosing PPHN. Differential diagnosis include cyanotic congenital heart disease (especially obstructed total anomalous pulmonary venous connection) and entities that predispose to PPHN.[10]

Management

The aim of treatment is to lower pulmonary vascular resistance, maintain systemic blood pressure, reverse right to left shunt, and improve arterial oxygen saturation.[11] For the majority of PPHN

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infants treatment frequently includes aggressive support of cardiac function and perfusion, with volume and inotropic agents to enhance cardiac output and systemic O_2 transport. Oxygen is well known as a pulmonary vasodilator and should be started at 100%.[12] Primary treatment of the neonate depends on the underlying disorder. A variety of treatment options includes surfactant, sedation, alkalinization, vasodilatation (e.g., inhaled nitric oxide, prostaglandin, milrinone, magnesium sulfate, adenosine, bosentan, sildenafil) and extracorporeal membrane oxygenation (ECMO).[13] Ventilation is crucial for PPHN treatment since it facilitates alveolar recruitment and lung expansion, improving ventilation/perfusion matching.[14] High frequency oscillatory ventilation may be useful in the management of infants who are being considered for treatment with extracorporeal membrane oxygenation (ECMO).[12] The combined use of inhaled nitric oxide (iNO) and high occupancy vehicle (HFOV) has been demonstrated to be more successful than use of iNO or HFOV alone.[7]

However, many developing countries and resource limited centers do not have the funds or the technical expertise required for these expensive therapies.[15] Sildenafil is a potent and selective inhibitor of cGMP-specific phosphodiesterase 5 (PDE5). This isoenzyme metabolizes cGMP which is the second- messenger of NO and a principle mediator of smooth muscle relaxation and vasodilatation. By inhibiting the hydrolytic breakdown of cGMP, sildenafil prolongs the action of cGMP. This results in augmented smooth muscle relaxation and cause pulmonary vasodilatation.[16] Sildenafil decreases pulmonary vascular resistance in pulmonary hypertensive neonate.[17] Fatema et al[18], Mamun et al[19] and Wadud et al[20] found that sildenafil is very effective in the treatment of PPHN among Bangladeshi neonate. So where nitric oxide facilities are not available, cheap alternative like sildenafil for first line treatment of PPHN Can be effectively used.

Conclusion

PPHN is a devastating disease affecting neonates with high mortality and morbidity. Resource limited centers do not have the funds or the technical expertise required for these expensive therapies. Proper identification along with alternative and less expensive treatment leads to better outcome in PPHN in countries with limited resources.

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LEADING ARTICLE

Sildenafil in the Management of Pulmonary Hypertension in Newborn

Mohammad Abdullah Al Mamun

Introduction

Pulmonary hypertension in the newborn is a complicated, often a life threatening disease. It has been a difficult condition to treat for a long time and characterized by an increased pulmonary vascular resistance, right-to-left shunt at atrial and ductal level with severe hypoxemia.[1] The incidence of Persistent Pulmonary Hypertension of Newborn (PPHN) in term or near-term infants is reported to reach around 2-6.8 per 1000 live births with a mortality of 10% to 20%.[2,3] It occurs when the high pulmonary vascular resistance characteristic of fetal circulation fails to decrease at birth, resulting in right to left shunting of blood through fetal channels, diminished pulmonary blood flow and profound hypoxaemia.

For the majority of PPHN cases aggressive support of cardiac function and perfusion, with volume and inotropic agents to enhance cardiac output and systemic O_2 transport is essential.[4,5] The principal goal of PPHN treatment is selective pulmonary vasodilatation. Pulmonary vasodilators such as magnesium sulfate, sildenafil, bosentan, prostacyclin and specific agents like inhaled nitric oxide (iNO) is effective. Although iNO and extracorporeal membrane oxygenation (ECMO) are the gold standards of the PPHN therapy, they are expensive therapeutic modalities associated with technical difficulties in developing countries, making it necessary to search for cheaper therapies, assuring quick effectiveness and stabilization of the patient going through a very high-risk situation.[6,7] However, any single therapy can not be labelled as a magic bullet for PPHN, more clinical trials are required to demonstrate the efficacy and safety of available therapeutic options as well as to develop newer strategies targeted to the underlying pathophysiology.[8]

Sildenafil has been used for the treatment of pulmonary hypertension in adult.[9] It is recommended in children by European Society of Cardiology (ESC) for pulmonary hypertension, for those aged 1-17 years.[10] But its use in neonate is controversial.[11] Role of sildenafil in the treatment of PPHN was first reported in 2002.[12] Initially there was criticism regarding its use. But it was justified by others at that time as there was no option for the attending neonatologist in face of non-availability of iNO and ECMO.[13] Recent studies also concluded that sildenafil can offer a less expensive but effective alternative treatment.[14,15]

Sildenafil has been shown to selectively reduce pulmonary vascular resistance in humans. Several controlled studies document improved oxygenation measured by pulse oximetry, significant improvement in oxygenation index (OI) as well as echocardiographic evidence of reduced pulmonary arterial pressures and significant decrease in mortality following the administration of sildenafil in newborns with PPHN.[16,17] Meta-analysis including randomized trials of sildenafil compared with placebo in PPHN also found significant reduction in mortality.[18] Fatema et al[19], Mamun et al[20] and Wadud et al[21] found that sildenafil is very effective in the treatment of PPHN among Bangladeshi neonate. This review of the recent literature focuses on effectiveness of sildenafil in newborns with pulmonary hypertension.

Mechanism of action of sildenafil

Sildenafil is a selective phosphodiesterase type 5 (PDE-5) inhibitor which potentiates the downstream effects of Nitric oxide (NO). NO induces smooth muscle relaxation and vasodilation through its effects on the cyclic guanosine monophosphate

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(cGMP) pathway. In pulmonary vascular smooth muscle NO is synthesized by nitric oxide synthase (NOS) from the terminal nitrogen of L-arginine. NO stimulates soluble guanylatecyclase (sGC) to increase intracellular cGMP and mediate pulmonary vasodilatation. cGMP breakdown into GMP by PDE-5 enzyme. Sildenafil inhibit the hydrolytic breakdown of cGMP to GMP and thus prolongs the activity of endogenous NO and potentiate cGMP mediated pulmonary vasodilation (Fig 1).

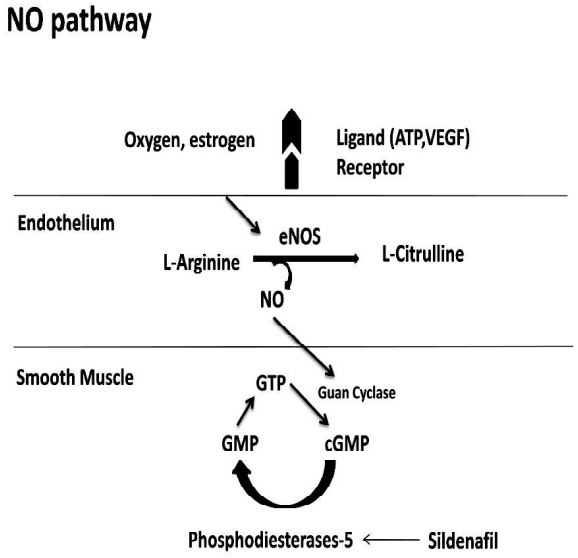

Fig 1 *NO signaling pathways in the regulation of pulmonary vascular tone.*

Dosage, administration, safety, response and duration of therapy of sildenafil

Time of maximum action and duration of the effect varies depending on the dose, the route of administration and the clinical situation in which sildenafil has been used. The most used route is oral, can be used IV and the duration of the effect goes from 20 minutes to 6 hours afterward.[22,23] Oral sildenafil is fairly well tolerated, although absorption can be erratic at times. If intravenous preparation is not available, it can be given orally.[24] It can also be administered intratracheally at a dose of 0.75 or 1.5 mg/kg per dose which can induce a rapid decrease in mean pulmonary arterial pressure, occurred as soon as 2 minutes and lasted for 120 minutes.[25]

The optimal dose of oral sildenafil in neonates and children is still not entirely clear. The British National Formulary for Children advises starting doses of 0.5 mg/kg/dose up to a maximum of 2 mg/kg/dose every 6 hours.[26,27] In neonate dose of sildenafil is 0.5 mg/kg/dose 6 hourly and considering, if there is no response, increase the dose up to a maximum of 2 mg/kg/dose.[16] Because of a relatively short half-life, sildenafil may be given 4 hourly although it is usually administered 6 hourly.[28]

Clinical indicators of a successful response would be improved oxygenation indices, a >10% increase in SaO_2 with a reduced differential between pre and post ductal values, a 3 kPa increase in PaO_2, ability to wean FiO_2, an increase in the a/APO_2 ratio and a decrease in OI. Duration of treatment is not yet well defined and one approach is to observe the individual response and stop the medication after a clear response and improvement. The treatment should also be discontinued after 6-8 doses if there is no improvement and reduction in dose or cessation of treatment is necessary if hypotension develops despite inotropic support.[28]

Side effects and complications

As for safety profile, systemic reviews of 49 studies concerning the safety of sildenafil administration revealed no evidence of serious adverse events in infants.[29] Considering sildenafil's mechanism of action, which decreases pulmonary arterial pressure, concerns have been raised that sildenafil could cause serious systemic hypotension and severe haemodynamic instability. Sildenafil was first considered as an anti-hypertensive agent. So one must watch the systemic blood pressure closely, although this has been rarely a problem.[14] There have been reports of hypotension when it is used in conjunction with nitric oxide.[30] Common side effects of sildenafil treatment are usually non-life-threatening including vomiting, pyrexia, cough, diarrhoea and nasopharyngitis (nasal stuffiness).[27,31,32] Severe adverse effects like stridor, raised intra-ocular pressure and ventricular arrhythmias may also occur.[32] Additionally, the vasodilatation induced by the blockage of PDE-5 inhibitors can lead to nasal congestion, dyspepsia as well as flushing and can also lead to headaches.[33]

Another controversial aspect of sildenafil is its activity on the PDE-6 receptors localized in the rod and cone cells of the eye and whether or not the drug affects the normal development of the visual function of preterm neonates. There has been no

proven evidence of a direct link between sildenafil therapy and ocular complications but visual disturbances and photophobia has been observed in some subjects.[30,34]

Antenatal sildenafil in experimental congenital diaphragmatic hernia (CDH)

Congenital diaphragmatic hernia is an orphan disease with high neonatal mortality and significant morbidity. An important cause for this is pulmonary hypertension. Prenatal sildenafil administration to expectant mothers prevented fetal and neonatal vascular changes leading to pulmonary hypertension in several animal models, and is, therefore, a promising approach.[35] Antenatal sildenafil improved lung structure, increased pulmonary vessel density, reduced right ventricular hypertrophy, and improved postnatal NO which induced pulmonary artery relaxation. Antenatal sildenafil was not associated with adverse effect on retinal structure/function and brain development. Antenatal sildenafil improves pathological features of persistent pulmonary hypertension of the newborn in experimental CDH and does not alter the development of other PDE-5-expressing organs.[36]

Is pretern neonate are at risk of retinopathy of prematurity after using sildenafil?

Sildenafil is 10 times more selective for PDE-5 as compared to PDE-6. PDE-6 is found in the retina. If used in extremely preterm neonates, sildenafil may increase the risk of severe retinopathy of prematurity. Fang et al[37] in a retrospective, case-controlled study in neonates born before 30 weeks gestation showed sildenafil use did not increase the risk of retinopathy of prematurity.

Is sildenafil effective in BPD associated pulmonary hypertension

Sildenafil has been shown to enhance the lung alveolarization and vascularization in newborn animal models after lung injury and has possible therapeutic potential for the prevention of BPD. Systematic review shows that in the treatment of BPD-associated pulmonary hypertension in preterm infants, sildenafil may be associated with improvement in pulmonary artery pressure and respiratory scores.[38] Abounahia et al[39] found oral sildenafil did not benefits in the prevention of BPD or death in the extreme and very preterm infants. A retrospective series of 25 patients with BPD aged <2 years showed hemodynamic improvement in pulmonary hypertension in majority cases, with minimal adverse events.[40]

Is sildenafil more effective with iNO in management of PPHN?

Early use of oral sildenafil as an adjunctive therapy together with iNO in cases of PPHN was well tolerated and found to be more effective. Sildenafil may serve as a useful adjunct for infants with poor iNO responsiveness.[3,41] Combination therapy with iNO and sildenafil leads to a synergistic effect for pulmonary vasodilation, because under conditions of elevated cGMP concentration, sildenafil acts as a more powerful vasodilator by preventing breakdown of the high concentration of cGMP.[42]

Is sildenafil more effective than $MgSO_4$ in management of PPHN?

Uslu et al[43] in a prospective, randomized and controlled study, found that sildenafil was more effective than $MgSO_4$ in the treatment of PPHN with regard to time to adequate clinical response, duration of mechanical ventilation with fewer requirements for inotropic support. Shaltout et al[44] found sildenafil is a more effective therapeutic option in the treatment of PPHN as compared to $MgSO_4$. Mamun et al[20] found magnesium sulphate and sildenafil both are effective in improvement of oxygenation and reduction of pulmonary vascular resistance. Sildenafil was more effective than magnesium sulphate with regard to improvement of oxygenation among Bangladeshi neonate.

Is sildenafil more effective than Bosentan in management of PPHN?

Bosentan is a non-selective endothelin-1 (ET-1) receptor antagonist acting on both ET-A and ET-B receptors. Wadud et al[21] found sildenafil and bosentan both are effective in improvement of oxygenation and reduction of pulmonary vascular resistance. But sildenafil was found more effective than bosentan in improvement of oxygenation among Bangladeshi neonate with PPHN.

Is sildenafil alone is more effective than sildenafil plus bosentan in management of PPHN?

One study was performed by Nazia et al[45] to compare the effect of sildenafil alone and sildenafil with bosentan on severity of tricuspid regurgitation and duration of hospitalization in new-borns with PPHN. The combined use of sildenafil and bosentan is more effective than sildenafil alone for control of

pulmonary hypertension in resource limited centres. Goissen et al[46] reported a successful use of sildenafil as an adjunct therapy to iNO and bosentan in newborns with PPHN complicating transposition of the great arteries.

Is sildenafil more effective than inhaled iloprost in management of PPHN?

A study was performed to examine the effectiveness and safety of oral sildenafil and inhaled iloprost delivered by jet nebulizer in mechanically ventilated term newborns with PPHN. Iloprost appeared to be more effective than sildenafil in the treatment of PPHN with regard to time to adequate clinical response, ventilatory parameters, duration of drug administration, duration of mechanical ventilation, duration of return to normal values of respiratory failure indices, use of $MgSO_4$ as a second vasodilator and requirement for support with inotropic agents. No side effects on blood pressure or homeostasis was observed. These suggested that inhaled iloprost may be a safe and effective treatment choice in newborn infants with PPHN.[14]

Is sildenafil more effective than tadalafil in management of PPHN?

Tadalafil and sildenafil can similarly reduce severity of tricuspid regurgitation (TR), main pulmonary artery (MPA) diameter, mean pulmonary artery pressure (MPAP), and right ventricular end-diastolic diameter (RVEDD).[47]

Use of sildenafil in Pulmonary hypertension after use of ibuprofen

Pulmonary hypertension after prophylactic and therapeutic use of ibuprofen for ductal closure have been reported in some cases.[48] In such cases, Sildenafil as pulmonary vasodilators is found effective.[49]

Conclusion

Sildenafil is an effective treatment in neonate with a significant increase in the oxygenation, decrease pulmonary vascular resistance and a reduction in mortality with no clinically important side effects in PPHN. At this stage, sildenafil may be considered as a first-line treatment in settings where iNO, HFOV and ECMO are unavailable. More controlled multicenter study is needed to evaluate the safety, efficacy and long term outcome of treatment.

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ORIGINAL ARTICLE

Role of Sildenafil in the Treatment of Persistent Pulmonary Hypertension of Newborn (PPHN) - Should it Be Withdrawn from Market of Bangladesh due to Threat of being Misuses

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Abstract

Background: *Recently it has been apprehended that sildenafil, a drug which has been successfully using in the treatment of PPHN and erectile dysfunction in adult, is going to be withdrawn from the market of Bangladesh due to threat of its misuses.*

Objective*: The aim of this study was to see the extent of uses of sildenafil in the treatment of PPHN and importance of availability of this drugs in the market inspite of its probable misuses.*

Methods*: This cross sectional study was conducted in neonatal intensive care unit (NICU), special baby care unit (SCABU) and cardiac intensive care unit (CICU) of Dhaka Shishu (Children) Hospital from June, 2017 to May 2018. Neonates with PPHN were enrolled in the study. All cases were treated with oral sildenefil for PPHN along with others management according to hospital protocol. Data along with other parameters were collected and analyzed.*

Results: *Total 320 patients with suspected PPHN were admitted during the study period. Among them 92 (29%) cases had PPHN. Male were 49(53 %) cases and female were 43(47%) cases. Mean age at hospital admission was 29.7±13.4 hours. Based on echocardiography,13(14%) cases had mild, 38 (41%) cases moderate and 41(45%) cases severe PPHN. Mean duration of sildenafil therapy was 11.9±7.1 days. Improved from PPHN were 83 (90%) cases. Mortality was 10% (9).*

Conclusion: *In this study it was found that the incidence of PPHN is 29% among the suspected newborns. Sildenafil is successfull in improving the oxygenation of PPHN and to decrease the mortality of neonates.*

Key words*: Sildenafil, PPHN.*

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Introduction

Persistent pulmonary hypertension in newborn (PPHN) occurs in as many as 6.8 of 1000 live births. It is likely to be much more in developing countries, where little data is available.[1] Mortality is 10% to 20% with high-frequency ventilation, surfactant, inhaled nitric oxide, and extracorporeal membrane oxygenation but it is much higher when these therapies are not available.[2]

Nitric oxide alone does not appear to be a solution to the problem. Upto 30% infants fail to improve despite nitric oxide.[3] The cost of its use is prohibitive. Also inhaled nitric oxide has the ability to displace oxygen and bind to hemoglobin forming methemoglobin, thereby further reducing the oxygen carrying capacity of blood. The availability of extracorporeal membrane oxygenation (ECMO), even in developed countries, is limited to few specialist centers and almost always involves transport of a very sick baby to the nearest available centre. ECMO as an option is almost nonexistent in developing countries.[1]

The role of sildenafil in the treatment of PPHN was first reported in the lay press way back in 2002.[4] There were a few who felt that the use was justified[5] as there were no other options for the attending neonatologist in face of non-availability of inhaled nitric oxide and ECMO. There have been published reports of its usefulness in adult cardiac patients as well as in animal models, prior to its use in newborns.[6,7] Since then there have been many more case reports and some small randomized studies regarding the use of sildenafil in babies with severe PPHN. The drug is now frequently being used in many centers in Bangladesh and other developing countries where the availability of high frequency ventilation, nitric oxide (iON) and ECMO is extremely limited.[1]

The management strategies for PPHN must include optimization of ventilation, fluid, electrolyte and acid base balance along with the maintenance of blood pressure. Oral sildenafil can be a useful adjunct to the treatment of PPHN. It can also be used in conjunction with nitric oxide to facilitate quicker weaning off nitric oxide.[8]

Recently it is apprehended that sildenafil is going to be withdrawn from the market of Bangladesh due to threat of its misuse. But it has great role to reduce neonatal mortality and morbidity from PPHN. The aim of this study was to see the extent of use of sildenafil in the treatment of PPHN in neonates and importance of availability of this drugs in the market inspite of its probable misuses.

Materials and Methods

This cross sectional study was conducted in neonatal intensive care unit (NICU), special baby care unit (SCABU) and cardiac intensive care unit (CICU) of Dhaka Shishu (Children) Hospital from June, 2017 to May, 2018. Among the PPHN cases 20(21%) were managed in NICU, 42(46%) in CICU and 30(33%) in SCABU. All admitted patients with or without respiratory distress, presented with cyanosis that was not improved after oxygen therapy (FiO_2 >40%) and/or with murmur and/or with difference in pre-post ductal oxygen saturations of more than 15%[9], were suspected and evaluated for PPHN by echocardiogram. Clinical features of cardiac problems were included for suspicion of PPHN as it is sometimes associated with PPHN. Then neonates including term and preterm who had hypoxemia and pulmonary hypertension confirmed by echocardiogram were taken as cases. The neonates having moderate to severe PPHN and need FiO_2 100% were selected for sildranafil therapy. Besides, the neonates with mild PPHN and having respiratory distress with oxygen requirement >40% with comorbidity including meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pnumonia, perinatal asphyxia and culture positive sepsis were also given sildranafil. Neonates whom pulmonary pressure fall below 25% during sildenafil therapy were considered as improvement and neonates who required >40% oxygen having respiratory distress with comorbidity when decreased oxygen need and respiratory distress were considered as improvement. Discontinuation of sildenafil was done when mild pulmonary pressure achieved and in mild PPHN cases when distress and oxygen requirement decreased (<40% of FiO_2). All cases were monitored in hospital and repeated echocardiogram was done to see the

pulmonary pressure. Few patients discharged with moderate PPHN without having distress and needed extra oxygen, and were followed up for discontinuation of sildenafil. All patients were managed as per hospital protocol even in case of sildenafil. Doses of sildenafil were 2mg/kg/day 3 times daily and decreasing the doses when response occurred. Data regarding number of cases getting sildenafil, improved from PPHN and mortality along with other parameters were collected and statistical analysis were done by using SPSS version-17.

Results

Total 320 patients with suspected PPHN admitted during the periods of July 2017 to June 2018 in Dhaka Shishu (Children) Hospital. Among them 92 cases (29%) cases were PPHN. Male were 49(53%) cases and female were 43(47%) cases. Mean gestational age was 37.5±1.9 wks. Term baby was 59 (64%) and Preterm was 33 (36%) cases. Mean weight was 2718.3±450.4 gms. Mean age at hospital admission was 29.7±13.4 hours (Table-I).

Table I
Basic characteristic of cases

Sex	
Male	49(53%)
Female	43(47%)
Gestational age (mean±SD)	37.5±1.9 wks
Term	59(64%)
Preterm	33(36%)
Birth weight (mean±SD)	2718.3±450.4gms
Age at admission ((mean±SD)	29.7±13.4 hours

Associated conditions were present in 29(32%) cases. These were perinatal asphyxia (9,10%), meconium aspiration syndrome (7,8%), respiratory distress syndrome (3,3%), pneumonia (3,3%) and culture positive sepsis (7,8%) (Table II).

Table II
Associated conditions with PPHN (N=92)

Associated condition	Number (%)
Meconium aspiration	7(8)
Respiratory distress syndrome,	3(3)
Perinatal asphyxia	9(10)
Pneumonia	3(3)
Culture positive sepsis	7(8)
Total	29(32)

Based on echocardiogram, 13(14%) cases had mild, 38 (41%) cases moderate and 41(45%) cases severe PPHN (Table III).

Table III
Grading of PPHN (N=92)

Grading (Pulmonary pressure)	Number (%)
Mild (<36-45mmHg)	13(14)
Moderate (46-60mmHg)	38(41)
Severe (>60mmHg)	41(45)

Mean duration of sildenafil therapy was 11.966±7.1 days. Among the studied neonates with PPHN 90% (83/92) were improved. Mortality was 10% (92) (Table-IV, Table-V).

Table IV
Duration of Sildenafil therapy

Duration of therapy (days)	Mean ±SD
Total	11.9±7.1
Cases in SCABU	7.1±1.6
Cases in NICU+CICU	14.5±7.5

Table V
Outcome of patients with PPHN (N=92)

Outcome	Number (%)
Improved	83 (90)
Death	9 (10)

Discussion

Total 320 admitted cases were evaluated for PPHN. Among them 92 (29%) cases had PPHN. In different study it was shown that the incidence of PPHN in as many as 6.8 of 1000 live births.[2] Rate is high in this study as only suspected cases were analyzed, not among all sick neonates.

In this study male were 49 (53%) cases and female were 43(47%) cases. In the study of Hernando et al[2] the male was 57% and female was 43%. Mean gestational age was 37.5±1.9 wks in this study and it was found 38.4 ±2.6 wks by Hernando et al[2]. In this study term baby was 59 (64%) and preterm was 33 (36%) cases. In other study 72% patients were term and 28% cases were near term (35-37 weeks).[9] Mean birth weight was found 2718.3±450.4gms in this study and Hernando et al[2] found mean weight 2803±617 gms in their study. In this study mean age at hospital admission was 29.7±13.4 hours. In the study of Hernando et al[2] they showed that the median age of the 13 infants at the time of entry was close to 25 hours (range: 3-72 hours).

In this study associated conditions were present in 29(32%) cases. These were perinatal asphyxia (9,10%), meconium aspiration syndrome (7,8%), respiratory distress syndrome (3,3%), pneumonia (3,3%) and culture positive sepsis (7,8%). In the study of Ali et al[9] associated conditions were respiratory distress syndrome 5(28%), meconium aspiration syndrome 5(28%) pneumonia 1(5.6%) and Hernando et al[2] found meconium aspiration, in 57%% cases and respiratory distress syndrome in 43% cases.

Based on echocardiogram, 13(14%) cases had mild, 38 (41%) cases moderate and 41(45%) cases severe PPHN in this study whereas in the study of Ali et al[9] it was found that 17% patients had mild, 28% moderate and 55% severe PPHN.

In this study mean duration of sildenafil therapy was 11.966±7.1 days and it was 12.6 days in study of Ali et al[9]. In this study 83 (90%) cases were improved from PPHN and the mortality was 10% (9). Ali et al[2] showed in their study that mortality was 33%.

Recently it has been apprehended that sildenafil is going to be withdrawn from the market of Bangladesh due to threat of its misuses despite its successful use in PPHN and erectile dysfunction in adult. Since sildenafi is easily available and convenient to administer, it has the potential for inappropriate use. This drug is the most commonly used 5 Phosphodiesterase (PDE5) inhibitor and the most commonly misused PDE5 inhibitor. Studies have reported the increasing misuse of unprescribed sildenafil for enhancing sexual performance among college going males, night clubbers and illicit drugs users. It is used along with other recreational agent like cocaine, amphetamine, marijuana, testosterone, steroids etc. Athletes also abuse sildenafil for enhancement of on-field performance.[11-18]

All this misuses occurred in other countries specially developed countries. At present there is no definite data regarding misuse of this drugs in Bangladesh. But threat of misuse of this drug is present. Sildenafil has great role to reduce neonatal mortality and morbidity from PPHN that has also seen in this study. As at present no alternative treatment like inhaled nitric oxide and ECMO are available to treat this disease, it should be available in market to ensure the treatment of PPHN inspite of threat of its misuses.

Though the misuse of sildenafil is not so many in Bangladesh, nevertheless it is the time to take measurement against its abuse. Here is the some way of prevention of misuse of this drug. Firstly prepare tablets in small doses (5mg/10mg). Secondly dispensing should be done by only prescriptions from registered, qualified physicians. Thirdly small amounts (5 to 10 tablets at a time) should be dispensed for a particular patient. Fourthly stocks of pharmacies should be checked time to time and regulated, and finally create public awareness.

Conclusion

In this study it was found that the incidence of PPHN is 29% among the suspected newborns. Sildenafil is successfull in improving the oxygenation of PPHN and to decrease the mortality of neonates. This drug is essentials in the management of PPHN and thereby to reduce neonatal mortality. At this time alternative drugs are not available to treat this disease in Bangladesh. So sildanafil should be available in the market and necessary actions should be taken to prevent its misuses as well.

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ORIGINAL ARTICLE

Role of Macronutrient in Better Survival of Critically Sick Neonates Admitted in Neonatal Intensive Care Unit (NICU)

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Abstract

Background*: Neonates are considered more susceptible to macronutrient deficits. During critical illness, sick children cannot normally be fed by mouth, and as a result a pronounced macronutrient deficit often develops after a few days. This macronutrient deficit has been associated with weakness, infections and increased risk of mortality.Therefore, macronutrient as energy source is an important key concern to care and for overall to achieve better survival.*

Objective*: The present study is intended to evaluate the role of macronutrient such as blood glucose, serum calcium, hemoglobin as iron status, serum albumin, in critically sick neonates admitted in NICU and their outcome.*

Methods*: This observational prospective study was carried out at NICU of Dhaka Shishu (Children) Hospital from January 2014 to July 2014. Total 121 neonates were enrolled and analyzed their essential macronutrient profile e.g, blood glucose, serum calcium, hemoglobin, serum albumin and other relevant investigation as complete blood count with film, CRP, blood culture and chest X ray as a part of management as well as to predict their survival.*

Results*: Macronutrient of critically sick neonates play important role to predict their better survival. Perinatal asphyxia and sepsis were major diagnosed pathological conditions of these neonates. In sepsis lower value of serum albumin were statistically significant. Lower value of glucose, calcium, hemoglobin and albumin were also statistically significant in Non-survivors than Survivors.*

Conclusion: *During critical illness in neonates, emphasis should be paid on of adequate macronutrient as energy source. This is necessary for better optimization survival of critically sick neonates.*

Keywords*: Macronutrient, survival, critically sick neonates.*

Introduction

Neonates can acutely decompensate from a variety of causes. However, they have a limited repertoire of responses to stress and their presenting signs are nonspecific. Therefore prompt evaluation, initial stabilization with proper management of critically ill neonates present a special challenge for pediatrician to encounter the compromised condition. Critical

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illness in newborn, major devastating health problems with survival in Bangladesh like other developing countries.

Critical illness is accompanied by a hypermetabolic state related to stress response inducing catabolic state with activation of various catabolic hormones[1] characteristic of the critically ill newborn infant.[2] Their activation are critical short-term adaptations to promote survival[2] allows the body to quickly catabolize macronutrient from their stores, in order to cover the immediate high energy demands.[3] This situation results in elevated energy expenditure and thereby increased energy requirements.[4] Therefore, on any critical situation energy source is the valuable need.Poor energy reservoir or less intake increased incidence of complications as infections, even organ failure and increased risk of mortality.[5,6] During critical illness should provide essential macronutrient as glucose, calcium, hemoglobin, albumin- important impact on the patient's positive clinical outcome.[7]

Neonates are considered more susceptible to macronutrient deficits.[8] Critically ill neonates cannot normally be fed by mouth, as a result a pronounced macronutrient deficit often develops after a few days. This macronutrient deficiency has been associated with infections, weakness, and delayed recovery.[9-12] Hypoglycemia can occur in stress situation of any critical ill newborn due to an inability to perform adequate gluconeogenesis. Glucose serves as the major source of energy for living cells in the form of ATP. Most tissues of the body can live without O_2 for several minutes even as long as 30 minutes. During this time as anaerobic metabolism, the tissue cells obtain their energy through breaking down glucose and glycogen at the expense of consuming tremendous amounts. However, it does keep the tissues alive.[13] Undernormal conditions most brain energy is supplied by glucose.The neonatal brain is highly dependent on glucose as an energy source to support its high metabolic rate.[14] Hypoglycaemic neonates may have used their glycogen stores during perinatal asphyxia.[15] So in asphyxia at the molecular level as a failure of energy supply sufficient to cause cellular damage.[16] The body makes metabolic adaptations to increase the chance of survival. The adaptations produce additional fuel, primarily in the form of glucose from glycogen, de-aminated amino acids and triglycerides. Peripheral insulin resistance is prominent presumably as a mechanism to shunt glucose to organs necessary for survival such as the brain and the heart. The response is similar in critically ill children.[17] Regular ward monitoring of blood glucose with dipsticks or tapes is standard practice.[15]

Calcium is another major need for living cells, an important second messenger in the body helps carrying out muscle function and acts as cofactor for several enzymatic activities. Hypocalcemia is common in critically sick neonates due to defective hydroxylation of 25-hydroxycholecalciferol as in intrapartum hypoxia or physiological immaturity. Experienced clinicians will recognize slight jitteriness as a good guide to this condition.[18] Maintaining homeostasis and normal serum concentrations of calcium is important because hypocalcemia can affect optimal respiratory and cardiac function. Transient neonatal hypocalcemia often is exacerbated by acute respiratory disease and, when severe, can cause tetany and cardiac arrhythmias.[19] Therefore, correct measurement of serum calcium level is more important and proper remedy as supplement to better survival of critically ill neonates[19]. Hypoglycemia and hypocalcemia are common nutritional problems and have direct consequences in neonatal period. Prompt identification and treatment to prevent worse outcome.

Protein status is also negatively influenced by illness in neonates. Protein breakdown is an essential part of stress physiology because de-aminated amino acids are recycled through the liver as carbon sources for gluconeogenesis, particularly when the glycogen stores of the neonate have been utilized.[14] Protein catabolism occurs during neonatal sepsis,[20] presumably driven by pro-inflammatory cytokines.[21] Hypoalbuminemia is frequent among critically ill neonates with sepsis.[22] Lower albumin status leads to low oncotic pressure, which can result in or exacerbate edema might be associated with a poorer prognosis of newborn.[19] Hypoalbuminemia also affect on calcium concentration.[23] Therefore, protein specially albumin is more than essential for optimal life survival.

Although it may be important to maintain normal hemoglobin concentrations in neonates who have acute respiratory disease to optimize oxygen

delivery. Most infants are born with sufficient iron stores to maintain them through the period of acute disease, rapid decrease in hemoglobin(due to blood drawing) are treated by transfusion, not by infusion of parenteral iron.[19]

Timely recognition, a high index of needed and a through understanding of common macronutrient as energy source are necessary to ensure their adequate provision as well as reduce mortality of critically ill neonates. This study was carried out in neonates with various ailments admitted in NICU at a tertiary care hospital, Dhaka Shishu Hospital, Dhaka, Bangladesh.

Materials and Methods

This observational prospective study was conducted at NICU, Dhaka Shishu (Children) Hospital during the period of January 2014 to July 2014. For each neonate, a detailed history from mother or other care-giver was recorded in a preset questionnaire.

Total 161 neonates admitted during this period. Out of them, 40 were excluded from this study due to congenital anomalies(medical or surgical), jaundiced due to blood group incompatibilities or received LAMA (Left against medical advice). Before enrollment, parent of each neonate was given a detail explanation about nature and purpose of the study.

Total 121 neonates were analyzed for essential macronutrients parameter, e.g., blood glucose, serum calcium, hemoglobin, albumin as well as other baseline investigations for proper management. Blood glucose was done using glucometer and values were estimated by glucose oxidase method. Serum calcium was measured by calorimetric test method.

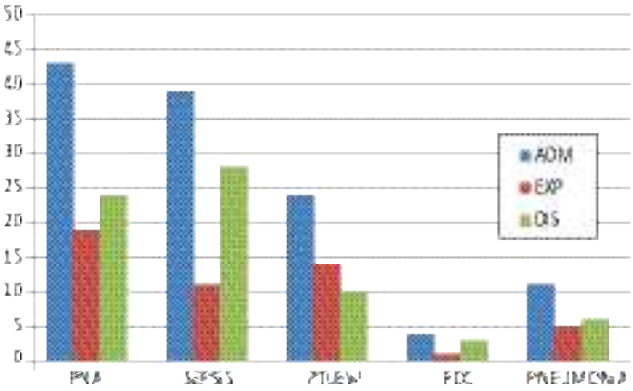
Each case was thoroughly examined and follow-up regularly. Definite neonatal septicemia was diagnosed by positive blood culture and probable septicemia was diagnosed by a scoring system[24] or positive CRP.

Normal range of blood glucose (2.75-4.4mmol/L),[25] Serum calcium (2.25-2.65mmol/L),[26] Hemoglobin (14-20 gm/dl with an average value of 17gm/dl)[27] and Serum albumin (25-43gm/2)[23] were considered.

For further follow-up nutritional parameter and relevant investigations were done as required. Unpaired t-test was used to test significance difference of macronutrient status of critically ill neonates and also significance difference among survivors and non-survivors.

Results

The study was carried out on the basis of neonates suffering from a wide variety of disease pattern admitted NICU care and their mortality (Fig1). The selection was unbiased and generalized.



ADM=Admission, EXP=Expired, DIS=Discharge

Fig 1 *Disease pattern of enrolled neonates and their outcome*

This study was carried out over a period of six months. The median age of neonates was 7 days. Preponderance of males in this age group. Among 121, eighty four (84%) neonates were male and thirty seven (37%) were female, 2.27:1.

Non-survivors had significantly lower glucose, calcium level (at admission/initial) than Survivors (Table I). Among major diagnosed pathological diseases of critically sick neonates, neonatal sepsis had significantly lower value of serum albumin (Table II). Even non-survivors had significantly lower not only glucose, calcium level also hemoglobin and albumin than survivors (at discharge/death) (Table III).

Table I

Baseline Macronutrient profile (Mean ±SD) in Survivors and Non-Survivors (admission/initial)

	Survivors (n=71) Mean±SD	Non-Survivors (n=50) Mean±SD	p value
B. Glucose	3.61±2.25	3.22±0.07	**0.020^{s}**
S. Calcium	2.06±0.17	2.03± 0.15	**0.020^{s}**
Hemoglobin	17.61±4.42	15.50±6.33	0.055^{ns}
S. Albumin	23.04±0.24	25.92±4.11	0.060^{ns}

p value reached from unpaired t-test

Table II
Macronutrient profile (Mean ± SD) in major diagnosed pathological condition Perinatal Asphyxia (PNA) & Sepsis of critically ill neonates (admission/initial)

	PNA(n=43) Mean±SD	Sepsis(n=39) Mean±SD	p value
B. Glucose(mmol/L)	2.18±0.39	3.08±0.15	0.109[ns]
S. Calcium(mmol/L)	2.03±0.24	2.07±0.15	0.346[ns]
Hemoglobin(gm/dl)	16.85±3.46	13.97±5.59	0.070[ns]
S. Albumin(gm/L)	26.14±4.75	22.20±4.12	0.040[s]

p value reached from unpaired t-test

Table III
Macronutrient profile (Mean ±SD) in Survivors and Non-Survivors (discharge/death)

	Survivors (n=71) Mean±SD	Non-Survivors (n=50) Mean±SD	p value
B. Glucose	7.14±6.06	6.15±3.24	0.013[s]
S. Calcium	2.06±0.20	2.09± 0.18	0.048[s]
Hemoglobin	15.44±5.06	14.33±6.88	0.022[s]
S. Albumin	24.46±1.61	23.7±0.14	0.034[s]

p value reached from unpaired t-test

Discussion

The study was carried out in critically ill neonates. Detection of essential macronutrient as energy source is an important key concern in admitted sick neonates are discussed as follows to predict their survival. Macronutrient, e.g., blood glucose, serum calcium, hemoglobin as iron status, serum albumin play important role in that aspect. The focus of neonatal macronutrient has become increasingly evident that nutrition during the first few weeks of life while the infant is struggling for survival is crucial.[28] Faisy et al. demonstrated that negative energy balance is an independent determinant of intensive care unit (ICU) mortality in very sick patients.[5] In this study similar to that, non-survivor had significantly lower macronutrient parameter (glucose, calcium, hemoglobin, albumin) than survivors. Martin et al.[29] observed that patient who received proper nutrition had better clinical outcome. These findings are in agreement with the results from the work of van Schijndelet al.[30] who conducted a prospective observational cohort study. They assessed the effects of achieving optimal nutrition in ICU patients. In another study by Singer et al[31] who conducted a review and analysis of literature related to nutrition in the ICU. Targeting the energy goal, optimal energy supply in critically ill patients. The metabolic changes from the stress response have an impact on the macronutrient requirements of critically ill patients.[1,3] Several clinical studies in neonates who had sepsis or any critical illness have demonstrated increased levels of both TNF alpha and IL6, cytokines known to be involved in the stress response and multisystem organ failure syndrome. Energy requirements in these neonates were elevated in proportion to the degree of illness. The septic neonates required more energy delivery during the acute phase of their illness than similarly ill non-septic neonates.[19] In our study, there was lower mean value of albumin and hemoglobin in septic neonates (Table II).

Glucose is a ready source of energy in the form of ATP, and neonates are particularly dependent on glucose as an energy source.[19] ATP is confined to living cells. As the energy currency of cells ATP depletion sufficient to cause irreversible or partially reversible cellular damage, which also accelerates damage by hypoglycemia.[16] The body makes metabolic adaptations to increase the chance of survival by use of additional fuel, primarily glucose to shunt to organs for survival such as the brain and the heart. The response is similar in critically ill children.[17] In our study glucose level was significantly lower in non-survivors than survivors (Table I, Table III) (both admission and death/ discharge).

Calcium balance are difficult to maintain in critically sick neonate.[32] Hypocalcemia can affect optimal respiratory and cardiac function.Transient neonatal hypocalcemia often is exacerbated by acute respiratory disease and, when severe, can cause tetany and cardiac arrhythmias.[19] So more hazardous may be happened in hypocalcemia of critically sick neonates.

Hypoglycemia and hypocalcemia are common in critically ill neonate, significant concern among neonatal and pediatric critical care specialists.[33,20] In our study both level were significantly lower in non-survivors than survivors (Table I, Table III) (both admission and death/discharge).So initial

prevention of both by accurate measuring techniques and monitoring potentially improve survival of critically ill neonates.

The divalent metals iron also at risk during neonatal illness. Certain subgroups of neonates are born with low iron stores.[34,35] It is likely that inflammation or stress situation significantly alters iron absorption and trafficking in the sick newborn.[36] Additional hemoglobin should be synthesize or required. Otherwise, the consequence of hemoglobin deficit becomes worst outcome.[37] In our study, similar to that as non-survivors had lower value of hemoglobin than survivors.

Hypoalbuminemia was frequent among critically ill neonates with sepsis.[11] Sepsis alters protein requirements more acutely by its effect on cytokine-mediated muscle catabolism. This condition causes a dramatic increase in muscle catabolism, most likely to provide a ready source of amino acids in the liver for acute phase reactant synthesis. Sepsis causes the most profound changes in negative nitrogen balance among in septic neonates in which the degree negative nitrogen balance is related directly to the degree of the severity of physiologic instability. There are concomitant increases in cytokine and acute phase reactant protein concentration. The same study demonstrated that critically ill infants remained in negative nitrogen balance for as long as 10 days after the sepsis began. The concern is that this duration of negative nitrogen balance would lead to worst outcome as morbidity (predisposition to further episodes of sepsis) and mortality.[19] Therefore, lower albumin levels might be associated with a poorer prognosis of newborn[23] similar in our study (Table III).

Conclusion

In this brief overview, the main message is that during critical illness in neonates, emphasis should be placed on the provision of adequate macronutrient source. This is necessary for better optimization survival of critically ill neonates.

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ORIGINAL ARTICLE

Effectiveness of a Multidisciplinary Lifestyle Intervention to Reduce Obesity among Children and Adolescents

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Abstract:

Background: *Now a days unhealthy lifestyle primarily responsible for the dramatic increase obesity among children and adolescents.*

Objective: *The purpose of the study is to see the effects of a multidisciplinary lifestyle intervention to reduce obese children and adolescents. The main outcome was cardiometabolic risk based on the waist-to-height ratio (WHTR) measurement. Secondary outcomes were (1) changes in body composition; (2) adherence to a Mediterranean diet; and (3) physical performance.*

Methods*: The study involved 64 overweight/obese children or adolescents conducted at Dhaka Shishu Hospital from October 2017 to September 2018. The intervention was multidisciplinary including nutrition, exercise, and psychological aspects based on a family-based approach; it was delivered for six months for children and three months for adolescents. Before and after the intervention, several anthropometric measures height, body weight, body mass index (BMI), waist circumference, and body composition, cardiometabolic risk index waist-to-height ratio (WHTR), and dietary habits of the participants and their families were evaluated. In addition, a set of functional motor fitness tests was performed to evaluate physical performance measures.*

Results: *After the intervention both children and adolescents showed a significant reduction in body weight, BMI, waist circumference, fat mass, and WHTR index and an improvement of fat-free mass, adherence to the Mediterranean diet, and physical fitness performance.*

Conclusion: *A short term family-based multidisciplinary approach is effective in ameliorating the health status, dietary habits, and physical performance in children and adolescents.*

Key words: *Lifestyle intervention, obesity, children, adolescents.*

Introduction

The lack of physical activity (PA) or low levels of PA and sedentary habits with overeating/unhealthy eating are the most causes of the increase obesity.[1-4] More specifically, nutrition education efforts should be directed towards children to establish healthy eating habits that will have beneficial effects in adulthood. Perhaps children and adolescent

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populations are those with the most deteriorated Mediterranean diet profile, and thus are worthy of priority attention.[5] Obesity is a multifactorial disease, the product of the complex interaction of genetic, hormonal, physical, nutritional, social, and environmental factors.[6] Overweight and obesity are growing in childhood and adolescence all over the world. In 2014 the World Health Organization (WHO) estimated more than 41 million overweight children under the age of five.[7] European data show that the prevalence of overweight ranged from 18% to 57% among boys and from 18% to 50% among girls; 6-31% of boys and 5-21% of girls are obese.[8] Childhood obesity is a risk factor for adult noncommunicable diseases (NCDs) and represents a health care cost for society.[9] For these reasons childhood obesity is one of the most serious public health problems in our time and a new challenge.[10] Studies show that sedentary behaviors independent of physical activity levels are associated with increased risk of all-cause mortality and psychological problems.[11,12] So, the promotion of physical activity among children and adolescents is considered a strategic way to tackle childhood obesity.[13] Physical activity habits is necessary to develop in early life and persisting into adulthood.[14,15] The prevention and the treatment of childhood obesity is complex and requires a multicomponent approach involving the family and addressing individual and social aspects,[16] focusing not only on physical activity but also on nutrition and enhancing motivation toward a healthy lifestyle.[17-20] As adolescents become more autonomous from their parents they look more to their friends for behavioral and social cues.[21] The family-based approach was defined as the "gold standard" treatment.[22-23] As suggested by Kitzman et al[24] the use of a family-oriented approach to pediatric treatment of obesity can be defined as the active involvement of parents in the treatment of overweight and obesity in children. Family, in particular parents, has been consistently and strongly linked with children's physical activity and sports involvement.[25-29]

Materials and Methods

Total number of 64 children and adolescents subjects with obesity were recruited at Institute of the Dhaka Shishu Hospital, Sher-E-Bangla Nagar, Dhaka from March October 2017 to September 2018. The total sample was divided into two subgroups by age: the children group (n=38, age 3-12 yrs.) and the adolescent group (n=26, age 13-14 yrs.). In the children's group (57.9% male and 42.1% female) there was a mean age of 9.79 ± 1.8 years (min 5-max 12), with no differences for gender, while in the adolescent group (38.5% male and 61.5% female) there was a mean group age of 13.72 ± 0.41 (min 13-max 14), with no differences for gender. Children were evaluated at the Pediatric Clinic of the local hospital and those who met the inclusion criteria were referred to Dhaka Shishu Hospital, Sher-e-Bangla Nagar, Dhaka. At the first visit patients were assessed for the anthropometric values. Inclusion criteria for the enrolment were BMI over 85^0 percentile[30], the absence of contraindications to perform physical exercise, and parents' informed written consent to the lifestyle intervention. The intervention followed the Centro Universitario Ricerca Interdepartmentale Attivita Motorica (C.U.R.I.A.Mo) lifestyle approach for children and adolescents (approved by the Dhaka Shishu (Children) Hospital), a multidisciplinary structured program including the nutritional intervention, the exercise intervention, and the psychological intervention.[31]

All participants followed the three different parts of intervention described later. The 9% of the total sample recruited (4 children) did not start the program because they were still engaged in other sports activities or due to family difficulties in managing the timetable of the activities. Parents' work difficulties were cited as the main barriers to participation. The sample size was calculated based on WHTR endpoint as a main predictor of cardiometabolic risk. A sample size of 74 achieves 89% power to detect a mean of paired differences of 3% with an estimated standard deviation of differences of 8% and with a significance level (alpha) of 0.05 using a two-sided paired t-test. Descriptive analysis in terms of mean, standard deviation, and percentages were computed for the variables investigated. Student's t-test for paired sample was used to compare all assessment measures (anthropometry, diatary habits, and physical activity) before and after intervention (T0-T1). Analyses were limited to participants with baseline data on the different measurements and performed using SPSS, version 22.0.

Results

Anthropometric data at the baseline and after the intervention are reported in Table I for the children's group and in Table II for the adolescent group. In children group after the intervention (T1) data showed a significant decrease in all the measures. BMI (p=0.001), waist circumference (p=0.003), and WHTR index (p<0.001) showed a significant reduction with a small effect size. Regarding body composition (subgroup of 33) data showed a significant decrease with a large effect size of percentage for fat body mass (p <0 .001) and a significant increase in percentage of fat-free mass with a medium effect size (p =0.004) (Table I).

In Adolescents group after the three months intervention adolescents showed a significant decrease in waist circumference (p= 0.012). The subgroup (N=23) assessed with BOD POD showed a reduction of fat body mass percentage (p=0.001) with a medium effect size and an increase of fat-free mass (p=0.004) (Table II).

Table I
Children's anthropometric measure at T0-T1

Anthropometric data	T0	T1	p
BMI (kg/m^2)	26.65±2.41	25.11±2.46	0.001
WC (cm)	90.36±8.46	86.13±7.13	0.003
WTHR (cm)	0.58 ± 0.03	0.54± 0.02	<0.001
FM (kg)	24.01 ± 6.32	20.38 ± 7.30	0.003
FM (%)	40.98± 7.57	35.12 ± 5.41	<0.001
FFM (kg)	35.66 ± 6.23	38.67 ± 7.55	0.015
FFM (%)	61.45 ± 5.40	64.41 ± 5.98	0.004

Data are presented as mean±SD. Statistical significance was considered at p <0.05; BMI = Body mass index; WC = waist circumference; WHTR = waist to height ratio; FM = fat body mass; FFM = fat-free mass.

Table II
Adolescent's anthropometric measure at T0 and T1

Anthropometric data	T0	T1	p
BMI (kg/m^2)	31.93 ±4.31	30.24 ± 4.51	0.032
WC (cm)	105.85 ± 10.63	101.4 ±9.20	0.012
WHTR (cm)	0.65 ± 0.08	0.62 ± 0.07	0.025
FM (kg)	36.74 ± 10.45	33.02 ± 9.33	0.035
FM (%)	40.51 ± 6.82	36.51 ± 7.14	.001
FFM (kg)	51.21 ± 7.17	54.21 ± 8.63	.034
FFM (%)	59.45 ± 7.28	63.12± 6.91	.004

Statistical significance was considered at p<0.05; BMI=body mass index; WC=waist circumference; WHTR=waist to height ratio; FM=fat body mass; FFM=fat-free mass.

Children showed a significant improvement in KIDMED scores with a medium effect size (t=-3.33; p=.002) from T0 =6.73 2.27 to T1=7.93±1.74.

Adolescents showed a significant improvement in KIDMED scores with a large effect size (t=-5,94; p <0.001) from T0 =5.68±2.76 to T1 8.39±2.42.

As reported in Table III, the mean distance walked within six minutes increased (A=37.03±144.03) after three months of exercise, with no statistical difference between two times of evaluation.

Strength values were raised, as expected, in response to the progressive work load proposed during the exercise period. The data showed a significant increase with a medium effect size in ball throw ($p<0.001$ and $p<0.001$). The sprint time of the 30 m test improved significantly, with a large effect size ($p<0.001$). Finally, flexibility improved only the bending test results from the seating position ($p=0.05$) with a small effect size.

As shown in Table IV, maximal oxygen consumption (VO_2 max) increased (A=0.48±4.53) after three months of exercise, with no statistical difference between two tests. In strength values there was a significant increase with a large effect size in every exercise at the isotonic machine (except in a leg press test that presented $p<0.001$), while the flexibility value improved only in bending test from standing position with a small effect size ($p=0.025$).

Table III
Children's physical activity measurement at T0 and T1

Children's physical activity measurement	T0	T1	P
6 MinWT (cm)	678.91 ± 87.5	715.2 ± 154.8	0.105
Ball TA (cm)	4.61 ± 0.75	5.07 ± 0.87	0.002
Ball TB (cm)	4.69 ±1.03	5.56 ± 1.32	0.001
30 m sprint (s)	7.25 ± 0.78	6.36 ± 0.81	<0.001
VB (cm)	-3.12 ± 7.31	-2.21 ±7.81	0.497
HB (cm)	31.68 ± 8.87	33.21 ± 7.87	0.304
Sargent (cm)	23.11 ± 5.42	26.58± 7.02	0.002

Data are presented as mean ± SD. Statistical significance was considered at $p<05$; 6 MinWT = six minutes' walking test; ball TA = medicine ball throw ahead; ball TB = medicine ball throw behind; 30 m sprint = 30 metres' speed test; VB = vertical bending value at sit and reach test, HB = horizontal bending values at sit and reach test; Sargent = Sargent Test Value.

Table IV
Adolescents physical activity measure of the adolescents (13-14) at T0 and T1 of the intervention

Adolescents physical activity measurement	T0	T1	P
VO_2 max (ml/kg/min)	31.20± 7.25	31.32 ± 6.9	0.923
Lat (kg)	35.74 ± 7.85	43.28 ± 8.96	<0.001
Chest (kg)	31.12 ± 7.63	39.21 ±9.36	<0.001
Press (kg)	177.12 ± 51.21	214.91 ± 45.01	<0.001
Lext (kg)	41.21± 11.02	51.93 ± 10.74	.000
VB (cm)	-6.81 ± 7.28	-4.17 ± 6.87	0.037
HB (cm)	30.21 ± 8.87	31.02 ± 9.41	0.617

Data are presented as mean±SD. Statistical significance was considered at $p<0.05$; VO_2 max=maximum rate of oxygen (O_2) consumption; Lat=Lat machine test value; chest=chest press test value; press=leg press test value; Lext=leg extension test value; VB=vertical bending value at sit and reach test, HB=horizontal bending values at sit and reach test.

Discussion

The aim of the present study was to investigate the effects of a multidisciplinary family-based lifestyle intervention to treat overweight/obese children and adolescents. The first results of our structured intervention demon-strate effectiveness in reducing the cardiometabolic risk through a significant reduction of WHTR and changes in body composition. The structured multidisciplinary intervention shows changes in nutritional habits (greater adherence to Mediter-ranean diet) and improvements in physical performance. Many studies[32-35] showed significant positive effects of physical activity in favors of the intervention.

The results of this study seem to be able to show how a multidisciplinary approach based on the family is effective not only in children but also in the adolescent group, where a significant decrease in waist circumference ($p<.001$), a significant reduction of fat body mass percentage ($p< .001$), and a significant decrease in waist circumference ($p<.001$) and in fat body mass percentage ($p<.001$) were observed as well as improvement of the nutritional habits ($p<.001$) and strength parameters. PA attitudes are influenced by individual, social, environmental, and community aspects.[36] Participants with higher perceived peer acceptance, friendship quality, and soccer competence were more likely to continue on with the sport.[37] Family, in particular parents, has been consistently and strongly linked with youth's PA and sport involvement.[25,37-41]

Family influences and friend support can act in improving physical activity habits.[42-44] Children and adolescents are more physically active when in the presence of peers and it is likely that these positive feelings increase the enjoyment and youth motivation to engage in physical activity (PA).[45-47] Decrease of sedentary behavior showed effective in children in the meta analysis presented by Kamath et al[48], and in adolescents in the study by Biddle et al[49]. Interestingly, similar conclusions have been drawn for lifestyle interventions in children to reduce obesity.[50] In its recommendations WHO indicates that children and young people aged 5-17 years should accumulate at least 60 minutes of physical activity every day.[51] The present results confirm that this strategy is effective in ameliorating, in the short term (3-6 months), the health status, the nutrition habits, and the physical performance of children and adolescents. In particular, the present data demonstrate that after the intervention the participants significantly reduced BMI, WC, WHTR, and fat mass and improved fat-free mass, adherence to the Mediterranean diet, and physical fitness.

At baseline, the participants in the study did not follow this recommendation. As shown previously in Tables 3 and 4 improvements in (1) dynamic strength; (2) cardiorespiratory efficiency; (3) the speed of the children, and (4) flexibility were observed. In addition, to train aerobic capacity and flexibility resistance training was also included in the exercise intervention. In adolescents cardiovascular activity was presented using ergometers and with gradually increasing work intensity (5% every two weeks) from 50% up to 70-80% of heart rate reserve[52] combined with free loads and work at isotonic machines with a gradual increase from 55% up to 70-80% of 1 repetition maximum (RM), according to an adolescent's basal fitness level. After three months of exercise, data showed that strength values increased, as expected, in response to gradually augmented load used during exercise periods. In particular, relevant changes in the dynamic strength of the upper limbs and trunk and lower extremity strength were observed, with a medium and large effect size.

In adolescents, we tested the effects of the intervention on VO_2 max and did not observe significant changes. As regards flexibility, the existing studies confirm a role for genetic influences on the individual differences but estimates vary widely. 18-55% of the variation in flexibility (as measured by the sit and reach test) in children and young adults could be explained by genetic influences.[53]

Conclusion

Multidisciplinary lifestyle intervention based on a family-based approach, demonstrating that such kind of approach allows obtaining positive results in lifestyle habits changing in not only children but also adolescents groups with obesity, after a short period (3 to 6 months).

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ORIGINAL ARTICLE

Pediatric Germ Cell Tumors: An Experience of 7 Years in a Tertiary Hospital of Bangladesh

SM Rashed Zahangir Kabir[1], Md. Waheed Akhtar[2], Farida Yasmin[3]

Abstract

Introduction: *Germ cell tumors are a group of tumors with different clinical presentation and histological and biological characteristics. Malignant germ cell tumors occur at all ages with a trend of bimodal distribution in infancy and adolescence.*

Objective: *To evaluate the demographic characteristics, distribution of different types of germ cell tumor, treatment modalities and outcome of germ cell tumor in children in a tertiary care hospital of Bangladesh.*

Methods: *In this retrospective study, data regarding age and sex distribution, location, types of tumors, management of germ cell tumor in children were retrieved from the medical records of pediatric oncology department in NICRH, Dhaka from 2008 to 2014.*

Results: *Out of total 87 patients female were 50 and male 37. Most of the patients were up to 5 years of age. The gonadal germ cell tumors (80%) were more than extragonadal tumor (20%) in both male and female patients. The most common germ cell tumor was dysgerminoma (32%) followed by yolk sac tumor (29.8%) and teratoma (19.5%). Yolk Sac Tumor (51.4%) was the most common in male and dysgerminoma (56%) the commonest in female. Out of 87, seventy two (82.7%) received chemotherapy following surgery. Among those 72 patients who received chemotherapy 49 (68 %) patients completed their treatment. Until the last follow up 71.4% patients remained alive and tumor free.*

Conclusion: *Germ cell tumors are the most variable tumor of all childhood malignancies that has difference in age, sex, location and histological subtypes. Gonadal tumors have better prognosis than extragonadal tumors in both the sex.*

Key words: *Pediatric germ cell tumour.*

Introduction

Pediatric germ cell tumors (GCTs) are rare and heterogeneous tumors hypothesized to occur as a result of events in utero,[1,2] although the etiology is largely unknown. GCTs are grouped together due to their presumed common cell of origin, the primordial germ cell (PGC). During normal fetal development, PGCs originate in the embryonic yolk sac and migrate to the gonads.[3] GCTs typically occur in the testes or ovaries; however, extragonadal GCTs can occur and have been hypothesized to result from abnormal germ cell migration during development.[4]

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These tumors are felt to arise from a common progenitor germ cell but have a wide range of histologies. GCTs are grouped into two broad classes: seminomas comprised of the seminomas of testes and dysgerminomas of the ovaries; and nonseminomas, comprised of yolk sac tumors, teratomas, embryonal carcinomas and choriocarcinomas.[5] In this study, we analyzed the age and sex distribution, location, types of tumors, management, outcome and complications of GCTs in children.

Materials and Methods

This retrospective study was done in pediatric oncology department of National Institute of Cancer Research and Hospital, Bangladesh from 2008 to 2014 by using the data from the patients registry. Medical records of patients aged 18 years or younger, who were diagnosed with GCT and were treated between 2008 and 2014, were retrospectively reviewed. The files were reviewed in terms of age, sex, types, location, management as well as prognosis and outcomes. Histopathological subtypes and their locations were investigated. The different types of tumor according to age and gender were analyzed. The treatments of the patients and the final status were recorded in detail. All statistical analysis of the results were obtained by using window based software devised with Statistical Packages for Social Sciences (SPSS) version 22. This study had power 95%. In all statistical tests 5% level of significance that is a p value < 0.05 was considered as significant.

Results

In present study, a total of 87 patients were included. Out of them female were 50 (57.5%) and male 37 (42.5%). The age of the most of the patients were 5 years or below (47%), followed by those above 10 years (37%) and others between 5 to 10 years (16%) (Fig-1). Male were more commonly affected up to 5 years of age (p = 0.019) and after 10 years female were more affected by malignant germ cell tumors in this study (p = <0.001). The gonadal germ cell tumors (80%) were more than extragonadal tumors (20%) in both male and female patients. The most common germ cell tumor was dysgerminoma (32%), then yolk sac tumor (29.8%), followed by teratoma (19.5%). The yolk sac tumor was more common in male (51.4%) than female (14%). In male patients most common germ cell tumor was yolk sac tumor (51.4%, p =< 0.001) followed by immature teratoma (18.9%) and in female dysgerminoma (56%) followed by teratoma (20%).

Testis (83.8%) was the commonest site followed by abdomen, sacrococcygeal region and mediastinum in male patients. In case of female patients ovary (78%) was most commonly affected followed by sacrococcygeal region, abdomen and mediastinum.

Out of 87, seventy two (82.7%) received chemotherapy following surgery. Out of 72 patients who received chemotherapy 49 (68%) patients completed their treatment.

Out of 49 patients who completed their chemotherapy, 5 patients developed local recurrence (12%), 4 patients abdominal metastasis (9.5%), 3 patients had lung metastasis (7.1%) and 30 (71.4%) patients did not have any complaint about their disease (11 up to 2 years, 15 up to 3 years and 4 above 3 years). Remaining 7 patients lost to follow up.

In case of male, prognosis was good up to 5 years of age (35.7%) and in female more than 10 years of age had good prognosis (42.8%).

According to histological types, out of 42 patients who completed treatment, yolk sac tumor (33.3%) was most curable in case of male and in female dysgerminoma (33.3%) was found the most curable one.

Table I

Clinical characteristics of the patients (N=87)

Variables	Male-37 (42.5%)	Female-50 (57.5%)	P value
Age of Patient			
0 to 5 years	30(81.2)	11(22)	0.019
> 5 to 10 years	4(10.8)	10(20)	0.248
> 10 years	3(8)	29(58)	< 0.001
Histological Types			
Yolk Sac Tumor	19(51.4)	7(14)	< 0.001
Dysgerminoma	-	28(56)	-
Seminoma	3(8)	-	-
Immature Teratoma	7(18.9)	10(20)	0.898
Embryonal Carcinoma	6(16.1)	0(0)	0.003
Malignant Mixed	2(5.6)	4(8)	0.664
Germ Cell Tumor			
Teratocarcinoma	0	1(2)	0.386
Site /Location of Tumor			
Ovary	-	39(78)	-
Testis	31(83.8)	-	-
Abdomen	3(8)	4(8)	1.00
Sacrococcygeal	2(5.5)	5(10)	0.446
Mediastinal	1(2.7)	2(4)	0.742

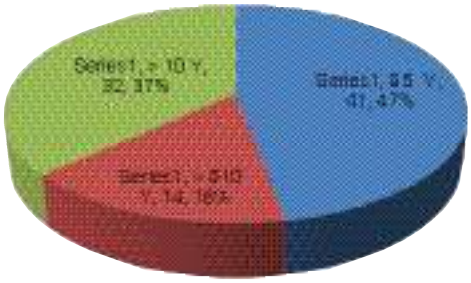

Fig 1 *Age distribution of patients*

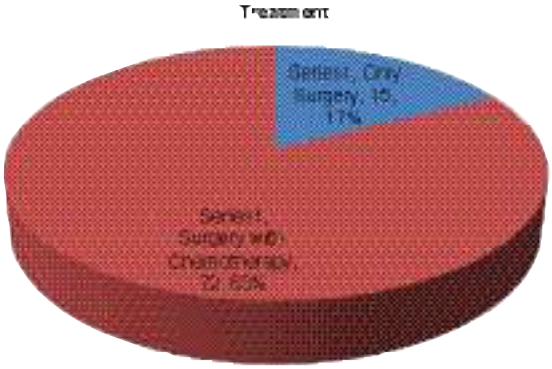

Fig 2 *Treatment modality of the patients*

Table II
Outcome of the patients (n=42)

Outcome	Number (%)	95% CI
Good	30(71.4)	65.41 - 75.54
Local Recurrence	5(12)	2.50 - 21.70
Metastasis	7(16.6)	5.31 - 27.40

Discussion

Malignant germ cell tumors are infrequent in childhood, occurring at a rate of 2.4 cases per million children and representing approximately 2% to 3% of cancers diagnosed below 15 years[6].

There are differences in distribution of tumor by location in pediatric age groups. Extragonadal tumors comprise of larger percentage in children before 4 years than in children diagnosed after the age of 10 years. It was consistent with the statement that 40% to 55% of pediatric GCTs are found in extragonadal locations[7-11].

The incidence of GCTs was similar in boys and girls in the age group of birth to 9 years, whereas the incidence was much higher in boys in the age more than 10 years reported in one study[12].

But in our study, up to 5 years of age GCTs were more common in boys and after 10 years it was found commoner in girls. Overall, female were more affected than male by GCTs, In general, the gonadal tumors occurred more than extragonadal ones regardless of the gender in this study.

The cure rate and survival are very high for pediatric GCTs, mainly due to the effectiveness of platinum based chemotherapy[13-15]. Although overall survival rate was higher, difference was observed in survival by location, histological type and staging of tumors, with gonadal tumors having more favorable prognosis than extragonadal locations. This observation is supported by numerous publications demonstrating lower survival rates in pediatric patients diagnosed in extragonadal locations.

Considering the histological types, yolk sac tumors and dysgerminoma had better prognosis than others found in this study.

The higher survival rate reported in gonadal as compared to extragonadal tumors could be explainable for having more complete tumor excision of tumors located in the gonads[14].

Conclusion

Germ cell tumors are the most varied tumors of all childhood malignancies having differences in age, sex, location and histological subtypes. Survival rate also differed depending on site and tumor types. In male prognosis was better in younger age group and that in female was better in adolescence.

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ORIGINAL ARTICLE

Predictors of Mortality in Newborn Admitted in Special Care Baby Unit (SCABU) of Dhaka Shishu Hospital

MA Kamal[1], Mahbubul Hoque[2]

Abstract

Background: *The current neonatal mortality rate of Bangladesh is very high compared to developed countries.*

Objective: *The objective of the study was to find out the predictors that are associated with mortality in newborn admitted in Special Care Baby Unit (SCABU) of Dhaka Shishu (Children) Hospital.*

Methods: *This prospective study was conducted in the SCABU of Dhaka Shishu (Children) Hospital from 1st June 2016 to 30 November 2016. A semi-structured questionnaire was prepared before the study. Data were collected from the attendents of each neonate by asking questions who died at the neonatal period after hospital admission. Detail history regarding gestational age, birth weight, place of birth, person conducting delivery, mood of delivery, problem at birth, residence, reasons of referral, vehicle during transport, condition of baby at arrival, time taken during transport and need for any resuscitation was recorded. Data were analyzed by using SPSS version 16.*

Result*: Total 970 neonates were admitted during data collection period out of them 98(10.10%) died. Majority (58.16%) of the death occurred in neonate who was admitted before 72 hours of age having gestational age <37 weeks (65.31%). Majority of the neonates were from urban area (56.12%) but from poor socioeconomic status (54.08%) and only 32.65% were on regular antenatal care. Majority were delivered by normal delivery at home and attended by TBA. Among the neonates 30.61% reached hospital only by ambulance and 64.29% were found hypothermic during admission. Majority 70(71.43%) were died within 24 hours of hospital admission. Neonatal sepsis, perinatal asphyxia and prematurity contributed majority of neonatal death.*

Conclusion: *Early (age <72 hours) and premature neonates, neonates from poor socioeconomic background, lack of antenatal care, home delivery, lack of facility in local areas, inadequate transport and unstable initial condition contributed majority of neonatal death. Neonatal sepsis, perinatal asphyxia and prematurity contributed most of neonatal death.*

Key words: *Predictors, mortality, newborn, Special Care Baby Unit.*

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Introduction

High neonatal mortality remains a challenge for many low-income countries[1,2] and a major threat to the achievement of the fourth Millennium Development Goal (MDG-4).[3-5] Worldwide neonatal mortality represents more than half of the overall infant mortality and over one third of under five deaths. Neonatal mortality rates vary from five in developed countries to 34 per 1,000 live births in the less-developed regions of the world. Although there has been a remarkable worldwide decline in child mortality in the last quarter of the 20th century, this reduction in death rate has occurred mainly among older children, mostly due to the effects of immunization and infectious disease-control programmes.[6]

Mortality of neonatal unit of Dhaka Shishu (Children) Hospital, the largest paediatric teaching hospital in Bangladesh was 237/1000 admissions in mid nineties.[7] Some improvement of mortality has been evident for the last 10 years though not satisfactory. Standard of neonatal service has improved in Bangladesh in last four decade but the mortality rate still remains unacceptably and alarmingly high.[8] The current neonatal mortality rate of Bangladesh is also very high compared to developed countries.[9] Various factors are responsible for the high mortality like socioeconomic condition, hygiene and sanitation, education especially female education, culture, local medical facilities etc. contribute to this high neonatal mortality rate. On an average 85% of our population lives in rural area with minimal educational qualification.[10] Communication system is very poor dependent mainly on primitive type of transport. Majority of the deliveries are conducted at home by traditional birth attendants. The care during pregnancy, child birth and infancy is often compromised due to a large number of traditional beliefs and cultural practices.[11]

The Millennium Development Goal for child survival cannot be met without Substantial reduction in neonatal mortality.[12] Neonatal mortality rate is a reliable yardstick for evaluating the overall progress of potential care in a community. Knowledge of local or regional health problems is a prerequisite for establishing an effective health care delivery system.[13] Although 40% reduction of neonatal mortality was achieved over the past two decades, it still remains high compared to the developed countries.[3]

Bangladesh is one of the most populous countries in this world. Too many mothers and children are suffering and dying each year in this country.[14] Neonatal mortality is unacceptably high in Bangladesh. About 30-50% of newborn are of LBW, which causes mortality and morbidity to a large number of subjects. Perinatal and neonatal mortality and morbidity rate are the reflection of a country's obstetric and neonatal services, which again is determined by various complex interrelated medical, socio-economic, cultural and infrastructural factors.[15] Neonatal mortality contributes a great deal to infant mortality rate.[16,17]

Causes of neonatal deaths in immediate postpartum period is different in developing countries from developed countries. Thus causes of neonatal mortality vary across the nations and from rural to urban set up.[18] The major direct cause of neonatal deaths were prematurity, infections and birth asphyxia. In a report which was published in the Lancet, the major direct causes of the deaths were preterm birth, infections, asphyxia, congenital anomalies, tetanus, and diarrhea.[19] Non institutional birth constitutes a significant proportion of total births with a high incidence of low birth weights, hypothermia and perinatal and neonatal mortality. Though institutional delivery and in utero transport of newborn is safest but unfortunately pre term delivery and perinatal illness cannot always anticipated resulting in continued need of transfer of these babies after delivery.[20] These babies are often critically ill and outcome also dependent on effectiveness of transport system.[21] Most of the neonatal transports are self transport without any pretreatment stabilization or care during transport. Many of these newborns thus transported are cold, blue and hypoglycemic.[22]

In high-income countries when deaths occur they are usually reported and investigated but in low-income countries most neonates are born and die without any record.[23] Peer reviewed literature has drawn attention to the absence of reliable data for births, deaths, and causes of death, and the need to count and account for these deaths to set priorities for action and strengthen health systems.[24] While neonatal deaths due to infection and preterm complications have solutions that can potentially be taken to scale,[25]

even in weak health systems,[26] solutions for intrapartum related outcomes are more challenging and require strengthening the quality and responsiveness of the health system at all levels.[27]

Bangladesh has made considerable progress in child survival rate as the mortality has declined rapidly over the last 10-12 years. Despite this progress, there still remain challenges. While the mortality rates have declined substantially, inequalities in terms of access and utilization of health services among the populations still need to be addressed.[28] In a developing country like Bangladesh, where neonatal support systems are mainly concentrated in metropolitan cities, it is important to understand the predictors that are contributory to neonatal mortality amongst newborns referred to tertiary centers. The present study was done to assess the associations between mortality and condition of newborns delivered outside (home, government health centers and private hospitals at arrival to a tertiary care center) and assessment of predictors which contribute to mortality.

Materials and Methods

This study was conducted in the SCABU of Dhaka Shishu (Children) Hospital for a period of six months from 1st June 2016 to 30 November 2016. This center is a tertiary care center, where most of babies referred are high- risk babies. A semi-structured questionnaire was prepared and before enrollment, parent/ attendants of the neonate was given a detail explanation of the study. Data were collected from the attendents of each neonate by asking questions who died at the neonatal period after hospital admission. Detail history regarding gestational age, birth weight, place of birth, person conducting delivery, mood of delivery, problem at birth, residence, reasons of referral, vehicle during transport, condition of baby at arrival, time taken during transport and need for any resucitation was recorded. Weight of neonates are measured using electronic weighting machines having gram as smallest division. Gestrational age was calculated from last menstrual period (LMP). Time taken to receive the neonate after admission, time of death after admission and diagnosis was recorded from hospital record. The purpose and procedure of the study was explained to the parents/attendants and their consents were taken. Data were analyzed by using SPSS version 16.

Results

During the 6 months period there were 970 neonatal admissions and out of them 98 died (10.10%). Among them 10.2% were admitted before 12 hours of age, 27.55% were between 12-24 hours, 20.41% between 24-72 hours and 41.84% were >72 hours of age. Majority (58.16%) of the death occurred in neonate who was admitted before 72 hours of age (Fig.-1).

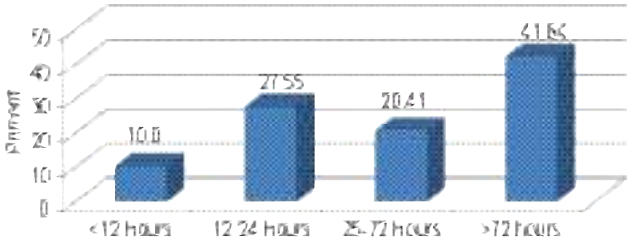

Fig 1 *Age distribution of the study neonates*

Among the neonates 57.14% were male and 42.86% were female with a male female ratio 1.33:1 (Fig 2).

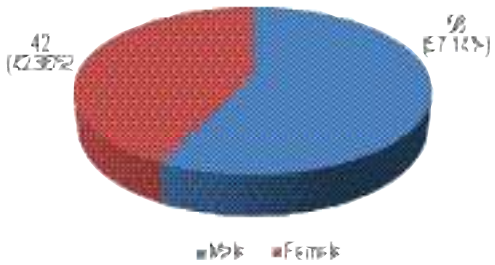

Fig 2 *Sex distribution of the study neonates (n=98)*

Mortality was high among preterm neonate (65.31%). Mortality was 34.69% among term neonate. Mortality decreases along with advencement of gestational age (Fig.-3).

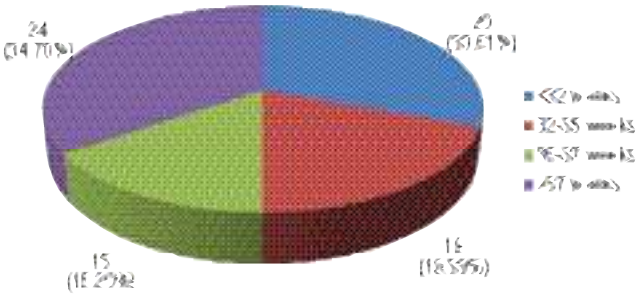

Fig 3 *Distribution of gestational age of the study neonates (n=98)*

Majority of the neonates were from urban area but from low socioeconomic status. Only 32.65% were on regular antenatal care. Majority were delivered by normal delivery at home and attended by TBA (Table-I).

Table I
Sociodemography, antepartum and intra-partum history (N= 98)

Variable		Number	%
Residence	Rural	43	43.88
	Urban	55	56.12
Socioeconomic status	Poor	53	54.08
	Middle class	35	35.72
	Higher class	10	10.20
Antenatal Care	Yes	32	32.65
	No	66	67.35
Maternal Illness During Pregnancy	Yes	25	25.51
	No	73	74.49
Place of delivery	Hospital/Clinic	28	28.57
	Home	70	71.43
Delivery conducted by	Doctor	30	30.61
	Nurse	22	22.45
	TBA	46	46.94
Type of Delivery	Normal	64	65.31
	Caesarean	34	34.69
Pre-lacteal Feed	Yes	30	30.61
	No	68	69.39

Majority of the neonates (51.02) were referred due to lack of facility in local areas, 20.41% were referred from local hospital as the condition was not improved and 28.57% came with their own interest (Table-II).

Table II
Causes of referral of neonates (n=98)

Causes of referral	Number	%
Lack of facility	50	51.02
Condition not improved in local hospital	20	20.41
Own interest	28	28.57

Among the neonates 17.34% reached hospital within 2 hours, 41.84% within 2-5 hours, 24.49% within 6-10 hours and 16.33% needed >10 hours (Fig.-4).

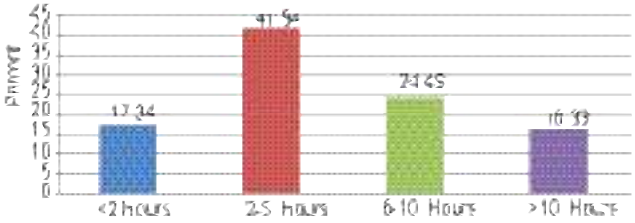

Fig 4 *Time taken to reached hospital from referral hospital (n=98)*

Among the neonates 9.19% reached hospital by

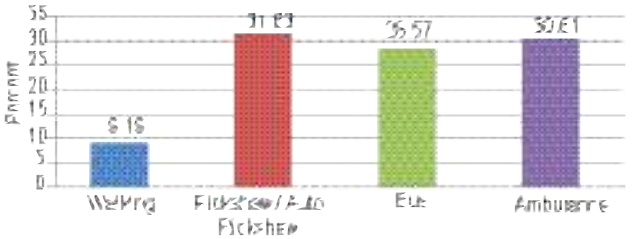

Fig 5 *Mode of transport of neonates from referral hospital (n=98)*

walking, 31.63% by rickshaw or auto rickshaw, 28.57% by bus and only 30.61% by ambulance (Fig.-5).

Among the neonates 64.29% were hypothermic, 40.82% had respiratory distress, 10.2% had gasping respiration, 62.25% had arrhythmias and 34.69% had prolong capillary refill time (Table-III).

Table III
Clinical conditions of neonates on arrival of hospital

Clinical conditions	Number	%
Hypothermia	63	64.29
Respiratory distress	40	40.82
Gasping respiration	10	10.20
Tachycardia	23	23.47
Bradycardia	38	38.78
Prolong capillary refill time	34	34.69

After admission treatment were given within 30 minutes in 40.82% neonates, 32.65% after 30 minutes and time was not recorded in 26.53% cases (Fig-6).

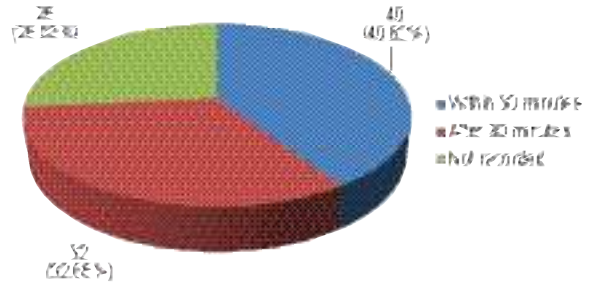

Fig 6 *Time taken to start treatment after hospital admission (n=98)*

Only 10(10.2%) neonate died within 6 hours of hospitl admission, 40(40.82%) during 6-12 hours, 20(20.41%) during 12-24 hour and 28 (28.57%) more than 24 hours. Majority 70 (71.43%) were died within 24 hours of hospital admission (Fig.-7).

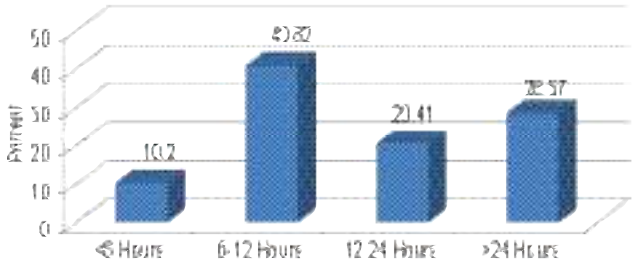

Fig 7 *Time of death after admission (n=98)*

Mortality was high (30.61%) among the neonates admitted with perinatal asphyxia. Second most common cause was (23.47%) PTLBW with sepsis and neonatal sepsis (23.47%). Sepsis contributed 46.94% of neonatal death. So neonatal sepsis, perinatal asphyxia and prematurity contributed majority of neonatal death (Fig.-8).

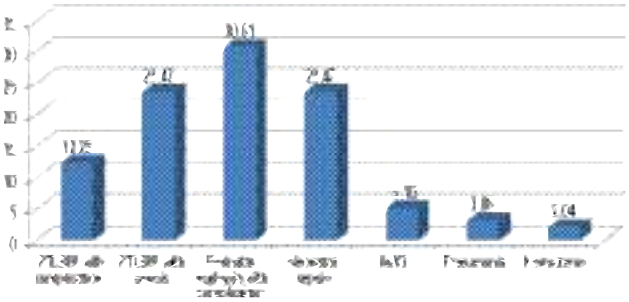

Fig 8 *Diagnosis of the death cases (n=98)*

Discussion

Neonatal death is a serious concern both in developing and developed countries. While infant mortality rates have been decreasing steadily worldwide, changes in neonatal mortality rate have been much slower.[29] The present study showed mortality was 10.10%. Khan et al[30] in Bangladesh found neonatal mortality 10.9% which is similar to present study. Hossain et al[8] found 15.7% mortality among the neonates admitted in SCABU of Dhaka Shishu (Children) Hospital. A high mortality rate was found in India (37%) by Basu et al[29] and 44.2% was reported by Jumah et al[31].

The present study showed majority (71.43%) of the neonates were died within 24 hours of hospital admission. Hoque et al[32] found most of the neonate death occurred within 24 hours of hospital admission. In this study mortality was high (30.61%) among the neonates admitted with perinatal Asphysia. Second most common cause was PTLB with sepsis (23.47%) and neonatal sepsis (23.47%). Sepsis contributes 46.94% of neonatal death. In Bangladesh the leading cause of neonatal death are perinatal Asphysia, neonatal infection & prematurity.[9] Nahar et al[12] found similar report in their study. Advances in perinatal and neonatal care have significantly reduced neonatal mortality rates. Variations in mortality rates are important because they permit inferences about quality of care. Examination of care practices associated with

variations in mortality rates can provide insights into how care practices might be changed to improve outcomes.[33] Present study showed majority (58.16%) of the death occurred in neonate who was admitted before 72 hours of age. Hossain et al[8] showed that 65% of the neonatal admission occurred within 3 days of age. Male accounted for more of the death in present study. Hoque et al[32] found higher mortality in male neonates. Mortality was high among preterm neonate (65.31%) and mortality decrease along with advancement of gestational age. Basu et al[29] and Khan et al[30] also found higher mortality in preterm neonates.

Majority of the neonates died in their early neonatal period. This period is a highly vulnerable time for the neonate who is completing many of the physiological adjustments required for extra uterine existence. Almost two-third of infant deaths occur in the first month of life, among these, more than two-thirds die in their first week and among those also, two-thirds die in their first 24 hours.[3] The World Health Organization reported that most deaths in the neonatal period occur in the first few days after birth and this constitutes approximately 75% of neonatal mortality in all regions of the world.[34]

The present study showed majority of the neonate with low socioeconomic status, came from urban area and reached hospital within 2-5 hours and only 30.61% by ambulance with minimum (32.65%) regular antenatal care and most of neonates delivered by normal vaginal delivery at home and attended by trained birth attendant. Various factors are responsible for the high mortality like socioeconomic condition, hygiene and sanitation, education especially female education, culture, local medical facilities etc. contribute to this high neonatal mortality rate. Communication system is very poor dependent mainly on primitive type of transport. Majority of the deliveries are conducted at home by traditional birth attendants. The care during pregnancy, child birth and infancy is often compromised due to a large number of traditional beliefs and cultural practices.[11]

Conclusion

Early (age <72 hours) and premature neonates, neonates from poor socioeconomic background, lack of antenatal care, home delivery, lack of facility in local areas, inadequate transport and unstable initial condition contributed majority of neonatal death. Neonatal sepsis, perinatal asphyxia and prematurity contributed most of neonatal death.

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ORIGINAL ARTICLE

Bacteriological Profile and Antibiotic Sensitivity of Neonatal Septicemia Admitted in Neonatal Intensive Care Unit (NICU) of Dhaka Shishu Hospital

Md. Mosharaf Hossain[1], Mir Mohammad Yusuf[2], Md. Kamrunzzaman[3], Maksudur Rahman[4] , Md. Jahangir Alam[5]

Abstract

Background: *Septicemia in neonates refers to bacterial infection documented by positive blood culture in the first four weeks of life and is one of the leading causes of neonatal mortality and morbidity.*

Objective: *To isolate and identify the bacterial etiologic agents responsible for neonatal sepsis and to determine the susceptibility pattern of isolates in A NICU of Dhaka Shishu (Children) Hospital.*

Methods: *This is a prospective observational study conducted in the NICU from July 2018 to December 2018. Two hundred ninty blood samples were collected and processed from patients in accordance with standard protocols. Antibiotic susceptibility of the isolates was done.*

Results: *Blood culture reports were positive in 9.31% cases. Among the culture positive cases, there were 65.5% males and 34.5% females. Early onset sepsis was present in 74.8% and late onset sepsis was observed in 25.2% of the cases. Best overall sensitivity among Gram negative (*Acinetobacter, Klebsiella, Pseudomonas*) isolates was to netilmycin (61%), followed by ceftazidim (57%) and amikacin (56%).Gram positive (*Staphylococci, streptococci*) isolates had sensitivity of 50% to levofloxacin, 50% to ceftriaxon.*

Conclusion: *Gram negative organisms are the leading cause of neonatal sepsis in this study and most of them are resistant to multiple antibiotics. Therefore the results of this study suggest that, surveillance of antimicrobial resistance in our hospital is necessary.*

Key words: *Antimicrobial resistance, antibiotics, neonatal septicemia.*

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Introduction

Septicemia in neonates refers to generalized bacterial infection documented by positive blood culture in the first four weeks of life[1] and is one of the leading causes of neonatal mortality and morbidity in Bangladesh.[2-4] Neonatal septicemia continues to be a major problem for neonates in neonatal intensive care units around the world.[5] There could be various reasons for neonatal mortality but septicemia continues to be a major cause of neonatal mortality and morbidity worldwide. Incidence varies from country to country, but it is much higher in developing countries than in developed nations.[6] According to World Health Organization (WHO) estimates, there are about 5 million neonatal deaths a year, with 98% occurring in developing countries.[7] Neonatal sepsis is broadly divided into two types according to age of onset: Early onset sepsis (<72 hrs) and late onset sepsis (≥72 hrs-28 days). Early onset sepsis is acquired during fetal life, delivery, or at the nursery.[8] Neonatal sepsis is caused by a variety of Gram positive as well as Gram negative bacteria, and sometimes yeasts.[5] The spectrum of organisms that causes neonatal sepsis changes over times and varies from region to region. This is due to the changing pattern of antibiotic use and changes in lifestyle.[9] Periodic evaluation of organisms responsible for neonatal sepsis is essential for the appropriate management of neonates. Therefore, this study was undertaken to determine the profile and antibiotic sensitivity patterns of aerobic isolates from blood cultures of neonates in a tertiary care hospital in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh.

Materials and Methods

An analysis was conducted on all blood culture reports obtained between July 2018 and December 2018 from newborns admitted to the Department of Neonatal Intensive Care Unit (NICU) of Dhaka Shishu (Children) Hospital, Dhaka. Blood culture was done for all neonates suspected to have septicemia. Blood culture sample included a single sample collected from a peripheral vein or artery under aseptic conditions. The local site was cleansed with 70% alcohol and povidone iodine (1%), followed by 70% alcohol again. Blood cultures were done. Approximately, 3 ml of blood was inoculated into the broth and incubated at 37°C. Subcultures were done on sheep blood agar and MacConkey agar at the earliest visual detection of turbidity. Isolate was identified by their characteristic appearance on their respective media, Gram staining and confirmed by the pattern of biochemical reactions using the standard method.[10] Members of the family enterobacteriaceae were identified by indole production, H_2S production, motility test, urease test, oxidase, carbohydrate utilization tests, and other tests. For Gram-positive bacteria, coagulase, catalase, bacitracin and optochin susceptibility tests and other tests were used. Blood culture broth that showed no microbial growth within seven days was reported as culture negative, only after result of routine subculture on blood, MacConkey, and chocolate agar.[10]

Antimicrobial susceptibility testing was performed for all blood culture isolates as recommended.[11] The drugs were in the following: levofloxacin, chloramphenicol, ceftriaxon, ceftazidime, ciprofloxacin, erythromycin, co-trimoxazole, amikacin, netilmicin, imipenem, piperacillin/tazobactam, azithromycin and meropenam. The discs were obtained from Department of Microbiology, Dhaka Shishu (Children) Hospital.

Results

During the study period, a total of 290 newborns with clinical sepsis were admitted. Blood culture reports were positive in 27cases (9.31%). Among the culture positive cases, there were 65% male and 35% female neonates with the male to female ratio of 1.9:1. Early onset sepsis cases were found to be three times higher than late onset sepsis.

Out of 27 cases, 74.8% had early onset sepsis and 25.2% had late onset sepsis. Detailed aetiology of the 27 isolates is provided in Table I. These included Gram-negative bacilli (25/27, 92.59%) and Gram-positive cocci (2/27, 7.40%). *Acinetobacter, Klebsiella, Pseudomonas* were the most common Gram-negative and *Staphylococci, streptococci* were Gram-positive organisms.

Table I
Microbiological profile of pathogens in the NICU (N-27)

Gram negative	Number	%
Acinetobacter	7	25.93
Klebsiella	7	25.93
Pseudomonas	4	14.81
E-coli	2	7.41
Citrobacter	2	7.41
Salmonella	2	7.41
Serratia	1	3.70
Gram Positive	1	3.70
Staphylococci Streptococci	1	3.70
Total	27	100

Table II
Sensitivity profile of Microorganisms in the NICU

Organisms	Meropenem %	Amikacin %	Netilmycin %	Ceftazidim %	Chloramphenicol %	Ciprofloxacin %	Cotrimoxazol %	Piperacilin %	Ceftrixon %	Imipenem %	Levofloxacin %
Acinetobacter*	5	11	42	21	5	21	32	16	11	0	21
Klebsiella	38	50	50	0	38	25	50	13	13	38	50
Pseudomonus	13	25	25	25	0	50	0	25	13	25	25
E-coli	50	50	50	50	25	25	25	0	0	25	25
Serratia	100	100	100	100	0	100	100	0	100	100	0
Salmonella	0	0	0	50	50	100	50	0	100	0	50
Citrobacter	100	100	100	100	100	100	100	50	100	0	50
Streptococci	0	0	0	0	0	0	100	50	100	0	100
Staphylococci	50	0	0	0	50	0	0	0	0	50	0

* Acinetobacter resistant to all in 25% cases

(Table I) show the antibiotic susceptibility pattern in Gram-negative and Gram-positive isolates. Best overall sensitivity among Gram-negative isolates was to netilmycin (61%), followed by ceftazidime (57%) and amikacin (56%). Gram-positive isolates had sensitivity of 50% to levofloxacin and 50% to ceftriaxon (Table II).

Discussion

The uncertainty surrounding the clinical approach to treatment of neonatal septicemia can be minimized by periodic epidemiological surveys of aetiological agents and their antibiotic sensitivity patterns leading to recognition of the most frequently encountered pathogens in a particular geographical area. For effectual management of septicemia cases, study of bacteriological profile along with the antimicrobial sensitivity pattern plays valuable role.[12,13] Out of the 290 clinically suspected cases of sepsis in our study, 27 were culture positive with a blood culture positivity rate of 9.31%. The incidence of Gram-negative and Gram-positive organisms was 92.59% and 7.40%, respectively. There were 74.8% isolates from early onset septicemia cases, while 25.2% were from late-onset illness. In this study, a male predominance with male to female ratio of 1.9:1 was found in our study, which agrees with previous report.[14] This might be because of the importance given to the male infants and also because of more number of male infants born compared to female infants born. Culture positivity for aerobic organisms in neonates vary from 25% to 60%.[15-17] In this study, blood culture-positivity rate is 9.31%. This finding is comparable with other reports.[9] However, a high blood culture-positivity rate in septicemia children (56%) had been reported by Sharma et al[18] and Jain et al[19]. A low blood culture isolation rate could be due to administration of antibiotic before blood collection from the primary centers or the possibility of infection with anaerobes. A negative blood culture does not exclude sepsis and about 26% of all neonatal sepsis could be due to anaerobes.[9] The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall, Gram-negative organisms are more common and mainly represented by Acinobacter, *Klebsiella*, *Pseudomonas*, *Escherichia coli*, Citrobacter, *Salmonella and serratia*. Of the Gram-positive organisms, *Staphylococcus and Streptococcus* are most commonly isolated. Gram-negative and Gram-positive septicemia was encountered in 93% and 7% of the culture-positive cases in this study, which is comparable to a study conducted by Agnihotri *et al.*,[1] which reported that Gram-negative and Gram-positive organisms were responsible for 59%and 41% of the septicemia cases, respectively. Similar observations were made by other workers.[4,6] The report of the National Neonatal Perinatal database showed *Klebsiella* as the predominant (29%) pathogen.[15] Both *Klebsiella* spp.(31%) and

Acinobacter spp. were the predominant Gram-negative species isolated in this study, which agrees with previous reports.[2,9]

Antibiotic resistance is today a global problem. Reports of multi-resistant bacteria causing neonatal sepsis in developing countries are increasing. The wide availability of over the counter antibiotics and the inappropriate use of broad-spectrum antibiotics in the community may explain this situation. It is difficult to compare antibiotic resistance between countries because the epidemiology of neonatal sepsis is extremely variable.[7] Antibiotic susceptibility pattern was studied for all isolates causing neonatal sepsis. The analysis of drug resistance pattern showed that, among Gram negative isolates, maximum numbers were resistant to ampicillin and lowest to ceftriaxon. Resistance was observed to be against commonly used antibiotics such as ampicillin, amoxiclav and cephalexin. Among Gram positive isolates, high resistance was seen to penicillin, cloxacillin, and amoxiclav. Resistance to Acinobacter was seen 21% to all in our study. The greater prevalence resistance to commonly used antibiotics has also been reported by other studies.[2,4]

Among aminoglycosides, netilmycin was found to have an edge over amikacin in Gram-negative septicemia, with sensitivity of 61% and 56% respectively. Similar observations have been made by previous group of workers.[20] In this study, maximum sensitivity was observed in ceftriaxon, levofloxacin and netilmicin. Sensitivity to netilmycin and levefloxacin was much higher than that to other antibiotics, but these two drugs should not be used indiscriminately and be kept as a reserve drugs, otherwise resistance to these drugs may develop, thereby threatening the treatment.

Conclusion

It is evident from this study that Gram-negative organisms are the leading cause of neonatal sepsis in this study, and most of them are resistant to multiple antibiotics. Therefore, suggest that surveillance of antimicrobial resistance is necessary. Also, an antibiotic policy should be formulated in the hospital. Depending on the antibiotic sensitivity pattern of the isolates, antibiotics should be used to avoid dangers of indiscriminate use of antibiotics.

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ORIGINAL ARTICLE

Role of Topiramete in Moderate to Severe Perinatal Asphyxia - A Randomized Controlled Clinical Trial

Naznin Akther[1], M Monir Hossain[2], Ahmed Ferdous Jahangir[3], Shayla Imam Kanta[4], Sayeeda Mehnaz Masud[5]

Abstract

Background: *Topiramate is an anticonvulsant drugs that has multiple mode of mechanism of action. Topiramate appears to be effective as both an anti-seizure and neuroprotective agent in animal models of newborn brain injury.*

Objectives: *To determine the neurological outcome of oral topiramate with moderate to severe hypoxic ischemic encephalopathy.*

Methods: *This one year randomized controlled trial was carried out in the Neonatal ward and ICU of a tertiary care specialized hospital. A total of 64 neonate were enrolled in this study and were randomly assigned intervention group (Group-A, n=32) and control group (Group B=32). In case group oral topiramate 10mg/kg was given for 3 consecutive days along with standard treatment protocol. And control was given only standard protocol. Finally outcomes are compared.*

Results: *Baseline clinical characteristics, age, sex, mode of delivery, arterial pH, residence, basic status of HIE cases were matched in both groups. This study has shown significant reduction of neurological impairment in all domain (gross motor, fine motor, vision hearing, speech) at 1 and 3 months in case than control. There is also early seizure control, early initiation of feeding, short duration of hospital stay in case (treatment) than control without any side effects.*

Conclusion: *Early administration of topiramate to infants with moderate and severe HIE in perinatal asphyxia was very effective in controlling seizures, improving USG findings, and producing favorable neurodevelopmental outcomes at1 and 3 months of age.*

Key words*: Topiramete, moderate to severe perinatal asphyxia, early seizure control.*

Introduction

Perinatal asphyxia is the most important cause of preventable cerebral injury occurring in the neonatal period.[1] It is a major preventable causes of mortality among newborn in the developing countries like Bangladesh. It is estimated that about 6.6 million perinatal death occur each year globally, mostly developing countries.[2] In Bangladesh 39% of neonatal death caused by perinatal asphyxia.[3] An epidemiological survey in childhood impairments disabilities around 5 medical colleges in Bangladesh" done by Sishu Bikas Kendro found that mean prevalence of cerebral palsy is 63 per thousands.[4]

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Prenatal asphyxia is an insult to the fetus or newborn due to lack of oxygen (hypoxia) and or lack of perfusion to various organ which will manifest as difficulty in establishing spontaneous respiration evident by delayed cry after birth at least after 1 minute. Hypoxic-ischemic injuries develop in two phases. Neuroprotective treatment targeting the latent phase may limit the secondary neuronal damage due to perinatal asphyxia. The new knowledge about cellular repair mechanism can also pave the way for types of treatment that not merely limit damage, but can also repair the defects of immature nervous system.[5]

Topiramate is an anticonvulsant drugs that has multiple mode of mechanism of action. Topiramate appears to be effective as both an anti-seizure and neuroprotective agent in animal models of newborn brain injury. Neuronal anti apoptotic mechanisms, angiogenesis and neurogenesis are stimulated andmodulated by the topiramate.[6] Topiramate is safe, easily available, andcan administered orally.

Therefore with this idea study was conducted to determine the neurological outcome of oral topiramate with moderate to severe hypoxic ischemic encephalopathy.

Materials and Methods

This one year randomized control clinical trial was conducted in SCABU and other ward at Dhaka Shishu Hospital from 2015 to 2016. Total 64 babies were selected as sample. 32were in case group and 32 in control group. Outcome of oral topiramate with moderate to severe hypoxic ischemic encephalopathy were studied.

Comparison was done by time taken to control seizure,time of the initiation oral feeding,duration of hospital stay,neurological outcome at 1 month and 3 month of age.

Among the admitted neonates, gestational age ≥37 weeks, age less than 24 hours and by sarnat and sarnat staging diagnosed as moderate to severe asphyxia were selected and obtaining an informed written consent from the parents or guardian for enrolment in the study. Sample subjects were assigned into two groups, Group A - interventional group (n=32) received topiramate and standard treatment protocol, and Group B or Control group (n=32) received only standard treatment protocol. This division was done by simple randomization (lottery method). In which a numbered card was picked by the attending nurse from a box for each of the neonates. If the card had an odd number then the neonate was assigned to control group and if the card had an even number then the neonate was assigned to case group. The picked cards were not put back into the box so the sampling was without replacement. Baby who had selection criteria but born with congenital anomalies, hemodynamically unstable, neonatal sepsis were excluded from the study. The treatment group were given topiramate 10 mg/kg orally daily for 3 days with supportive treatment e.g. oxygen, volume expanders, inotropes, diuretics, anticonvulsants, antibioticswithin 24 hours of birth.

The control group were given supportive treatment only. During therapy Serum electrolytes, RBS, ABG, Serum calcium, Blood grouping and USG of brain were done before and after intervention. Complete physical and neurological examination was done at 1 month and 3 months. Neurological assessment was done by RNDA method. Gross motor, fine motor, vision hearing, speech were assessed at one and three months by RNDA method. Renal function test, Liver function test were done if required.

The data were analyzed according to standard procedure. SPSS Win version 20 and Epi Info. (Version 6) has been used for data analysis: Results of the findings was verified by doing standard test for significance like Unpaired student "t" test, Man-whitny test, Chi-Square (χ^2) tests, and finding out the p value.

Results

During the study period total 110 neonates were assessed for eligibility. Out of them 35 were excluded according to exclusion criteria and 75 eligible neonates were assessed and randomized in two groups, 37 in case and 38 in control Group. After enrolment, 5 patients in case and 6 in control group had lost. Finally, 64 neonates completed the study 32 neonates in control group and 32 in intervention group. Baseline characteristics of case and control groups are described in Table I & II, it is noted that except topiramete use, all other characteristics were symmetrically distributed between both groups.

We matched with hospital stay of both case and control groups also, details in Table III. It was also statistically similar.

It was argued that there were significant difference in case and control considering immediate outcome like duration of seizure control, initiation of feeding etc (Table IV).

After 1 month and 3 month follow up there was significant difference in both neurological and brain USG findings (Table V, VI, VII).

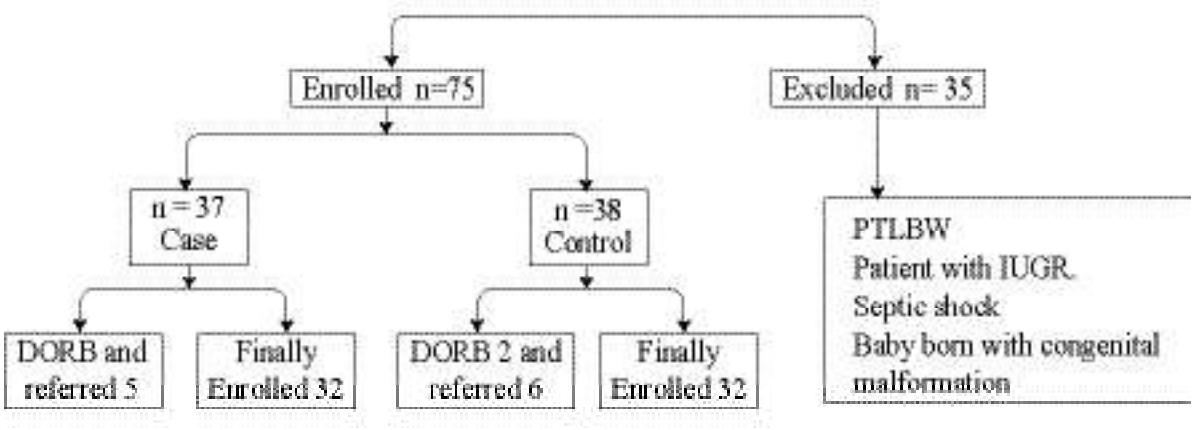

Fig 1 *Flow chart of patients enrollment*

Tabl I
Base line characteristic of study neonate

Parameters		Case(32) n (%)	Control (32) n (%)	p value
Gender	Male	17(53)	21(66)	0.44
	Female	15(47)	11(44)	
Perinatal asphyxia with HIE	Stage II	18(56)	20(62)	0.79
	Stage III	14(44)	12(38)	
Age (hour), Median, IQR	5(3,7.75)	5.5(4,7.75)	0.421	
Birth weight (gm), mean±SD	2890±223	2912.5±196	0.68	
Arterial pH	7.2±0.08	7.2±0.07	0.55	

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test, Man-whitney test, t test considering significant level p<0.05 at 95% CI.

Table II
Base line characteristic mothers of study neonate

Parameters		Case(32) n (%)	Control (32) n (%)	OR,95% CI	p value
Gestation (weeks)		38.97±0.86	39±1.02	1.5(0.52-4.2)	0.89
Mode of delivery	Vaginal	22(69)	19(59)	0.6	
	CS	10(31)	13(41)		
Residence	Urban	18(56)	15(47)	1.46(0.54-3.90)	0.62
	Rural	14(44)	17(53)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test, t test considering significant level p<0.05 at 95% CI.

Table III
USG findings of brain during hospital stay

USG findings	Case (n=32) n(%)	Control (n=32) n(%)	OR, 95% CI	p value
Normal	12(38)	13(41)	0.88(0.32-2.39)	1.00
Abnormal	20(62)	19(59)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test considering significant level p<0.05 at 95% CI.

Table IV
Immediate outcome

Duration of seizure control	Case (n=32) n(%)	Control (n=32) n(%)	p value
Median, IQR	24(19.536)	72(48,72)	0.00
Initiation of oral feeding (Mean ± SD days)	2.63±1.1	4.5±1.3	0.00
Duration of hospital stay (Mean ± SD, days)	6.3±1.7	10.3±2.7	0.00

Table V
USG findings at 1 month of age

USG findings	Case (n=30) n (%)	Control (n=27) n (%)	OR, 95% CI	p value
Normal	28(93)	14(52%)	0.08(0.02-0.39)	0.00
Abnormal	2(7)	13(48)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by Fisher exact test considering significant level p<0.05 at 95% CI.

Table VI
Neurological outcome at 1 month

Outcome	Case (n=29) n(%)	Control (n=27) n(%)	OR, 95% CI	p value
Normal	24(73)	11(41)	0.14(0.04-0.49)	0.002
Abnormal	5(17)	16(59)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test considering significant level p<0.05 at 95% CI.

Table VII
Neurological outcome at 3 month

Outcome	Case (n=28) n(%)	Control (n=26) n (%)	OR,95% CI	p value
Normal	24(85.7)	10(38)	0.19(0.59-0.60)	0.008
Abnormal	4(14.3)	16(62)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by Fisher exact test considering significant level p<0.05 at 95% CI.

Discussion

The current treatment for hypoxic-ischemic encephalopathy (HIE) is predominantly supportive, to maintain physiologic parameters. This study showed significant improvement in control of seizure, early initiation of feeding and hospital stay in intervention group with to piramate. Zhu et al[7] found similar result in asphyxiated neonates. This study showed there was significant difference in hospital stay between two groups. In intervention group range of hospital stay was 5-10 days Mean ± SD 6.93±1.91 and in control group range of hospital stay was 3-14 days Mean ± SD 9.13±2.87. That is there was significant reduction of hospital stay in intervention group then control group (p=0.001.

The study shows that topiramate treatment improves outcome at discharge for neonates with HIE. The neuroprotective mechanisms of TPM appear to be related not only to AMPA and kainate receptors inhibition, but also to blockade of Na+ channels, high voltage-activated calcium currents, carbonic anhydrase isoenzymes, and mitochondrial permeability transition pore (MPTP). This causes reduction of neuronal swelling, maintain neuronal cell interigty as result prevent cerebral odema.

This study also showed that topiramate is neuroprotective that was reflected by fewer neonates with neurologic abnormalities in intervention group. The outcome of study population in intervention and control group showed 24(73%) normal at one month in treatment group and 11(41%) in control group, abnormal neurological outcome occurred 5(17%) in treatment group and 16(59%) in control group, the findings are statistically significant (P<0.05).

At 3 months the neurological outcome were normal 24(85.7%) in treatment group and 10(38%) in control group, abnormal neurological outcome occurred 4(14.3%) in treatment group and 16(62%) in control group, the findings are statistically significant (P<0.01). Improvements were assessed clinically by developmental assessment by RNDA method at 3 months. These results consistent with previous findings.

At 1 and 3 month neurological assessment was done by RNDA. For newborns and very young infants, interrate reliability was high and concurrent validity was good between the RNDA and standard psychometric testing for the entire range of functions.[8]

In this study topiramate had no effect in reducing the mortality rate, but the rate of disability was reduced from 62% to 14 % (P=.008) at 3 months. This is analogous to the results noted after head cooling, which reduced significantly the rate of disability.[7]

Clinical seizures also significantly decreased in the topiramate group. These results were consistent with the results of previous studies in which topiramate is used as seizurecontrol in neonate refractory to other anti-epileptic drugs.[9]

Previous studies have shown increased cerebral echogenicity due to cerebral oedema on USG of brain. There is no significant difference in USG of brain findings in treatment and control group during hospital stay. At 1 month 2(7%) in cases are abnormal in case, 13(48%) in control group and normal USG findings at 1 month 28(73%) in case and 14(52%) in control group. The difference is statistically significant (p value =00). And this result is correlates with previous study done by Bhat et al.[10] USG was not done at 3 month follow up in this study due to financial constrain.

Conclusion

Early administration of topiramate to neonates with moderate to severe HIE in perinatal asphyxia wasvery effective in controlling seizures, improving USG findings, and producing favorable neurodevelopmental outcomes at1 and 3 months of age.

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ORIGINAL ARTICLE

Detorsion Plus Tunica Vaginalis Flap Coverage in the Management of Ischemic Testis Following Torsion: Experience in Dhaka Shishu (Children) Hospital

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Abstract

Background: *Testicular torsion leads to devastating consequences in young boys, about 42% undergo an Orchiectomy resulting in reduced fertility, testicular hormonal dysfunction and psychological trauma.*

Objective: *The aim was to evaluate the testicular salvage rate after detorsion plus tunica albuginea incision with tunica vaginalis flap coverage with orchiopexy.*

Methods: *This was an observational study conducted from January 2016 to December 2017. Data were collected from operation theater and surgery ward register. Data were analyzed using SPSS version 20 statistical software. Continuous data were presented as mean ± SD and categorical data were presented as percentage.*

Results: *Total numbers of patients were 15. Most of the patients presented after 24 hours. Rate of atrophy of testis after orchiopexy was higher in patients presented after 24 hours. Only 4 patients had recognizable testicular atrophy. Surgical site infection was not present in this study.*

Conclusion: *Tunica albuginea incision with tunica vaginalis flap coverage after detorsion with orchiopexy provides more salvage rate in the management of ischemic testis following torsion.*

Key words*: Torsion testis, compartment syndrome, fasciotomy, testicular atrophy.*

Introduction

Testicular torsion is the twisting of spermatic cord and its contents. This surgical emergency affects 3.8 per 100,000 males younger than 18 years every year.[1] It constitutes 10% to 15% of acute scrotal disease in children and around 42% of these boys need orchiectomy.[2] Prompt recognition and treatment are most crucial for testicular salvage and torsion must be excluded in all patients who present with acute scrotum. Delay in the treatment of torsion results in substantial tissue damage or even complete necrosis of the testicle. In unilateral torsion also the contralateral testicle may be damaged, most probably by ischemic reperfusion injury.[3]

The standard operative management of testicular torsion includes detorsion followed by orchiopexy or orchiectomy depending on the subjective gross viability of the testicular parenchyma.[4] Orchiectomy can result in reduced fertility, testicular hormonal dysfunction and psychological trauma.[1,5]

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Kolbe et al[6] introduced the idea of a compartment-like syndrome in an animal study. Conceptually the testicle is an organ at risk because of the characteristics of the tunica albuginea, a fairly strong and inelastic layer. A limited case series suggested that decompression of the tunica albuginea in humans may be beneficial in the reperfusion of the testicular parenchyma after detorsion, despite the lack of similar evidence in animal studies.[6,7] Kutikov et al[8] suggested that post-detorsion compartment syndrome (i.e., testicular compartment syndrome) may be amenable to decompression by generous incision of the tunica albuginea or fasciotomy. Based on those results Figueroa et al[4] introduced the tunica albuginea incision followed by tunica vaginalis flap coverage as a therapeutic alternative for testes that remain grossly ischemic after detorsion. In their study, they have shown that this intervention increases the testicular salvage rate with a consequent decrease in the number of orchiectomy.

This study was undertaken to evaluate the testicular salvage rate after detorsion and tunica albuginea incision with tunica vaginalis flap coverage and orchiopexy.

Materials and Methods

This was an observational study conducted from January 2016 to December 2017. Patients with ischemic testis following torsion confirmed per-operatively by bluish discoloration of testis were included.

Ethical clearance was taken from ethical committee of Bangladesh Institute of Child Health & Dhaka Shishu (Children) Hospital. Informed written consent was taken from all the parents or legal guardians of the patients after adequately explaining them, the purpose of the study. They were assured of protection of patients' autonomy, privacy, confidentiality.

After detorsion the affected testis was wrapped in warm saline soaked gauze. Attention was then directed to the contralateral testis, which was evaluated and orchiopexy done prophylactically to prevent future torsion. The affected testis was then reevaluated after a period of observation, color and appearance was noted, a generous longitudinal anterior incision of the tunica albuginea was made. The gross enhancement in parenchymal blood flow was observed, the defect of the albuginea was covered with a vascularized tunica vaginalis flap and the gonad was fixed. The scrotal skin was closed with interrupted sutures (Fig 1).

Patients attended the Pediatric Surgery operation theater at 2 week, 3 months and 6 months after operation. In each visit patients were assessed clinically for the followings:

At 2 weeks after operation: Scrotal hematoma, surgical site infection, Doppler USG to examine the testicular blood flow.

After 3 months of operation: Condition of the testis by USG.

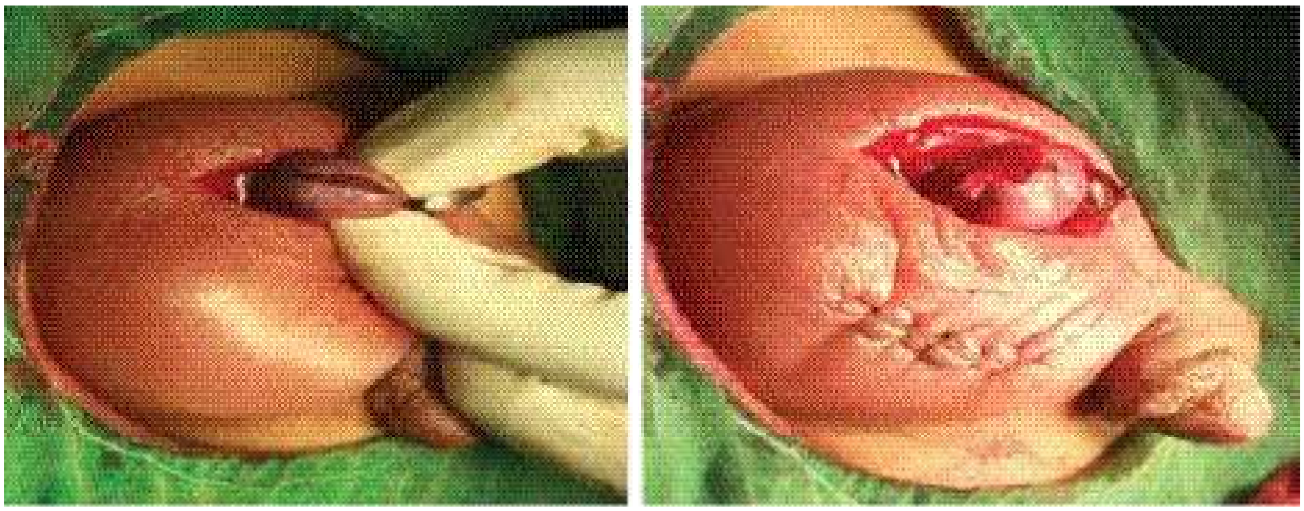

Fig 1 *Tunica albuginea incision with tunica vaginalis flap coverage*

After 6 months of operation: Doppler USG, Testicular blood flow, Testicular atrophy.

The statistical analysis was conducted using SPSS (statistical package for social science) version 20. The findings of the study were presented by frequency, percentage in tables. Means and standard deviations for continuous variables and frequency distributions for categorical variables were used to describe the characteristics of the total sample.

Results

Total number of patients was 15. Mean age, mean weight, involved site and type of torsion showed (Table I). Only 4 patients presented within 24 hours, while most of the patients presented after 24 hours (Table II). Rate of atrophy of testis after orchiopexy was higher in patients presented after 24 hours. Only 4 patients had recognizable testicular atrophy. No surgical site infection was present (Table III).

Table I
Comparison of independent variables of the participants (n=15)

Variables	(n=15)
Age (in months)	44.60 ± 47.53
Weight (in kg)	15.01 ± 13.32
Involved side	R-5, L-10
Type of torsion	Intra vaginal-14 Extravaginal-1

Table II
Comparison of duration of torsion of the participants (n=15)

Duration (hours)	No. (%)
Less than 24 hours	4 (26.7)
Within 24 to 48 hours	4 (26.7)
After 48 hours	7 (46.7)

Table III
Comparison of testicular atrophy and surgical site infection (n=15)

Comparison		No. (%)
Testicular atrophy	Absent	11 (73.3)
	Present	4 (26.7)
Surgical site infection	Absent	15 (100.0)
	Present	0(00.0)

Discussion

Testis-preserving surgery may have testicular function if the testis is not obviously necrotic. Testicular torsion does not necessarily cause the circulation to cease completely and preserving surgery can also sometimes be attempted after delayed diagnosis.[9]

The present study addressed the increase testicular salvage rate after detorsion and tunica albuginea incision with tunica vaginalis flap coverage with orchiopexy.

In this study, the mean duration from torsion to operation time was more than other study as patients from all over the country come for better treatment as it is the largest children hospital. It is the problem of the socioeconomic condition of a developing country like Bangladesh. There is always a delay in seeking of appropriate medical care. This study again proved that time is crucial for this urological emergency, since pain lasting more than 4-8 hours is highly associated with testicular death if no intervention occurs.[10] The surgical technique as described by Kutikov et al[8] was performed in 15 patients. Tunica vaginalis patch was sewn to the tunica albuginea after "testicular fasciotomy" to decrease the intratesticular pressures and to preserve perfusion of the testis. No patient developed scrotal haematoma and skin infection within 6 months follow up.

Testicular atrophy is a significant complication in patients who undergo salvage procedures for testicular torsion.[11] Here testicular size was measured by ultrasonography (USG). In this study no patients developed atrophy that was explored within 24 hours. In adolescent boys, necrosis is likely after 24 hours of symptoms.[12] The rate of atrophy was more in patients who had duration of torsion more than 48 hours as percentage of testicular salvage rate decreases with time passes from onset of symptoms to surgical.[4]

Figueroa et al[4] retrospectively reviewed all cases of acute scrotal pathology that underwent surgical exploration during a 10-year period. They compared the salvage rate between detorsion alone versus detorsion and tunica albuginea decompression (fasciotomy) with tunica vaginalis flap coverage in the surgical management of prolonged testicular ischemia. They found no statistical differences between the two groups regarding salvage rate. In

their study, there were significant statistical differences in duration of torsion 31.2 hours in tunica albuginea incision plus tunica vaginalis flap coverage. In this study, the sample size in tunica albuginea incision plus tunica vaginalis flap coverage group was 15 in 2 years.

Conclusion

Testicular torsion is an important and frequent condition affecting the male child population, with it there is a significant risk for testicular loss and possible impact on fertility. Tunica albuginea incision with tunica vaginalis flap coverage with orchiopexy provides more salvage rate in the management of ischemic testis following torsion.

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ORIGINAL ARTICLE

Effect of Intravenous Dexamethasone in Combination with Caudal Analgesia on Post Operative Pain Control after Herniotomy in Children

Md. Jahirul Islam[1], Ismat Jahan[2], Aminul Islam[3]

Abstracts

Background: *Dexamethasone has a powerful anti-inflammatory action and has demonstrated reduced morbidity after surgery.*

Objectives: *The aim of this study was to examine the effects of a single i.v. dose of dexamethasone in combination with caudalblock on postoperative analgesia in children.*

Methods*: This study was a randomized, double blind clinical trial, in which 77 children of ASA I and II, aged 3-10 years, undergoing elective unilateral herniotomy operation, was allocated in a double blind manner. Control Group I consist of 39 patients and Dexamethasone Group II consists of 38 patients. Group II received i.v. Dexamethasone 0.5 mg/Kg (Maximum 20 mg) and Group I received the same volume of i.v. saline after induction of anaesthesia. After inhalation induction of general anaesthesia, children received either dexamethasone 0.5-1 mg/Kg (maximum 20 mg) (n=39) or the same volume of saline (n=38) i.v. A caudal anaesthetic block was then performed using 1.5 ml/kg of Bupivacaine 0.25% in all patients. After surgery, rescue analgesic consumption, pain scores, and adverse effects were evaluated for 24 h.*

Results: *Significantly, fewer patients in the dexamethasone group required fentanyl for rescue analgesia (7.9% vs38.5%, p<0.05) in the post-anaesthetic care unit or acetaminophen (23.7% vs 64.1%) after discharge compared with the control group. The time to first administration of oral acetaminophen was significantly longer in the dexamethasone group (646 vs 430 min). Postoperative pain scores were lower in the dexamethasone group and the incidence of adverse effects was similar in both groups.*

Conclusion: *Intravenous dexamethasone 0.5-1 mg/Kg in combination with a caudal block augmented the intensity and duration of postoperative analgesia with out adverse effects in children undergoing herniotomy.*

Keywords: *Caudal anaesthesia, postoperative pain, dexamethasone, herniotomy.*

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Introduction

A caudal block is a popular reliable and safe technique for paediatric pain management after infraumbilical surgical procedures. However, in a significant proportion of patients, despite good initial analgesia from a caudal blockade with local anaesthetic, moderate or severe pain develops as the block resolves.[1-2] The addition of various drugs such as opioids, ketamine, clonidine, or dexmedetomidine to local anaesthetics has been used to improve or prolong caudal analgesia, but their use has been limited by un acceptable adverse effects in children undergoing day-case surgery.[3-7]

Dexamethasone, a corticosteroid with strong anti-inflammatory effects, provides post operative analgesia and has shown improvement in morbidity such asnausea, vomiting, fever and delayed oral intake in children.[8] Therefore, we performed this prospective randomized double-blind study to examine the effects of single intraoperative dexamethasone combined with a caudal block on recovery in children undergoing herniotomy.

Materials and Methods

Eighty ASA status I & II unpremedicated children, aged 3 to 10 yr and under-going day-case unilateral herniotomy, were enrolled in this prospective, randomized, and double-blind study. Patients were excluded from the study if they had a contraindication for caudal block including a hypersensitivity to any local anaesthetics, bleeding diathesis, infections at the puncture sites, orpre-existingneurologicaldisease. On the day of the pre-anaesthetic visit, parents were taught to perform the irrole in the study and the use ofvisual analoguepain scores (VAS, 'no pain' and 10 'the worst imaginable pain') after discharge.

The children were induced by inhalational technique with sevoflurane 8% in 100% oxygen. Standard monitoring of Non-invasive blood pressure, Electrocardiogram, Pulse oximeter were applied. After securing i.v. acecss, the children received i.v. fentanyl 1 mcgm/Kg and propofol 2mg/Kg. An appropriate sized LMA was inserted accordingly. The end tidal concentration of sevoflurane will be adjusted to deliver a minimum alveolar anaesthetic concentration (MAC) of 1. Then the children received either i.v. Dexamethasone or Normal saline according to their group allocation. After induction of anaesthesia, caudal block will be performed using a5cm short beveled 22G needle in the lateral decubitus position. After identifying the space with loss of resistance technique, the children will receive 1.5 ml/Kg bupibacaine 0.25%. Suppository paracetamol 20 mg/Kg will be given after completion of caudal block. Surgery was allowed to begain 10 minutes after performing the block. Children with an increase in heart rate of more than 20% from baseline indicating failed caudal block was given intravenous pethidine and discontinued from the study. After emergence from anaesthesia, patients were shifted to the postanesthesia care unit (PACU). Post operative pain was assessed at the end of the surgery.

Discharge criteria included clear consciousness, stability of vital signs, ability to tolerate oral fluids and void, age-appropriate level of ambulation, and absence of side-effects. Analgesia after discharge was provided with oral acetaminophen. The time to first supplemental oral acetaminophen was defined as the time from the end of surgery to the first registration of a VAS (0-10) ≥5 by parent's observation.

Results

Eighty patients were recruited to the study but three patients were excluded because of intra-operative administration of fentanyl or midazolam, so data from 77 patients were analyzed. There were no significant differences between the two groups with regard to the irage, weight, height, duration of surgery, and intra-operative fluid administration (Table I). There was no failure of caudal block in any patient.

Table I
Mean (± SD) of patient's data and intra-operative characteristics

Variables	Groups		p value[a]
	Control(n=39)	Dexamethasone (n=38)	
Age (months)	21.8 ± 6.3	20.2 ± 4.7	0.211
Weight (kg)	12.1 ± 2.7	11.9 ± 2.6	0.742
Height (cm)	84.8 ± 12.1	83.6 ± 12.4	0.669
Duration of surgery (min)	38.2 ± 11.7	38.7 ± 11.3	0.849

[a] 't' test was done to measure the level of significance
Data was expressed as Mean ± SD

The incidence of rescue fentanyl in the PACU and rescue oral acetaminophen after discharge was significantly lower in children who received dexamethasone compared with those who received saline. Eleven of the 39 in the control group and three of the 38 in the dexamethasone group receivedboth fentanylrescue in PACUand oralacetaminophenafterdischarge.Thetime to firstoral acetaminophen administration was significantly longer in the dexamethasone group compared with the control group (Table-II).

Pain scores using CHEOPS assessed at the PACU were significantly lower in the dexamethasone group than in the control group (Table III).

There were no significant differences in the incidence of adverse effects including vomiting (7.7% vs 10.5%), sedation (25.6% vs 31.6%), and shivering (2.6% vs 0%), all adverse effects were also well controlled by a single dose of antiemetic and meperidine. The majority of patients (79.5% of the control group and 97.4% of the dexamethasone group) were satisfied (excellent or good) with the postoperative pain management. Patients in the dexamethasone group were more satisfied than those in the control group (Table IV).

Table II
Distribution of postoperative rescue analgesics

Variables	Groups		p value
	Control(n=39)	Dexamethasone (n=38)	
Rescue fentanyl at PACU	15 (38.5)	3 (7.9)	0.002[b]
Rescue acetaminophen after discharge	25 (64.1)	9 (23.7)	<0.001[b]
Rescue fentanyl+oral acetaminophen	11 (28.2)	3 (7.9)	0.021[b]
Time of first acetaminophen (min)	430 ± 135	646 ± 107	<0.001[a]

[a] 't' test was done to measure the level of significance. [b] Chi square test was done to measure the level of significance Data was expressed as Frequency (Percent) or Mean ± SD

Table III
Post-operative pain score

Variables	Groups		p value
	Control(n=39)	Dexamethasone (n=38)	
No pain	8	2	0.002[b]
Wirst immaginable pain	31	36	

[b]Chi square test was done to measure the level of significance

Table IV
Distribution of postoperative variables

Variables	Groups		p value
	Control(n=39)	Dexamethasone (n=38)	
Required fentanyl for rescue analgesia	15 (38.5)	3 (7.9)	0.002[b]
Acetaminophen after discharge	25 (64.1)	9 (23.7)	<0.001[b]
Incidence of adverse effects			
Vomiting	4 (10.3)	3 (7.9)	0.999[c]
Sedation	12 (30.8)	10 (26.3)	0.665[b]
Shivering	0 (.0)	1 (2.6)	0.494[c]
Satisfaction			
Satisfied	31 (79.5)	37 (97.4)	0.029[c]
Not satisfied	8 (20.5)	1 (2.6)	

[b]Chi square test was done to measure the level of significance. [c] Fisher's Exact test was done to measure the level of significance. Data was expressed as Frequency (Percent) or Mean ± SD

Discussion

A single dose of i.v. dexamethasone (0.5-1 mg/Kg) in combination with a caudal block reduces post operative pain, decreases rescue analgesic requirements, and prolongs analgesic duration compared with a caudal block alone.

In the present study, we demonstrated a single dose of i.v. dexamethasone decreased the need for analgesia after discharge by 63% and increased the duration of analgesia by upto 50% compared with patients who received a caudal block alone. Furthermore, it must be stressed that i.v. dexamethasone was not associated with adverse effects in our study. Steriod have a powerful antiflammatory action and have a demonstrated reduced pain and swelling after oral surgery, spinal surgery, and laparoscopic surgery.

However, the exact mechanism by which dexamethasone may exert an analgesic effect is not fully understood. Systemic administration of steroids has been found to suppress tissue levels of bradykin in[9] and the release of neuropeptides from nerve endings,[10] both of which can enhance nociception in inflamed tissue. The established reduction in prostaglandin production might further contribute to analgesia by inhibiting the synthesis of the cyclooxygenase isoform-2 in peripheral tissues and in the central nervous system.[11] They also inhibit other mediators of inflammatory hyperalgesia, for example, tumour necrosis factor-a, interleukin-17b,and interleukin-6. Thus, despite the fact that the mechanism is not yet fully understood, a reduction in pain by steroids has been supported by many studies. The plasma elimination half-life is only about 6 h, and so there seems to be ongoing drug effects for a significant period of time after drug clearance from the plasma.

Many investigators have studied the effects of systemic steroids in reducing postoperative pain and morbidity; but, there is no consensus regarding the irroutineuse, particularly inchildren. Results have been conflicting; some studies demonstrating benefit and othersnot.[12-13] In addition, most published studies for children have been limited to the otolaryngology procedures with wide ranges of dexamethasone (0.4-1.0 mg/Kg) with maximum doses from 8 to 50 mg). Many studies have included children who exceeded the weight in kilograms over the maximum dose allowed; that is, there was no weight normalization of the treatment group. Differences in the dose of dexamethasone, surgical and anaesthetic techniques, intraoperative opioid use, and lack of standardization for pain scoring and management may explain in part the conflicting results reported in prior studies. Therefore, we chose a single dose of 0.5 mg/Kg dexamethasone for children (maximum dose of 20 mg).

One of the major end points of this study, the first oral acetaminophentime, represents the parent's subjective impression of the child's pain. Because oral acetaminophen was administered after discharge, parents were frequently the sole assessor of their child's analgesic requirements. Although parental assessment of pain may be subject to bias, it has not been well studied, and we used observer VAS measures of pain to determine the need for rescue analgesic after discharge. A number of studies have provided varying levels of support for the validity of CHEOPS for the assessment of pain in post operative children. However, as a consequence of the tight observational and recording inter-vals, and the numerous types of behaviour, evaluating pain is burden some for the parent. Further more, Beyer et al[14] found that CHEOPS scores were generally very low after discharge and that over time, self-reports of pain worsened. Thus, CHEOPS may be valid only during the immediate postoperative period. Tarbell et al[15] also noted that the strong correlation between CHEOPS and observer VAS measures of pain may mean that it is more practical to use observer VAS.

Dexamethasone may exert an antiemetic action via prostaglandin antagonism, serotonin inhibition in the gutandrelease of endorphins. In this study, we found no difference and the incidences of vomiting were very low in both groups. This may be related to the lack of administration of intraoperative opioids and combined pain management with caudal analgesia.

The risk to patients of a single dose of dexamethasone appears to be minimal. We did not measure the plasma concentrations of dexamethasone, cortisol or any other par- ammeters associated with i.v. dexamethasone because invasive blood samplings for hormonal assay sand long-term follow-ups were not applicable especially in children under-going day-case minor infraumbilical surgeries.

Conclusion

Intravenous Dexamethasone 0.5 mg/Kg after induction of anaesthesia provided better postoperative analgesia than placebo after herniotomy in children.

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ORIGINAL ARTICLE

Association of Admission Temperature and Outcome among Neonates with Sepsis in a Tertiary Care Hospital

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Abstract

Background: *Neonatal sepsis is one of the major causes of mortality in neonates. Hypothermia is also an important contributing factor of neonatal mortality. Neonates with sepsis can present with normal temperature, hypo or hyperthermia.*

Objectives: *This study was design to find out the pattern of temperature on admission and its association with mortality among neonates admitted with sepsis.*

Methods: *This cross-sectional study was conducted from September 2017 to April 2018 in the Department of Neonatal Medicine and NICU, Dhaka Shishu (Children) Hospital. Neonates up to thirty days of age, diagnosed as probable sepsis were enrolled. On admission, axillary temperature was recorded for 3 minutes and neonates were categorized according to the recorded temperature. Neonates were classified as early onset sepsis (EOS) and late onset sepsis (LOS) according to the age of onset of the sepsis. Outcome was also recorded. Statistical analysis was done by SPSS program version 25. Chi-square (χ^2) test was done to determine the association and p value, <0.05 was taken as significant.*

Results: *Among 493 enrolled neonates, 41.2% neonates were with early onset sepsis (EOS) and 58.8% were with late onset sepsis (LOS). Out of 493 neonates, 89(18.1%) died. Among the enrolled neonates, 54.4% had normal temperature, 16.6% had mild hypothermia, 14.6% had moderate hypothermia and 14.4% had hyperthermia. It was found that mild and moderate hypothermia were significantly more in EOS($p<0.05$). Mortality was significantly high in neonates with mild and moderate hypothermia ($p<0.05$).*

Conclusion*: This study found that mortality was associated with mild and moderate hypothermia in neonates admitted with sepsis.*

Keywords: *Neonate, sepsis, temperature.*

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Introduction

Neonatal period is the most critical time for child survival. Globally around 2.6 million deaths occurred during neonatal period.[1] In Bangladesh, under-five and infant mortality rate have decreased significantly over the last 3 decades, but neonatal mortality (23/1000 live birth)[2] remains high. Sepsis is an important cause of neonatal mortality and account for approximately one-third of the global burden of neonatal deaths.[3] Most of these deaths occur in the developing world.[4]

Signs and symptoms of infection in neonates are subtle and non-specific and may clinically be indistinguishable from those occurring in non-infectious conditions, including almost every sign of neonatal distress.[5] Neonates with sepsis may be presented with either fever or hypothermia and even with normal temperature. Hypothermia is common and a major contributor of significant morbidity and mortality in developing countries.[6-8] Febrile neonates are at risk for bacterial infection, including meningitis, bacteremia, and urinary tract infections. Schwartz et al[9] and Marom et al[10] reported that the rate of serious bacterial infections was 4 to 28% among those neonates who were presented with fever during admission. Voora et al reported on a prevalence of fever of 1% in term newborns with 10% of these febrile newborns having sepsis.[11] It was reported that fever is the presenting symptom of bacterial infection in term neonates whereas preterm neonates were more likely presented with hypothermia.[12]

There were studies reported the incidence and outcome of hypothermia at the time of admission among neonates with different diagnoses.[13,14] As sepsis is one of the major causes of neonatal mortality, it is necessary to evaluate the association of temperature on admission with mortality as in many cases fever or hypothermia is an important presentation of sepsis in neonates. So, this study was designed to find out the pattern of temperature on admission and its relation with mortality among neonates with sepsis.

Materials and Methods

This cross-sectional observational study was conducted from September 2017 to April 2018 in the Department of Neonatal Medicine and NICU, Dhaka Shishu (Children) Hospital. Neonates up to thirty days of age, diagnosed as probable sepsis with any 3 or more of the following sign/symptoms:[15] poor feeding, lethargy, hypo/hyperthermia, abdominal distension, bradycardia (HR<100/min), tachycardia (HR >200/min), respiratory distress, apnoea, tachypnea, cyanosis, CRT >3 sec and neonates age <72hrs having one or more maternal risk factors: foul smelling liquor, antepartum / intrapartum maternal fever, prolonged or premature rupture of membranes ≥18 hours, offensive vaginal discharge, single unclean vaginal examination(s) during labour were enrolled in this study after taking informed consent from the parents. Neonates with congenital heart diseases, congenital anomalies, hypoxic ischemic encephalopathy, respiratory distress syndromes and did not give consent were excluded from the study.

Those neonates with onset of sepsis within 72 hours of age were classified as early onset sepsis (EOS)[16] and neonates with onset of sepsis at >72 hours of age were classified as late onset sepsis (LOS).

Temperature was recorded in axilla by using clinical mercury in glass thermometer. Before measuring the temperature, it was confirmed that axilla was dry, and then the thermometer was placed high up in the middle of the axilla and the arm was pressed against the side of chest to prevent air pockets between skin and thermometer. Thermometer was kept in this position for 3 minutes. The thermometer was disinfected by using chlorhexidine-soaked cotton after every axillary temperature measurement. In this study recorded temperature was classified according to WHO criteria as: Normal temperature 36.5°C to 37.5°C, hypothermia <36.5°C and hyperthermia >37.5°C. Hypothermia was sub-classified into: mild (36.0°C to 36 .5°C), moderate (32.0°C to35.9°C) and severe (<32.0°C).[17]

Blood samples of all the patients were obtained for complete blood count (CBC), CRP and blood culture, after enrollment and collected blood samples were send to microbiology and pathology department of Dhaka Shishu (Children) Hospital.

At the time of enrollment, for each neonate, information including gender, gestational age, age, weight, birth history was recorded in a questionnaire. Recorded temperature with category, investigation reports and outcome were also recorded. All enrolled neonates received supportive care and appropriate antibiotics according to unit protocols.

Statistical analysis was done by SPSS program version 25. To determine the association between categorical variables, Chi-square (χ^2) test was done. P value, <0.05 was taken as significant.

Results

Out of 493 enrolled neonates, 70.6% were male with male to female ratio of 2.4:1, mean age of admission was 9.2±6.7 days with mean admission weight was 2337.2±732.04 gm. Mean gestational age was 36.4±2.7 week with 42% were preterm. All the enrolled neonates were out born; 70.8% were born at hospital and 60.6% delivered by normal vaginal delivery. Early onset sepsis (EOS) was present in 203 (41.2%) cases and late onset sepsis (LOS) in 290 (58.8%) cases. Among 493 study cases, 404 (81.9%) patients were discharged and 89 (18.1%) died (Table I). Among 493 neonates, 52 (10.5%) had growth of single organism in blood culture. Out of those 52 culture positive samples, highest isolated organism was gram negative bacteria, Acinetobacter (19/52) (Fig 1).

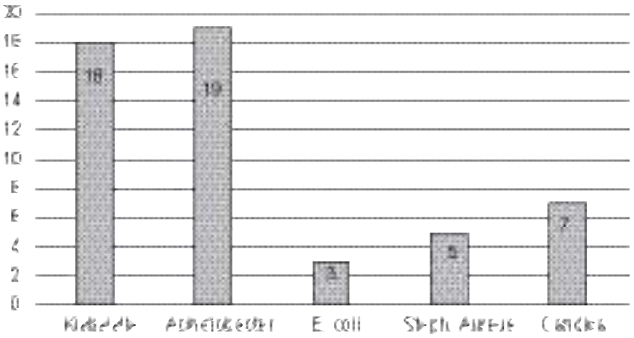

Fig 1 *Isolated organisms in blood culture (N=52)*

The mean axillary temperature was 36.66±0.72ºC with minimum and maximum axillary temperatures were 35.0ºC and 38.9ºC respectively. Among the enrolled neonates, 54.4% had normal temperature, 16.6% had mild hypothermia, 14.6% had moderate hypothermia and 14.4% had hyperthermia (Table II). Among the neonates who had normal temperature at the time of admission, 37.3% (100/268) and 62.7% (168/268) were suffering from EOS and LOS respectively. It was found that mild and moderate hypothermia were significantly associated with EOS (p <0.05). Hyperthermia was relatively more in neonates suffering from LOS than EOS (69.1% vs. 30.9%), though the difference was not statistically significant (p >0.5) (Table III). Mild and moderate hypothermia were associated with mortality (p <0.05) (Table IV). The mortality was also related to gestational age and was significantly high in preterm neonates (p=<0.05) (Table V).

Table I

Baseline characteristics of enrolled neonates (N=493)

Variables	Number (%)
Age on admission (day) mean±sd (min-max)	9.2±6.7 (1-28)
Weight on admission (gm) mean±sd(min-max)	2337.2±732.04 (800-4600)
Gestational age (week) mean±sd (min-max)	36.4±2.7 (26-42)
Preterm	207 (42.0)
Term	286 (58.0)
Gender	
Male	348 (70.6)
Female	145 (29.4)
Place of delivery	
Home	144 (29.2)
Hospital	349 (70.8)
Mode of delivery	
Normal	299 (60.6)
LUCS	194 (39.4)
Diagnosis	
EOS	203 (41.2)
LOS	290 (58.8)
Outcome	
Died	89 (18.1)
Cured	404 (81.9)

Table II
Category of neonates according to recorded axillary temperature (N=493)

Recorded temperature category (°C)	Number (%)
Normal (36.5-37.5)	268 (54.4)
Mild hypothermia (36-36.4)	82 (16.6)
Moderate hypothermia (<36-32)	72 (14.6)
Hyperthermia (>37.5)	71 (14.4)
Total	493 (100.0)
Mean±sd (min-max) °C	36.66±0.72 (35.0 - 38.9)

Table III
Association of temperature pattern with EOS and LOS (N=493)

Temperature Category (°C)	Total	Diagnoses		p* value
		EOS n (%)	LOS n (%)	
Moderate hypothermia (<36-32)	72	39 (54.2)	33 (45.8)	0.015
Mild hypothermia (36-36.4)	82	42 (51.2)	40 (48.8)	0.031
Hyperthermia (>37.5)	71	22 (30.9)	49 (69.1)	0.080
Normal (36.5-37.5)	268	100 (37.3)	168 (62.7)	0.070
Total	493	203	290	

*Chi square test (χ^2)

Table IV
Association of mortality with admission temperature (N=493)

Temperature category (°C)	Total	Died	Cured	p* value
Moderate hypothermia (<36-32)	72	20 (27.8)	52 (72.2)	0.017
Mild hypothermia (36-36.4)	82	22 (26.8)	60 (73.2)	0.023
Hyperthermia (>37.5)	71	7 (9.9)	64 (90.1)	0.077
Normal	268	40 (14.9)	228 (85.1)	0.063
Total	493	89	404	

*Chi square test (χ^2)

Table V
Association of mortality with gestational age (N=493)

Gestational age	Number	Died n (%)	Survived n (%)	p* value
Preterm	207	53 (25.6)	154 (74.4)	0.000
Term	286	36 (12.6)	250 (87.4)	
Total	493	89	404	

*Chi square test (χ^2)

Discussion

This study was conducted to identify the pattern of temperature on admission among neonates with sepsis and its relation with mortality. In this study, 36.1% neonates had early onset sepsis and 63.9% neonates had late onset sepsis respectively. But Getabelew et al[18] found 65% and 35% of neonates developed early onset neonatal sepsis and late onset neonatal sepsis, respectively, which was opposite to our findings. We found that the rate of isolation of single organism was about 10.5%. In a previous study reported from Bangladesh, the culture positivity rate was 36%.[19] Studies from different countries shown that culture positivity rate varies from 16%-54%.[20-22]

Presentation of neonatal sepsis is usually subtle and non-specific. Hypothermia or fever is the common presentation. Hypothermia is a common problem in neonates and to identify this problem, studies were conducted in Bangladesh[11] and other countries.[23,24] The prevalence of hypothermia varies widely in those studied. Factors like age, weight, gestational age, place of birth, early bathing, APGAR scores, season and ambient temperature can alter the prevalence of hypothermia in neonates.[18,25-27] All those studies included neonates with different diagnoses. But very few studies were conducted to evaluate the relationship of hypothermia with sepsis.[28,29] This study was among those where we found, 31.2% of the neonates had hypothermia on admission. Similarly, Ahmad et al[29] found 28.9% of the study patients had hypothermia on admission. We found mild and moderate hypothermia was significantly associated with EOS (p=0.000). Similar findings were reported by Ahmad et al.[29]

Hypothermia is associated with increase rate of mortality in neonates suffering from various diseases. Ogunlesi et al[30] found that mortality rate of neonatal sepsis was 32.2%. In the present study all enrolled neonates were out born and mortality rate was 17.6%, which was much less than the finding of Ogunlesi et al[30] and similar to the finding of Ahmad et al.[29] Ahmad et al[29] found that neonates with hypothermia had higher mortality rate as compared to patients with normal temperature among neonates with sepsis. We also found that hypothermia was significantly associated with mortality.

Like hypothermia, neonates with sepsis might be presented with hyperthermia.[28] Usually neonate with fever are at risk for bacterial infection. Approximately 10% of neonates with fever have a serious bacterial infection.[11] In this study 14.4% neonates had hyperthermia, which was similar to the findings reported by Ahmad et al.[29]

Conclusion

This study concluded that mild and moderate hypothermia were associated with mortality among neonates admitted with sepsis. Early onset sepsis was associated with hypothermia.

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REVIEW ARTICLE

Hypocalcemia in the Critically Ill Pediatric Patients: A Review

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Abstract

Hypocalcemia is common in the critically ill pediatric patients. However, the diagnosis of hypocalcemia in this population is complicated by interpretation of the total plasma calcium concentration. These limitations are principally the result of the effects of hypoalbuminemia and disorders of acid-base balance on the total calcium concentration. Thus, measurement of ionized calcium can be critical in determining an individual's true serum calcium status. In this review, we first described the regulation of normal calcium metabolism and then focus on the various etiologies of hypocalcemia, which are encountered in the pediatric critical care settings. The approach to the treatment of hypocalcemia and the current consensus on treatment of hypocalcemia in the critically ill pediatric patient is also presented.

Key words: *Critical illness, hypocalcemia.*

Introduction

Calcium has widespread extra and intracellular actions, including effects that influence hormone secretion and responsiveness, enzyme activity, nerve conduction, muscle contraction, and membrane potential. In addition, calcium plays a structural role as a component of the mineralized matrix of bone. Although a highly regulated system exists to maintain extracellular concentrations of ionized calcium within narrow physiological range, hypocalcemia is common in pediatric critically ill patients.[1-3] However, obvious metabolic defects in the hormonal control of calcium homeostasis (such as hypoparathyroidism or vitamin D deficiency) or physicochemical disturbances (such as massive transfusions precipitating calcium chelation) are present in a small subset of critically ill pediatric patients. More frequently, the precise basis for hypocalcemia is unknown. For instance, hypocalcemia is common in sepsis,[4-6] and when circulating cytokines that accumulate during sepsis can impair parathyroid hormone secretion.[7,8] In this article, we provide the guiding principles of calcium hemostasis and describe our current understanding of the pathophysiology of hypocalcemia in the critically ill paediatric patients.

The majority (99%) of total body calcium is stored in bone as (1) hydrtoxyapatite crystals and (2) to a lesser extent, as non-crystalline, readily mobilizable calcium salts. The remainder resides within extracellular fluids and soft tissues. At normal serum protein concentrations, approximately 50% of total serum calcium is in ionized form, biologically active (Ca2+). An additional 8% to 10% is complexed to organic and inorganic acids (e.g., citrate, sulphate, and phosphate). The remaining 40% of serum calcium is protein-bound, primarily to albumin (80%) and also to globulins (20%) and is not biologically active.[9] Changes in the ionized component of serum

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calcium are responsible for symptoms related to hypocalcemia. Increases in extracellular fluid concentrations of anions such as phosphate, citrate,

bicarbonate, or edetic acid, will chlelate calcium and decreases the concentrations of ionic calcium but will not affect the total calcium concentration. Similarly an alkaline pH will reduce the Ca2+ via an increase in the affinity of albumin for calcium, without altering the total serum calcium. Acidosis has the opposite effect. Free fatty acids also enhance the binding of calcium to albumin.[10]

Overall calcium homeostasis is controlled by a complex feedback system. Parathyroid hormone directly targets the bone resorption and renal calcium reabsorption and indirectly by stimulating renal[1-3] hydroxylase, the rate-limiting enzyme in vitamin D activation, to convert 25-hydroxyvitamin D into calcitrol. Renal tubules typically resorb about 99% of filtered calcium in the cortical portion of the thick ascending limb. Parathyroid hormone and calcitrol regulate active transport by increasing activity and/or expression of multiple calcium transport proteins in the distal nephron.[11]

Hypocalcemia

Neuromuscular irritability is the hallmark of hypocalcemia and manifests as tetany, a condition characterized by circumoral numbness, distal extremity paresthesias, and muscle cramps. When hypocalcemia is severe, patients may experience bronchospasm or laryngospasm that mimics asthma. Localized or generalized seizures as well as more vague symptoms as hyperirritability may also occur. Hypocalcemia delays ventricular depolarization and prolongs the Q-T and ST intervals on the ECG and rarely, a reversible form of congestive cardiac failure may develop.

Early neonatal hypocalcemia, which occurs within first 3 days of birth, arises from inadequate secretion of parathormone (PTH) by immature parathyroid glands,[12] and/or inadequate responsiveness of the renal tubule cells to PTH. Risk factors include prematurity,[13] low birth weight,[14] and maternal diabetes mellitus.[15] A more severe form of transient neonatal hypoparathyroidism occurs in infants born to mothers with hypercalcemia.[16] Neonatal hypocalcemia that occurs after the first 3 to 5 days of life classically arises from an excessive phosphate intake in infants who are fed cow's milk or cow's milk-based infant formulas.[17] The ensuing hyperphosphatemia leads to hypocalcemia. Transient hypoparathyroidism may also manifest during this time. Less commonly maternal hypercalcemia, congenital defects in PTH production, secretion, or action, and specific magnesium deficiency disorders can cause neonatal hypocalcemia.[16]

Congenital defects in parathyroid gland development may be isolated or, more commonly, occur in association with other developmental defects. In particular, syndromic hypoparathyroidism must be considered in infants and children with congenital heart defects, deafness, or immune defects. The extent of the parathyroid gland abnormality largely dictates whether hypoparathyroidism develops. For some individuals, hypoparathyroidism may only be unmasked with increased demands for PTH during growth or during intercurrent illness. The most common cause of congenital hypothyroidism is the DiGeorge syndrome, also known as velocardiofacial syndrome. The complete DiGeorge syndrome refers to the triad of congenital absence of the thymus, congenital hypoparathyroidism, and cardiac anomalies, commonly of the outflow tract or aortic arch,[18] heterozygous deletion of 22q11.2 is the most common cause with an incidence of 1 in 2000 to 4000 births. Familial occurrence of DiGeorge syndrome has been described. Other chromosomal abnormalities and teratogens have also been implicated in the DiGeorge syndrome. The degree of parathyroid hypoplasia is variable, many infants experience spontaneous improvement in parathyroid function and have normal serum calcium levels, while some patients do not develop parathyroid dysfunction until much later in life.[19] When spontaneous resolution of hypoparathyroidism occurs in infancy, hypocalcemia may occur years later during conditions of stress.[20]

Hypocalcemia in critical illness

Hypocalcemia is common in critically ill pediatric patients. In some cases, the basis will be clear: acute renal insufficiency, fluid overload after dialysis, transfusion with citrated blood or alkalosis. There are many drugs associated with hypocalcemia. Chemotherapeutic agents such as the use of 5-fluorouracil may result in mild hypocalcemia.

Cisplatinum, as well as many diuretics, can induce hypomagnesemia and thereby cause hypocalcemia.

For the majority of patients, hypocalcemia reflects a hypoalbuminemic state.[21] The cause or pathophysiology of hypocalcemia will not be readily apparent; in a study, >50% of patients had no identifiable etiology for the hypocalcemia.[22] Sepsis is a well-recognized risk factor for hypocalcemia. In nonseptic, critically ill patients hypocalcemia (defined as ionized calcium <1.16 mmol/L) has also been recognized.[4] Vitamin D deficiency as well as acquired, "relative" hypoparathyroidism, vitamin D resistance, and 1- hydroxylase deficiency are proposed mechanisms for hypocalcemia in critically ill pediatric patients.[7,22]

Patients with toxic shock syndrome or gram-negative bacterial sepsis may have elevated levels of tumor necrosis factor (TNF-α) that have also been associated with hypocalcemia. These observations suggest that increased sensitivity of parathyroid cells to the extracellular Ca2+ concentration can provide a mechanism for hypocalcemia in the setting of an inflammatory process such as sepsis. The direct contribution, if any, of hypocalcaemia to decreased survival is still being explored. In the pediatric populations, ionized hypocalcemia has been associated with more severe illness.[1] Thus hypocalcemia may be a marker of greater disease severity rather than a cause of increased mortality. Although neuronal irritability, a classic sign of hypocalcaemia is absent in critically ill patients with hypocalcaemia,[7] the relevance of this finding to other pathological effects of hypocalcaemia is not known. Perhaps most relevant to critically ill patients, hypocalcaemia has been shown to contribute to cardiac dysfunction and hypotension,[7,23] and case reports of cardiomyopathy and heart failure reversible with chronic hypocalcemia due to hypoparathyroid states.[23,24] Additionally, calcium administration improves ventricular function in critically ill patients with ionized calcium <1.05mm0l/L.[25] Heart failure has also been associated with hypocalcemia in the setting of vitamin D-deficient rickets.[26] However, the specific contributions to cardiac function of hypophosphatemia and vitamin D, both of which are important in muscle function,[27] have not been elucidated. Because of the association of hypocalcaemia with worse clinical outcomes, and the effects of hypocalcemia on cardiovascular status, a logical question is "does treatment of hypocalcemia in critically ill patients improve outcome?" In 1995, Jankowski and Vincent reviewed the available evidence for the use of calcium in providing cardiovascular support in critically ill patients and concluded "calcium may improve cardiovascular status in critically ill patients, but at the cellular level its administration may be deleterious," and called for additional studies.[25] Nearly 15 years later, we still lack evidence-based guidance as no randomized-controlled trial has been published that examined the effect of parenteral calcium administration on mortality, other markers of poor prognosis, or complications of calcium therapy.[28] By contrast in 2000, the American Heart Association updated practice guidelines in children that restricted the administration of parenteral calcium during cardiopulmonary resuscitation to pediatric patients with hypocalcemia, hypermagnesemia, hyperkalemia, and calcium channel blocker overdose.[29]

Despite these guidelines, a recent multicenter study found that nearly 5 years after publication of the revised American Heart Association (AHA) guidelines, calcium continued to be administered to nearly half of the children during cardiopulmonary resuscitation and was associated with increased mortality and worse neurologic outcomes except in patients with metabolic abnormalities.[30] Subsequent pediatric advanced life-support guidelines published by the AHA in continue to restrict the use of calcium to specific circumstances, including hyperkalemia, documented hypocalcemia, hypermagnesemia and calcium channel blocker overdose.[31] Finally, the guidelines developed by the Surviving Sepsis Campaign do not recommend calcium administration as a therapeutic measure.[32] The common practice of administering calcium during cardiopulmonary resuscitation to individuals who do not have specific metabolic abnormalities derive from a lack of evidence of benefit plus concerns that calcium administration may lead to worse clinical outcomes. One possible explanation may be that the administration of calcium may potentiate the accumulation of cytosolic calcium, which several studies have implicated as the final common pathway of cell death.[33] For instance, brain ischemia is associated with an increase in intracellular calcium. Accumulation of intracellular calcium

through specific routes can then over activate pathways for which calcium is a second messenger, generating reactive oxygen species and trigger cell death mechanisms, reviewed by Szydlowska and Tymianski.[34] Similarly, the cardiomyocyte, reviewed by Murgia et at[35] and other cell types are subjected to this same unrestrained activation of programmed cell death and necrosis.

Treatment

In classic endocrine disorders, the approach to management of severe, symptomatic hypocalcemia is fairly straightforward. The two most commonly used calcium solutions for intravenous use are 10% calcium chloride and 10% calcium gluconate. A 10mL ampoule of 10% calcium chloride contains three times more elemental calcium (272 mg) than a 10mL ampoule of 10% calcium gluconate (90 mg). Intravenous calcium solutions are hyperosmolar and should be administered through a large central vein if possible. Calcium gluconate has a lower osmolalitly and is the preferred calcium salt to administer if a peripheral vein is used. A bolus dose of intravenous calcium gluconate (1-2 mg of elemental calcium/kg) that is administered over 5 to 10 minutes can raise the serum calcium by 0.5 to 1mg/ml. A bolus dose of calcium will raise the serum level transiently and levels will begin to fall again after 30 minutes. Therefore, a bolus dose of calcium (1-3 mg elemental calcium/kg per hour in children) then 0.5 to 1.5 mg of elemental calcium/kg per hour is administered as a continuous infusion. Individual responses to intravenous calcium will vary, so calcium dosing must be guided by periodic monitoring of the level of ionized calcium in blood. Intravenous calcium is continued until a stable oral regimen is achieved.[36]

Magnesium depletion is common in patients in intensive care units and is a frequent cause of hypocalcemia. Thus, hypomagnesemia should also be treated. The concordant administration should also be treated as activated forms of vitamin D such as calcitriol (15-50 ng/kg per day in 2-3 divided doses), can provide more stable control of the serum calcium concentration and may allow early discontinuation of intravenous calcium.[37,38]

Administration of intravenous calcium should be reserved for specific situations as this treatment can have significant risks. Patients taking digitalis may have increased sensitivity to intravenous calcium. Rapid administration of calcium can result in cardiac arrhythmias so that intravenous calcium administration should be carefully monitored. Local vein irritation can occur with solutions Ã200 mg/dl of elemental calcium. Extravasation into soft tissues can lead to inflammation and local calcification. Calcium phosphate deposition can occur in any organ and is more likely to occur if the calcium-phosphate ratio exceeds solubility product. Calcium infusions can promote vasoconstriction and ischemia of vital organs, particularly in patients with low cardiac output and preexisting poor perfusion. Excessive cytosolic calcium can induce cell death. It seems most prudent to limit the use of intravenous calcium to patients who have signs or symptoms of hypocalcemia. Chronic treatment depends on underlying etiology: calcitriol and calcium supplementation in hypoparathyroidism, and vitamin D-resistant rickets.[23] Vitamin D deficiency is treated with ergocalciferol or cholecalciferol; dosing is based partly on underlying etiology with malabsorptive disorders requiring much larger doses long term. Over replacement of calcium and/or vitamin D can cause hypercalcemia or hypercalciuria, and nephrocalcinosis and nephrolithiasis are attendant risks.

The management of hypocalcemia in the critically ill patient is more problematic: hypocalcemia may produce symptoms ranging from seizures, laryngospasm, prolonged QT, and cardiac dysfunction and intravenous calcium as described above is appropriate. Treatment of hypocalcemia in the setting of hypotension or circulatory collapse in the absence of specific hypocalcemia-attributable symptoms has been called into question, however, for concerns that such treatment may aggravate the disease process. A recent systematic review of the literature identified no studies that examined meaningful outcomes beyond increases in calcium levels following intravenous calcium administration. The concluded that “there is no clear evidence that parenteral calcium supplementation impacts the outcome of critically ill patients”.[29,30]

Conclusion

Hypocalcemia is common in critically ill patients. Endocrine disorders and medication side effects are common culprits, and management is generally unambiguous in such cases. Frequently, however,

the etiology of hypocalcemia in the critically ill patient is uncertain and potentially multifactorial. While mechanisms that disrupt normal calcium homeostasis are being uncovered, the precise treatment approach that ultimately benefits the critically ill patient with hypocalcemia has yet to be delineated. So, on the evidence of the role of calcium supplementation in critically ill patients highlights the need for further investigation.

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REVIEW ARTICLE

Management of Dengue in Children: An Update

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Abstract

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence which often coincides with the onset of the critical phase. For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives, so long as correct and timely interventions are instituted. The main hemodynamic elements of dengue shock is hypovolemia with decreased vascular capacitance resulting from plasma leakage. Thus, the strategy of aggressive fluid resuscitation of septic shock is not applicable to severe dengue with plasma leakage. Volume replacement in children with dengue shock is a challenging management problem. Aggressive fluid resuscitation may indeed be harmful and should be limited to dengue shock with hypotension. There is a "narrow therapeutic index"; therefore, fluids have to be given timely, at the appropriate volume, rate, of the appropriate type (crystalloids, colloid and/or blood) and for the appropriate duration. Therein lies the challenge to physicians who are not familiar with the important practice of fluid titration through frequent and meticulous assessment. Progression of the disease through the critical phase should be tracked in hours of plasma leakage. Recognizing the cues to discontinue intravenous fluid therapy is just as important as knowing when to start it. Given time and hemodynamic stability, other issues such as thrombocytopenia, coagulopathy and raised liver enzymes will recover spontaneously or with supportive care.

Key words: *Dengue; children; shock; intravenous fluid therapy.*

Background

Dengue virus infections affect human populations of all age groups worldwide. In some parts of the world, dengue is mainly a pediatric health problem. The vast majority of dengue cases occur in children <15 years of age and around 5% of all severe dengue cases occur in infants.[1-4] In one dengue-endemic area, the incidence of dengue infection exceeded 10% in infants aged 2-15 months.[5]

Differentiation between dengue and other common infections in infants (such as pneumonia, bacterial sepsis, meningo-encephalitis, measles, rotavirus infections, etc.) is often not possible at the febrile stage. The presence of a febrile seizure, macular

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rash, petechiae and lower platelet counts early in the illness are significantly associated with dengue among infants with acute undifferentiated febrile illness.[5]

Most infants acquire primary dengue virus infections.[1,5,6] As in adults, dengue virus can cause a spectrum of outcomes in children, ranging from asymptomatic infection to mild or clinically significant, severe disease.[5] After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases "febrile, critical and recovery. Children with dengue typically have high fever that usually lasts 2-7 days. Upper respiratory tract symptoms (cough, nasal congestion, runny nose, dyspnea), gastrointestinal symptoms (vomiting, diarrhea), and febrile convulsions are more common in infants with dengue compared to older children.[3,5,6] In addition to the somatic symptoms, with the onset of fever patients may suffer an acute and progressive loss in their ability to perform their daily functions such as schooling, work and interpersonal relations.[7] Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence. During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve without going through the critical phase. Instead of improving with the subsidence of high fever, patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage.[3]

The warning signs mark the beginning of the critical phase and usually precede the manifestations of shock and appear towards the end of the febrile phase. These patients become worse around the time of defervescence, when the temperature drops to 37.5-38°C or less and remains below this level, usually on days 3-8 of illness. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. The patient becomes increasingly lethargic but usually remains mentally alert. These symptoms may persist into the shock stage. Weakness, dizziness or postural hypotension occur during the shock state. Spontaneous mucosal bleeding or bleeding at previous venipuncture sites are important hemorrhagic manifestations. Increasing liver size and a tender liver is frequently observed along with mean aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation and prolonged prothrombin time. Clinical fluid accumulation may only be detected if plasma loss is significant or after treatment with intravenous fluids. A rapid and progressive decrease in platelet count and a rising hematocrit above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (≤5000 cells/ mm3).[8,9] Splenomegaly is seen in almost 10% of dengue infants, seven times more frequently than in older children.[2,6] As the patient survives the 24-48-hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48-72 hours. General wellbeing improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes, and diuresis ensues. Some patients have a confluent erythematous or petechial rash with small areas of normal skin, described as "islets of white in the sea of red". Some may experience generalized pruritus.The hematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count. Respiratory distress from massive pleural effusion and ascites, pulmonary edema or congestive heart failure will occur during the critical and/or recovery phases if excessive intravenous fluids have been administered. Cases of dengue with warning signs will usually recover with intravenous rehydration. Some cases will deteriorate to severe dengue.[10]

The burden of severe dengue lies predominantly in infants 4-9 months of age.[1,4,6] A case of severe dengue[11] is defined as a suspected dengue patient with one or more of the following:(i) severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress; (ii) severe bleeding; (iii) severe organ impairment. Patients with severe plasma leakage may not have

shock if prompt fluid replacement has been carried out. Instead, they manifest with respiratory distress due to massive pleural effusion and ascites, which can also be exacerbated by unguided intravenous fluid therapy.[11] Shock occurs when a critical volume of plasma is lost through leakage and it often preceded by warning signs. The body temperature may be subnormal when shock occurs. However, some infants may still have fever at the onset of shock; in these patients a differential diagnosis of septic shock should be kept in mind.[6] With prolonged shock, the consequent organ hypoperfusion results in multiple organ dysfunction, metabolic acidosis and disseminated intravascular coagulation. The degree of increase above the baseline hematocrit often reflects the severity of plasma leakage. Hemoconcentration, manifested by an increase in hematocrit of ≥20% above the baseline hematocrit may be seen.[6,12]

Dengue shock syndrome (DSS) is a form of hypovolemic shock and results from continued vascular permeability and plasma leakage. This usually takes place around defervescence, i.e., on days 4-5 of illness (range of days 3-8), and is often preceded by warning signs. From this point onwards, patients who do not receive prompt intravenous fluid therapy progress rapidly to a state of shock. Dengue shock presents as a physiologic continuum, progressing from asymptomatic capillary leakage to compensated shock to hypotensive shock and ultimately to cardiac arrest. Tachycardia (without fever during defervescence), is an early cardiac response to hypovolemia. During the initial stage of shock, the compensatory mechanism that maintains a normal systolic BP produces tachycardia, quiet tachypnoea (tachypnoea without increased effort), and peripheral vasoconstriction with reduced skin perfusion (manifested as cold extremities and delayed capillary refill time of > 2 seconds and weak volume peripheral pulses).[13] As peripheral vascular resistance increases, the diastolic pressure rises towards the systolic pressure and the pulse pressure (the difference between the systolic and diastolic pressures) narrows. The patient is considered to have compensated shock if the systolic pressure is maintained at the normal or slightly above normal range but the pulse pressure is ≤20 mmHg in children (e.g., 100/85 mmHg) or if they have signs of poor capillary perfusion (cold extremities, delayed capillary refill, or tachycardia). Patients who have dengue and are in compensated shock often remain conscious and lucid. The inexperienced physician may measure a normal systolic pressure and a normal pulse oximetry (SpO_2 95-100%) in a conscious patient and underestimate the critical state of the patient. Worsening hypovolemic shock manifests as increasing tachycardia and peripheral vasoconstriction. Not only are the extremities cold and cyanosed but the limbs become mottled, cold and clammy. By this stage the breathing becomes more rapid and increases in depth " a compensation for the metabolic acidosis (Kussmaul's breathing). Finally, there is decompensation, both systolic and diastolic BPs disappear suddenly and dramatically, and the patient is said to have hypotensive or decompensated shock. At this time the peripheral pulses disappear while the central pulse (femoral) will be weak. Hypotension develops when physiologic attempts to maintain systolic BP and perfusion are no longer effective. One key clinical sign of this deterioration is a change in mental state as brain perfusion declines. The patient becomes restless, confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy. On the other hand, children and young adults have been known to have a clear mental status even in profound shock. The failure of infants and children to recognize, focus or make eye contact with parents may be an early ominous sign of cortical hypoperfusion, as is the failure to respond to painful stimuli such as venipuncture. Parents may be the first to recognize these signs but they may be unable to describe them, other than to say something is wrong. Hypotension is a late finding and signals an imminent total cardiorespiratory collapse. Prolonged hypotensive shock and hypoxia lead to severe metabolic acidosis, multiple organ failure and an extremely difficult clinical course. It may take a few hours for patients to progress from warning signs to compensated shock and another few hours for compensated shock to progress to hypotensive shock, but only minutes for hypotensive shock to progress to cardio-respiratory collapse and cardiac arrest. Hypotension is associated with prolonged shock which is often complicated by major bleeding.[14]

With profound and/or prolonged shock, hypoperfusion results in metabolic acidosis, progressive organ impairment, and disseminated intravascular coagulation. This in turn can lead to severe hemorrhage causing the hematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase as a stress response in patients with severe bleeding. In addition, severe organ involvement may develop such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding, without obvious plasma leakage or shock**.** Patients with severe dengue have varying degrees of coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation. Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen, or corticosteroids have been taken. Bleeding may occur in patients with previous peptic or duodenal ulcers.[15,16]

Most deaths from dengue occur in patients with profound and prolonged shock resulting from plasma leakage and complicated by bleeding and/or fluid overload.[17] Acute liver and renal failure and encephalopathy may be present in severe shock; these have been described even in the absence of severe plasma leakage or shock.[18-20] Cardiomyopathy and encephalitis have also been reported in a few dengue case series.[21,22]

Vertical transmission and neonatal dengue

Pregnant women with dengue virus infection can transmit the virus to their fetus and vertical dengue transmission has been described. In the vertical transmission cases, some newborns may be asymptomatic. Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly, to severe illness with clinical sepsis, pleural effusion, gastric bleeding, circulatory failure, massive intracerebral hemorrhage and death.[23-28] Clinical presentation in the newborn infant does not appear to be associated with maternal disease severity or dengue immune status, or mode of delivery.[29] However, timing of maternal infection may be important; peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn. A review of 17 mother-infant pairs with dengue infection found that the time intervals between the mothers' onset of fever and that of their neonates, were 5-13 days (median, 7 days); fever in neonates occurred at 1-11 days of life (median, 4 days), and the duration of fever in neonates was 1-5 days (median, 3 days)**.** Antibodies to the dengue virus in the dengue infected mother can cross the placenta and can cause severe dengue in newborn infants.[30]

Diagnostics issues of dengue

The objectives of dengue laboratory diagnosis are (i) to confirm the clinical diagnosis and (ii) to provide information for epidemiological surveillance. Laboratory diagnosis is not necessary for clinical management except in atypical cases or when carrying out differential diagnosis with other infectious diseases. Laboratory diagnosis of dengue is made by detecting the virus and/or any of its components (infective virus, virus genome, dengue NS1 Ag) or by investigating the serological responses present after infection (seroconversion of IgM or IgG from negative to positive IgM/IgG or four-fold increase in the specific antibody titre) in paired sera. Additional tests should be considered in patients with co-morbidities and severe disease as indicated. These may include tests of liver function, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, electrocardiogram (ECG) and urine specific gravity.[31-36]

A full blood count should be done at the first visit (it may be normal); and this should be repeated daily until the critical phase is over. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue. The hematocrit in the early febrile phase could be used as the patient's own baseline. Decreasing white blood cell and platelet counts make the diagnosis of dengue very likely. Leukopenia usually precedes the onset of the critical phase and has been associated with severe disease. A rapid decrease in platelet count, concomitant with a rising hematocrit compared to

the baseline, is suggestive of progress to the plasma leakage/critical phase of the disease. These changes are usually preceded by leukopenia (<5000 cells/ mm3). In the absence of the patient's baseline, age-specific population hematocrit levels could be used as a surrogate during the critical phase. A rising hematocrit precedes changes in blood pressure (BP) and pulse volume.[37-39]

Management of Dengue

On the basis of evaluations of the history, physical examination and/or full blood count and hematocrit, clinicians should determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and hemodynamic state of the patient, and whether the patient requires admission. Depending on the clinical manifestations and other circumstances, patients may either be sent home (Group A); be referred for in-hospital management (Group B); or require emergency treatment (Group C).[31, 34]

Management of Group A patients[33, 41]

Group A patients who may be sent home as they are able to tolerate adequate volumes of oral fluids, pass urine at least once every six hours and do not have any of the warning signs (particularly when fever subsides). The key to the success of ambulatory (out patient) management is to give clear, definitive advice on the care that the patient needs to receive at home: i.e. bed rest and frequent oral fluids. Patients with ≥3 days of illness should be reviewed daily for disease progression (indicated by decreasing white blood cell and platelet counts and increasing hematocrit, defervescence and warning signs) until they are out of the critical period. They should be advised to return to the nearest hospital immediately if they develop any of the warning signs.

Encourage oral intake to replace fluid loss from fever and vomiting. Small amounts of oral fluids should be given frequently for those with nausea and anorexia. Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance. Commercial carbonated drinks that exceed the isotonic level (5% sugar) should be avoided. They may exacerbate hyperglycemia related to physiological stress from dengue and diabetes mellitus. Sufficient oral fluid intake should result in a urinary frequency of at least 4 to 6 times per day. Paracetamol for high fever@10 mg/kg/dose, not more than 3-4 times in 24 hours. Sponge with tepid water if the patient still has a high fever. Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) or intramuscular injections, as these aggravate gastritis or bleeding. Patient should be brought to hospital immediately if any of the following occur: no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffeeground vomiting), shortness of breath, not passing urine for more than 4-6 hours. Admission during the febrile period should be reserved for those who are unable to manage adequate oral hydration at home, infants, and those with co-existing conditions. Ambulatory patients should be monitored daily for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding and complete blood counts.

Management of Group B patients[42-44]

Group B patients are those who should be admitted for in-hospital management for close observation as they approach the critical phase. These include patients with warning signs, those with co-existing conditions that may make dengue or its management more complicated (such as, extreme age, obesity, diabetes mellitus, hypertension, heart failure, renal failure, chronic hemolytic diseases such as sickle-cell disease and autoimmune diseases), and those with certain social circumstances (such as living alone, or living far from a health facility without reliable means of transport). Rapid fluid replacement in patients with warning signs is the key to prevent progression to the shock state. If the patient has dengue with warning signs or signs of dehydration, judicious volume replacement by intravenous fluid therapy from this early stage may modify the course and the severity of disease.

The action plan should be as follows:

Intravenous fluids are usually needed for only 24-48 hours.

Use the ideal body weight for calculation of fluid infusion for obese and overweight patients.

Obtain a reference hematocrit before intravenous fluid therapy begins.

Give only isotonic solutions such as 0.9% saline, Ringer's lactate or Hartmann's solution.

Start with 5-7 ml/kg/hour for 1-2 hours, then reduce to 3-5 ml/kg/hour for 2-4 hours, and then reduce to 2-3 ml/kg/hour or less according to the clinical response

Reassess the clinical status and repeat the hematocrit. If the hematocrit remains the same or rises only minimally, continue at the same rate (2-3 ml/kg/hour) for another 2-4 hours.

If the vital signs are worsening and the hematocrit is rising rapidly, increase the rate to 5-10 ml/kg/hour for 1-2 hours.

Reassess the clinical status, repeat the hematocrit and review fluid infusion rates accordingly.

Give the minimum intravenous fluid volume required to maintain good perfusion and a urine output of about 0.5 ml/kg/hour. Patients may be able to take oral fluids after a few hours of intravenous fluid therapy.

Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase which is indicated by urine output and/or oral fluid intake improving, or the hematocrit decreasing below the baseline value in a stable patient.

Patients with warning signs should be monitored until the period of risk is over.

A detailed fluid balance should be maintained.

Parameters that should be monitored include

vital signs and peripheral perfusion (1-4 hourly until the patient is out of the critical phase),

urine output (4-6 hourly),

hematocrit (before and after fluid replacement, then 6-12 hourly), blood glucose and

other organ functions (such as renal profile, liver profile, coagulation profile).

If the patient has dengue with co-existing conditions but without warning signs, the action plan should be as follows:

Encourage oral fluids.

If not tolerated, start intravenous fluid therapy of 0.9% saline or Ringer's lactate with or without glucose at the appropriate maintenance rate.

Management of Group C patients[45-53]

Group C patients are those with severe dengue who require emergency treatment because they are in the critical phase of the disease and have:

Severe plasma leakage leading to dengue shock and/or fluid accumulation with, respiratory distress

Severe hemorrhages.

Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).

Judicious intravenous fluid resuscitation is the essential and usually sole intervention required. The crystalloid solution should be isotonic and the volume just sufficient to maintain an effective circulation during the period of plasma leakage. Plasma losses should be replaced immediately and rapidly with isotonic crystalloid solution: in the case of hypotensive shock, colloid solution is preferred. If possible, obtain hematocrit levels before and after fluid resuscitation. Continue replacement of further plasma losses to maintain effective circulation for 24-48 hours. For overweight or obese patients, the ideal body weight should be used for calculating fluid infusion rates. Blood transfusion should be given only in cases with established severe bleeding, or suspected severe bleeding in combination with otherwise unexplained hypotension. Fluid resuscitation must be clearly separated from simple fluid administration. This is a strategy in which larger volumes of fluids (e.g., 10-20 ml/kg boluses) are administered for a limited period of time under close supervision, to evaluate the patient's response and to avoid the development of pulmonary edema. These fluids should not contain glucose. The degree of intravascular volume deficit in dengue shock varies. Input is typically much greater than output, and the input/output ratio is of no help in judging fluid resuscitation needs during this period.

The goals of fluid resuscitation include

Improving central and peripheral circulation - i.e. decreasing tachycardia, improving BP and pulse volume, warm and pink extremities, a capillary refill time <2 seconds.

Improving end-organ perfusion - i.e. achieving a stable conscious level (more alert or less restless), and urine output ≥0.5 ml/kg/hour or decreasing metabolic acidosis.

The action plan for treating patients with compensated shock is as follows:

Obtain a reference hematocrit before starting intravenous fluid therapy.

Start intravenous fluid resuscitation with isotonic crystalloid solutions at 10-20 ml/kg/hour over one hour.

Then reassess the patient's condition (vital signs, capillary refill time, hematocrit, urine output).

If the patient's condition improves, intravenous fluids should be gradually reduced to 5-7 ml/kg/hour for 1-2 hours; then 3-5 ml/kg/hour for 2-4 hours and finally 2-3 ml/kg/hour which can be maintained up to 24-48 hours.

Consider reducing intravenous fluid earlier if oral fluid intake improves.

The total duration of intravenous fluid therapy should not exceed 48 hours.

If vital signs are still unstable (i.e. shock persists), check the hematocrit after the first bolus:

If the hematocrit increases or is still high, change to colloid solution at 10-20 ml/kg/hour.

After the initial dose, reduce the rate to 10 ml/kg/hour for 1 hour, then reduce to 7 ml/kg/hour.

Change to crystalloid when the patient's condition improves.

If the hematocrit decreases compared to the initial reference hematocrit, and the patient still has unstable vital signs, this may indicate bleeding and following steps to be taken:

Look for severe bleeding.

Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding.

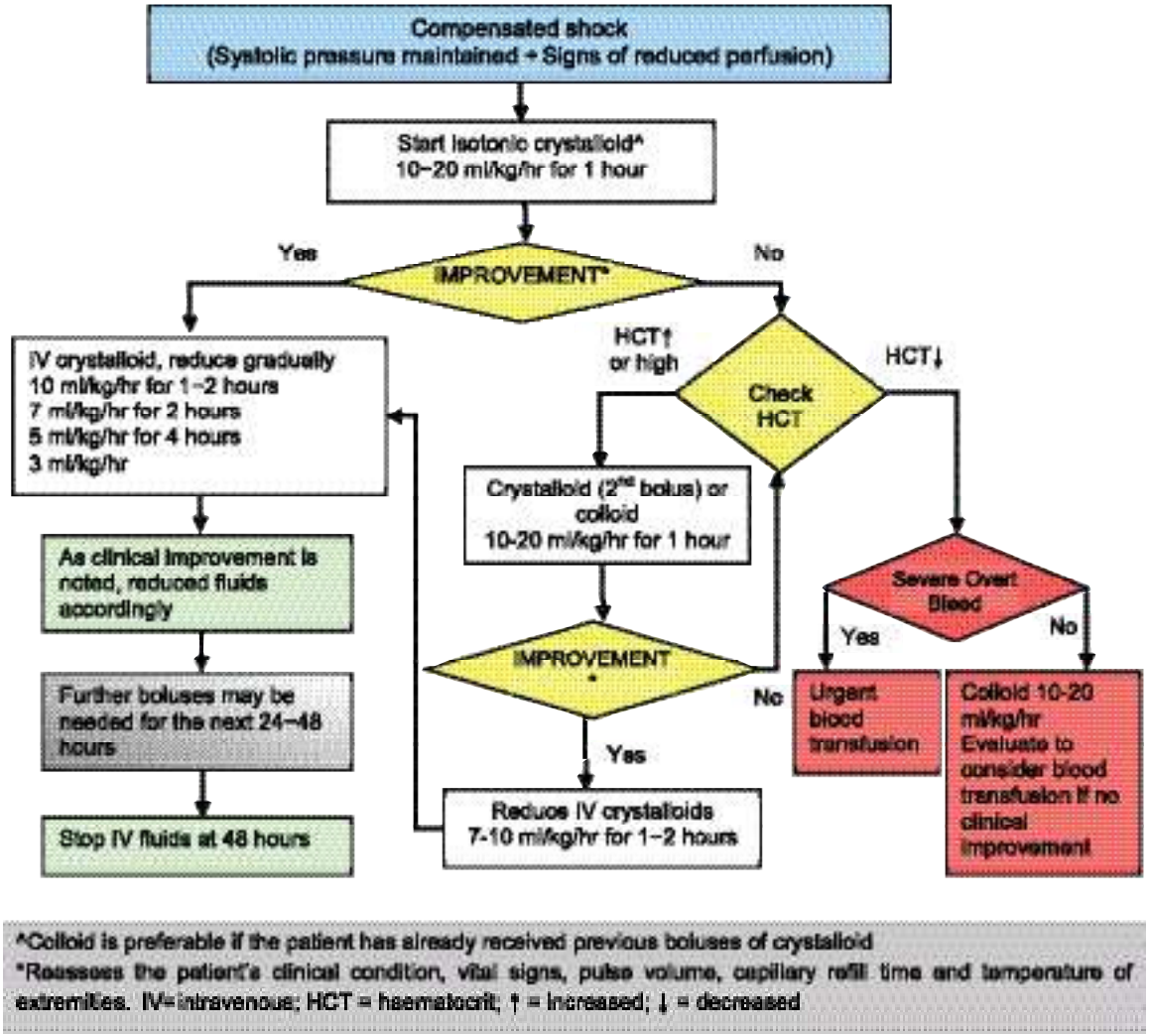

Fig 1 *Algorithm for fluid management of compensated shock in infants and children*[54]

If there is no bleeding, give a bolus of 10-20 ml/kg of colloid over 1 hour, repeat Mclinical assessment and determine the hematocrit level.

Further boluses of crystalloid or colloidal solutions may need to be given during the next 24-48 hours.

Clinicians should remember that a child with a low baseline hematocrit of 30%, presenting with dengue shock and a hematocrit of 40%, is relatively more hemo-concentrated than another child with a baseline value of 42% and a hematocrit of 50% at the time of shock. In patients with profound, recurrent or prolonged shock, a central venous catheter may be inserted through the antecubital basilic vein or internal jugular vein to guide intravenous fluid therapy. Intravenous fluids must be administered with special care to avoid fluid overload. Fluids account for a greater proportion of body weight in infants than children and minimum daily requirements are correspondingly higher. Infants have less intracellular fluid reserve than older children and adults. Moreover, capillary beds are intrinsically more permeable than those of older children or adults. Both early cardiovascular compromise and significant fluid overload are more likely if capillary leaks occur in these circumstances.[53]

Treatment of profound shock (hypotensive; undetectable pulse and BP)[45-47]

All patients with hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is outlined below:

Initiate intravenous fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus given over 15-30 minutes to bring the patient out of shock as quickly as possible.

Colloids may be the preferred choice if the BP has to be restored urgently, i.e. in those with pulse pressure less than 10 mmHg.

Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock.

Intra-osseous route should be attempted if peripheral venous access cannot be obtained.

If the patient's condition improves:

Give colloid infusion of 10 ml/kg/hour for 1 hour.

Then continue with crystalloid 10 ml/kg/hour for 1 hour, then to 7 ml/kg/hour for 2 hours, to 5 ml/kg/hour for 4 hours and to 3 ml/kg/hour, which can be maintained for up to 24-48 hours.

Consider reducing intravenous fluid earlier if oral fluid intake and urine output improve.

The total duration of intravenous fluid therapy should not exceed 48 hours. If vital signs are still unstable (i.e. shock persists), review the hematocrit obtained before the first bolus.

If the hematocrit is normal or low (<30-35% in infants, <35-40% in children), this may indicate bleeding.

Look for severe bleeding.

Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding.

If there is no bleeding, give a second bolus of 10-20 ml/kg of colloid over 30 minutes to 1 hour, repeat clinical assessment and hematocrit level to consider blood transfusion.

If the hematocrit is high compared to the baseline value (if not available, use population baseline), change intravenous fluids to colloid solutions at 10-20 ml/kg as a second bolus over 30 minutes to 1 hour.

After the second bolus, reassess the patient.

If the condition improves, reduce the rate to 7-10 ml/kg/hour for 1-2 hours,then change back to crystalloid solution and reduce the rate of infusion as mentioned above.

If the condition is still unstable, repeat the hematocrit after the second bolus:

If the hematocrit decreases compared to the previous value (<35% in infants, <40% in children), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible.

If the hematocrit increases compared to the previous value or remains very high (>50%), continue colloid solutions at 10-20 ml/kg as a third bolus over 1 hour.

After this dose, reduce the rate to 7-10 ml/kg/hour for 1-2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above when the patient's condition improves.

If the condition is still unstable, repeat the hematocrit after the third bolus:

Further boluses of fluids may need to be given during the next 24 hours.

The rate and volume of each bolus infusion should be titrated to the clinical response.

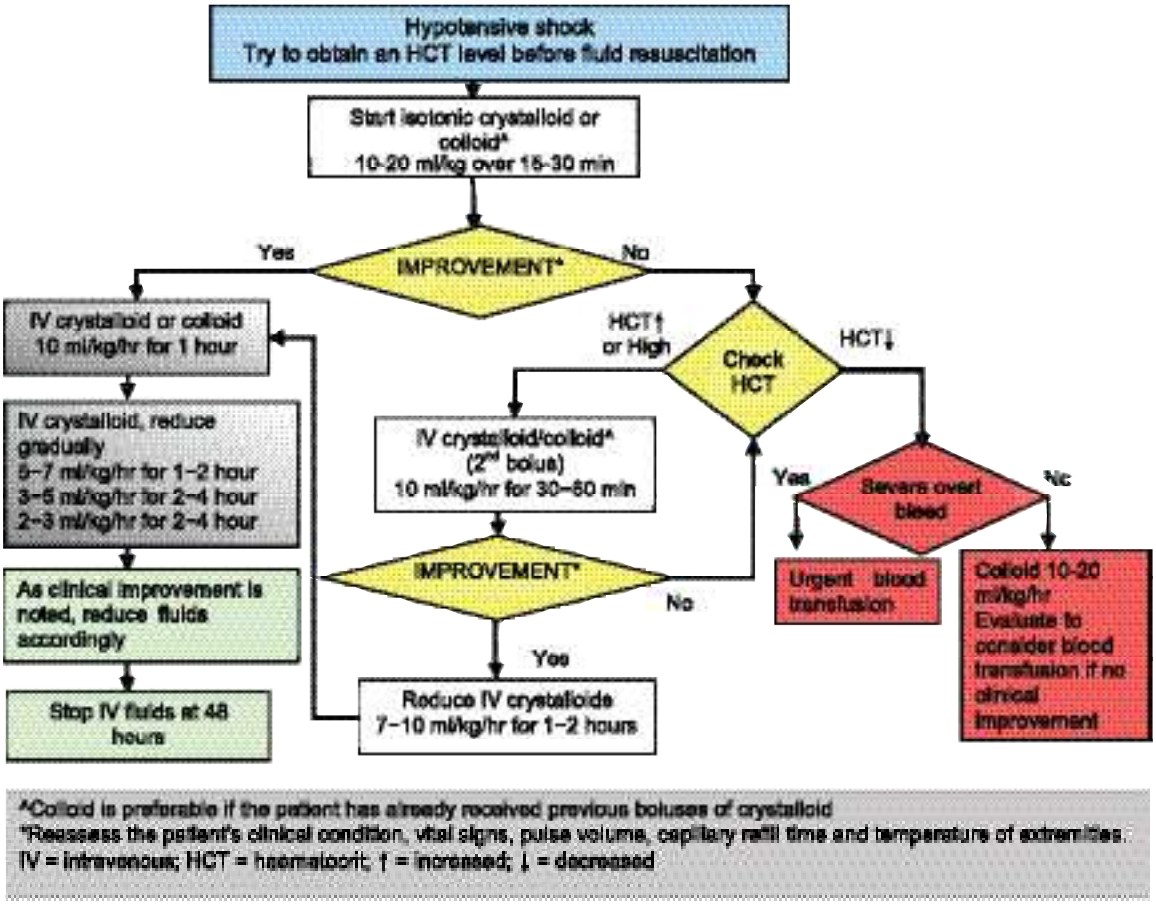

Fig 2 *Algorithm for fluid management in hypotensive shock-infants, children.*[54]

Monitoring patients with dengue shock[6,31,39]

Patients with dengue shock should be monitored frequently until the danger period is over. A detailed fluid balance of all inputs and outputs should be maintained. Parameters to be monitored include: alertness and comfort levels, vital signs and peripheral perfusion (every 15-30 minutes until the patient is out of shock then 1-2 hourly). In general, the higher the fluid infusion rate, the more frequently the patient should be monitored and reviewed in order to avoid fluid overload while ensuring adequate volume replacement. If previously not detectable, pleural effusion and ascites should be detectable after fluid boluses. Monitor their effects on breathing. Blood gas and/ or lactate analysis to be done to monitor changes in the circulation during fluid replacement. The advantage of an arterial line is that in shock states, estimation of BP using a cuff is commonly inaccurate. The use of an indwelling arterial catheter allows for continuous and reproducible BP measurements and frequent blood sampling to base decisions regarding therapy. Monitoring of ECG and pulse oximetry should be available. Urine output should be checked regularly (each hour until the patient is out of shock, then every 1-2 hours). A continuous bladder catheter enables close monitoring of urine output. The first urine volume after bladder catheterization should be discarded because the duration in the bladder is unknown. Thereafter, an acceptable urine output would be about 0.5 ml/kg/hour. Hematocrit should be monitored (before and after fluid boluses until stable then 4-6 hourly). In addition, there should be monitoring of: blood glucose (before fluid resuscitation and repeat as indicated); arterial or venous or capillary blood gases; lactate; and other organ functions (such as renal profile, liver profile, coagulation profile) before resuscitation and as indicated.

Recognizing when to decrease or stop intravenous fluids as part of the treatment of severe dengue is crucial to prevent fluid overload. When any of the

following signs are present, intravenous fluids should be reduced or discontinued:

- signs of cessation of plasma leakage
- stable BP, pulse and peripheral perfusion
- hematocrit decreases in the presence of a good pulse volume
- a pyrexia (without the use of antipyretics) for more than 24–48 hours
- resolving bowel/abdominal symptoms
- improving urine output.

Continuing intravenous fluid therapy beyond the 48 hours of the critical phase will put the patient at risk of pulmonary edema and other complications such as thrombophlebitis.

Hemorrhagic complications [49-51]

Mucosal bleeding may occur in any patient with dengue but if the patient remains stable with fluid resuscitation/replacement, this should be considered as a minor issue. The bleeding usually improves rapidly during the recovery phase. In patients with profound thrombocytopenia, ensure strict bed rest and protection from trauma. Do not give intramuscular injections. No evidence exists that prophylactic platelet transfusions are beneficial in hemodynamically stable patients. If major bleeding occurs it is usually from the gastrointestinal tract, and/or hypermenorrhea. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of severe bleeding are those who:

- have profound/prolonged/refractory shock;
- have hypotensive shock and multi-organ failure or severe and persistent metabolic acidosis;
- are given non-steroidal anti-inflammatory agents;
- have pre-existing peptic ulcer disease;
- are on anticoagulant therapy;
- have any form of trauma, including intramuscular injection.

Patients with hemolytic conditions are at risk of acute hemolysis with hemoglobinuria and may require blood transfusion. Severe and occult bleeding is the most common cause of profound/refractory/ prolonged shock, but can be difficult to recognize. This is because bleeding usually occurs after a period of prolonged shock in dengue.

The preceding plasma leakage causes the hematocrit to rise to very high levels. When bleeding occurs, the hematocrit will then drop from this high level and as a result hematocrit levels may not be as low as in the absence of plasma leakage. Even in severe bleeding, the hematocrit remains above the baseline and only drops to normal or low levels after several fluid boluses.

Severe bleeding should be recognized in the following situations:

- persistent and/or severe overt bleeding in the presence of unstable hemodynamic status, regardless of the hematocrit level;
- a decrease in hematocrit after boluses of fluid resuscitation together with unstable hemodynamic status;
- refractory shock that fails to respond to consecutive fluid resuscitation of 40-60 ml/kg;
- hypotensive shock with inappropriately low/ normal hematocrit;
- persistent or worsening metabolic acidosis in patients with a well-maintained systolic BP, especially in those with severe abdominal tenderness and distension.

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized. However, blood transfusion must be given with care because of the risk of fluid overload. Do not wait for the hematocrit to drop too low before deciding on blood transfusion.

The action plan for the treatment of hemorrhagic complications is as follows:

- If possible, attempts should be made to stop bleeding if the source of bleeding is identified e.g., severe epistaxis may be controlled by nasal adrenaline packing.
- If blood loss can be quantified, this should be replaced. If not, give aliquots of 5-10 ml/kg of fresh packed red cells or 10-20 ml/kg of fresh or fairly fresh whole blood (FWB) at an appropriate rate and observe the clinical response.

It is important that fresh whole blood or fresh red cells are given. Oxygen delivery at tissue level is

optimal with high levels of 2,3 diphosphoglycerate (2,3 DPG). Stored erythrocytes lose 2,3 DPG, low levels of which impede the oxygen-releasing capacity of hemoglobin, resulting in functional tissue hypoxia. A good clinical response includes improving hemodynamic status and acid-base balance. Consider repeating the blood transfusion if there is further overt blood loss or no appropriate rise in hematocrit after blood transfusion in an unstable patient. There is no evidence that supports the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding in dengue.

Observational studies show that transfusions of platelet concentrate and fresh frozen plasma in dengue were not able to sustain the platelet counts and coagulation profile. However, in the case of massive bleeding, they often exacerbate the fluid overload. Nevertheless, in certain situations such as obstetrical deliveries or other surgeries, transfusions of platelet concentrate with or without fresh frozen plasma should be considered in anticipation of severe bleeding. In gastrointestinal bleeding, H-2 antagonist and proton pump inhibitors have been used. Great care should be taken when inserting a nasogastric tube or bladder catheters which may cause severe hemorrhage. It is essential to remember that blood transfusion is only indicated in dengue patients with severe bleeding. Unnecessary blood transfusions cause the hematocrit to rise sharply, thus giving a false impression of hemoconcentration and severe plasma leakage leading to unwarranted fluid therapy.

Glucose control[53]

Hyperglycemia and hypoglycemia may occur in the same patient at different times during the critical phase through the following mechanisms.

Hyperglycemia is the result of a neuroendocrine stress response, occurs in diabetes mellitus and results from large quantities of glucose-fluids administered in resuscitation.

Starvation in young children, diabetic patients on oral hypoglycemic agents and severe liver involvement can cause hypoglycemia.

Hyperglycemia causes osmotic diuresis which worsens the hypovolemic shock. Osmotic diuresis also gives a false impression of a "good urine output". Hyperglycemia is associated with increased morbidity and mortality in critically ill patients. Hypoglycemia may cause seizures, mental confusion and unexplained tachycardia. Most cases of hyperglycemia will resolve with appropriate (isotonic, non-glucose) and adequate fluid resuscitation. When the hemodynamic state improves, normal blood glucose levels should be maintained with a glucose-isotonic fluid, such as dextrose 5%-0.9% sodium chloride, at 1-3 ml/kg/hour. In infants and children, blood glucose should be monitored frequently during the critical phase and into the recovery phase if the oral intake is still reduced. However, if hyperglycemia is persistent, undiagnosed diabetes mellitus or impaired glucose tolerance should be considered and intravenous insulin therapy initiated. Subcutaneous insulin should be avoided as absorption is unreliable in the shock state. Hypoglycemia should be treated as an emergency with 0.1-0.5 g/kg of glucose, rather than with a glucose-containing resuscitation fluid. Frequent glucose monitoring should be carried out and euglycemia should then be maintained with a fixed rate of glucose-isotonic solution and enteral feeding if possible.

Electrolyte and acid-base imbalances and Metabolic acidosis[6,33,52,53,55]

Hyponatremia is a common observation in severe dengue; the underlying mechanism is not fully understood. It could be related to gastrointestinal losses through vomiting and diarrhea or the use of hypotonic solutions for resuscitation and correction of dehydration. The use of isotonic solutions for resuscitation will prevent and correct this condition. Hyperkaliemia is observed in association with severe metabolic acidosis or acute renal injury. Appropriate volume resuscitation will reverse the metabolic acidosis and the associated hyperkaliemia. Life-threatening hyperkaliemia, in the setting of acute renal failure should be managed with Resonium A and infusions of calcium gluconate and/or insulin-dextrose. Renal support therapy may have to be considered. Hypokalemia is often associated with gastrointestinal fluid losses and the stress-induced hypercortisol state; it is usually encountered towards the later part of the critical phase. It should be corrected with potassium supplements in the parenteral fluids. Serum calcium levels should be monitored and corrected when large quantities of blood have been transfused or if sodium bicarbonate has been used. Compensated metabolic acidosis is an early sign of hypovolemia and shock. Lactic

acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in dengue shock. Correction of shock and adequate fluid replacement will correct the metabolic acidosis. If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding and check the hematocrit. Transfuse fresh whole blood or fresh packed red cells urgently. Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH ≥7.10. Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO_2 and a decrease in serum ionized calcium.

Complications and management [56,57,58]

Many of the complications seen in dengue are preventable if clinicians are alert to the physiological problems of the three different phases. When hypovolemic shock is adequately managed, patients appear to "sail out" of the critical phase with mere parenteral fluids. But that belies the effort that has been invested in the monitoring and careful titration of intravenous fluid therapy, guided by frequent clinical and hematocrit evaluation.

Causes of complications in dengue include:

missed diagnosis at the frontline;

inadequate monitoring and misinterpretation of vital signs;

inadequate monitoring of fluid intake and urine output;

late recognition of shock leading to profound and/or prolonged shock;

late recognition of severe bleeding;

too much or too little intravenous fluids i.e. not following/understanding the treatment guidelines;

careless attitude towards aseptic techniques.

Outcome of complications in dengue lead to a life-threatening situation characterized by one or a combination of the following:

prolonged and/or profound shock;

severe bleeding with severe disseminated intravascular coagulopathy;

fluid overload;

respiratory distress and failure;

multi-organ dysfunction of liver, kidneys and neurological system;

irreversible shock and death.

Prolonged/profound shock [45, 48]

Prolonged/profound shock is characterized by severe metabolic acidosis ± multi-organ failure. An urgent hematocrit will guide further fluid therapy. If the analysis indicates severe bleeding and matched fresh whole blood (FWB) is available, blood transfusion should be started as soon as possible. However, the following applies if blood is not available:

If the patient has received <2 boluses of resuscitation fluid, a colloid solution of 10-20 ml/kg over 15-30 minutes should be used.

If the patient has received more than 2 boluses of resuscitation fluid, fluids should be switched to a colloid solution of 10-20 ml/kg over 30 minutes for hypotensive shock, and over 1-2 hours for compensated shock.

If severe overt bleeding is apparent (hematemesis, melaena or hypermenorrhea), the colloid bolus should be followed urgently by transfusion of 10-20 ml/kg fresh whole blood (FWB), regardless of the hematocrit level. After transfusion of FWB, some degree of hemodynamic stability is usually achieved together with improvement of metabolic acidosis. Further colloid infusions may be necessary if the hematocrit rises again. A repeat transfusion of FWB will be required if bleeding continues. Bleeding will usually slow down towards the end of the critical phase. There is no evidence that transfusion of platelet concentrates or the disseminated intravascular coagulopathy (DIVC) regime is effective. This practice will contribute to third space losses and expose the patient to multiple blood donors. Prolonged stay in the intensive care unit (ICU) is also expected. If no overt bleeding is seen after the colloid bolus, a repeat clinical evaluation and hematocrit level should be performed. A decrease in hematocrit together with clinical improvement means there is restoration of circulatory volume with colloids. However, a decrease in hematocrit, not accompanied by clinical improvement should prompt the suspicion of severe internal/occult bleeding.

Acute respiratory distress and failure [59]

Causes of acute respiratory distress and failure are:

severe metabolic acidosis from severe shock;

fluid overload - large pleural effusions and ascites

acute pulmonary edema;

acute respiratory distress syndrome (ARDS);

Severe metabolic acidosis from severe shock[56]
Kussmaul's breathing will be observed in addition to tachycardia and other signs of shock. Tracheal intubation should not be the first treatment. Instead, these patients should be given treatment as for hypotension shock i.e., prompt resuscitation with fluid boluses after sampling blood for hematocrit determination. After fluid resuscitation, evaluate to ensure that the respiratory effort has subsided and that other parameters of adequate circulation are present. Otherwise the hematocrit needs repeating and the question of severe bleeding needs to be considered.

Fluid overload[15]
Some degree of fluid overload is inevitable in patients with severe plasma leakage. The skill is in giving them just enough intravenous fluid to maintain adequate perfusion to keep them alive, while waiting it out until the plasma leakage process spontaneously reverses, and at the same time avoiding excessive fluid overload. Recognizing when to decrease or stop intravenous fluids is crucial to preventing fluid overload.

Causes of excessive fluid overload are:

excessive and/or too rapid intravenous fluids during the critical phase;

incorrect use of hypotonic crystalloid solutions e.g. 0.45% sodium chloride solutions;

inappropriate use of large volumes of intravenous fluids in patients with unrecognized severe bleeding;

inappropriate transfusion of fresh-frozen plasma, platelet concentrates and cryoprecipitates;

prolonged intravenous fluid therapy, i.e., continuation of intravenous fluids after plasma leakage has resolved (>48 hours from the start of plasma leakage);

co-morbid conditions such as congenital or ischemic heart disease, heart failure, chronic lung and renal diseases.

Early clinical features of fluid overload are:

rapid breathing;

suprasternal in-drawing and intercostal recession;

respiratory distress, difficulty in breathing;

wheezing, crepitations;

large pleural effusions;

tense ascites, persistent abdominal discomfort/ pain/tenderness (this should not be interpreted as warning signs of shock);

increased jugular venous pressure (JVP).

Late clinical features are:

pulmonary edema (cough with pink or frothy sputum, wheezing and crepitations, cyanosis) - this may be mistaken as pulmonary hemorrhage;

irreversible shock (heart failure, often in combination with ongoing hypovolemia).

Investigations to be done:

blood gas and lactate analysis;

the chest X-ray which shows cardiomegaly, pleural effusion, upward displacement of the diaphragm by the ascites and varying degrees of "bat's wings" appearance ± Kerley B lines, suggestive of fluid overload and pulmonary edema;

ECG to exclude ischemic changes and arrhythmia;

echocardiogram;

cardiac enzymes.

Action plan:

Oxygen therapy should be given immediately

The further action plan for the treatment of fluid overload is dependent on the patient's hemodynamic stability, intravascular volume status and the timing of this event with respect to the timeline of the critical phase.

Strong pulses with warm extremities are positive indications to stop (≤48 hours of plasma leakage) or reduce (if ≤48 hours of plasma leakage) intravenous fluids.

If the patient has difficulty in breathing because of excessive third space fluid accumulation, it is all the more imperative to stop fluid therapy.

Small doses of furosemide 0.1-0.5 mg/kg/dose twice or thrice daily or a continuous infusion of furosemide 0.1 mg/kg/hour may be indicated for patients who are out of the critical phase.

Monitor serum potassium and correct the ensuing hypokalemia.

Watch out for hypertension and treat during the recovery phase otherwise hypertensive encephalopathy may occur.

Respiratory support may be indicated depending on the severity of respiratory distress.

Pulmonary edema and acute respiratory distress syndrome (ARDS)[45,47,48]

These two conditions will cause life-threatening hypoxemia. Pulmonary edema is more common than ARDS. Both are aggravated by rapid infusion of large volumes of fluid during the critical phase. The goals of therapy are to optimize oxygenation and ventilation with respiratory support and stabilize the hemodynamic situation.

Apart from increasing the fractional inspired oxygen, positive end-expiratory pressure (PEEP) is essential to maintain adequate oxygenation and reduce the work of breathing.

If the patient is out of the plasma leakage phase and has stable hemodynamics, intravenous fluid therapy should be discontinued and diuretic therapy can be commenced cautiously.

Indications for mechanical ventilation include:

patients who have shock and are restless, combative or confused;

respiratory failure from acute pulmonary edema/ARDS ± shock;

patients who fail to respond to non-invasive ventilation.

Co-infections and nosocomial infections[14, 35]

Co-infections with gram-negative bacteria have been reported in patients with diabetes mellitus and renal failure. Other tropical diseases such as leptospirosis, typhus, malaria, chikungunya and enteric fever may occur concomitantly. A high index of suspicion is necessary to recognize this, especially in those with atypical presentations such as prolonged fever, pulmonary hemorrhage, unexplained renal failure or liver failure in the absence of shock. It is not uncommon for patients to acquire a nosocomial infection, especially those with severe dengue and when intravenous therapy has been prolonged. Careful attention to aseptic techniques is necessary in procuring and accessing intravascular devices. Prompt and appropriate antibiotic therapy will be crucial to prevent morbidity and mortality.

Hemophagocytic syndrome[60-63]

Evidence of hemophagocytes in dengue was alluded to by the presence of numerous macrophages that have phagocytosed erythrocytes and lymphocyte phagocytosis in the spleen. The unusual incidence of phagocytic reticulum cells which phagocytosed all blood elements has been reported. Case reports of prolonged fever in dengue patients have been attributed to this phenomenon. The clinical picture is characterized by persistent high fever, variable cytopenia and multi-organ failure associated with macrophage activation, hemophagocytes and hypertyrosinemia. Serum ferritin levels are markedly elevated. Definitive diagnosis is made by bone marrow biopsy which demonstrates hemophagocytic activity. Response to methyl-prednisolone and immunoglobulin has been reported to be dramatic. However, supportive treatment leading to spontaneous recovery has also been reported.

Supportive care and adjuvant therapy[13,31,34]

Supportive care and adjuvant therapy may be necessary in severe dengue and includes vasopressor and inotropic therapy.

The use of vasopressor and inotropic therapy should be limited to the following clinical situations:

As a temporary measure to prevent life-threatening hypotension in dengue shock and during induction for intubation, while correction of intravascular volume is being vigorously carried out. Vasopressor therapy should be weaned off as intravascular volume is restored and end-organ perfusion re-established.

Evidence of cardiogenic shock due to myocarditis or ischemic heart disease. Dobutamine is the recommended choice. In concomitant septic shock, dopamine or norepinephrine are the vasopressors of choice. Vasopressor therapy should be carefully monitored since dengue shock is primarily a hypovolemic shock caused by plasma leakage ± hemorrhage. The most essential and effective strategy is the correction of intravascular volume with the appropriate types of fluids. Vasopressors, by further increasing the peripheral vascular resistance, may be able to maintain the central BP but

without improving end-organ perfusion. Paradoxically, vasopressors exacerbate tissue hypoxia and lactic acidosis when the intravascular volume has not been restored. The correct use of vasopressor therapy is reflected in an increased BP concomitant with a decreased tachycardia. If both the BP and tachycardia increase, then repletion of intravascular volume should be considered as the urgent alternative strategy.

Renal replacement therapy may be indicated in acute kidney injury. It should be commenced after hemodynamic stability has been achieved and maintained without further fluid resuscitation, usually after the critical period of plasma leakage. The preferred choice of renal replacement therapy is continuous veno-venous hemodialysis (CVVH). Peritoneal dialysis may be considered if CVVH is not available, but there is a risk of bleeding. When renal replacement therapy is not available or cannot be performed yet, the ensuing hyperuricemia, hyperkaliemia and hyperphosphatasemia should be managed with allopurinol, Resonium A and calcium carbonate respectively.

Other organ impairment[64]

Drug toxicity resulting from the use of paracetamol or acetaminophen should be suspected if liver enzymes have increased disproportionate to the severity of shock. Paracetamol should be discontinued in patients with liver enlargement or raised liver enzymes. Further treatment of organ impairment, such as severe hepatic involvement, encephalopathy or encephalitis may be needed otherwise cardiac abnormalities, such as conduction abnormalities, may occur (the latter usually not requiring interventions). The most critical issue for recovery is stabilization of the hemodynamic state; without this there can be no recovery of any organ. Once the critical period is over and stability of the hemodynamic state attained, it is essential to stop or reduce intravenous fluids to the minimum and to maintain euglycemia. The body will heal itself remarkably over the next few days to weeks. Excessive fluid is cleared by the kidneys and normal liver function returns gradually, coagulation abnormalities and platelet counts return to normal. During this period any suspected nosocomial sepsis should be treated vigorously, but without adding further insults to the kidneys or liver. Supportive treatment (for the liver and kidneys) and enteral nutrition is all that is required in most cases.

Management of neonatal dengue[67, 68, 69]

When a pregnant or parturient woman develops signs consistent with dengue, the diagnosis of dengue should be considered in her neonate even if the neonate appears well in the first several days of life. Remember that some neonates have become ill as long as 11 days after birth**.** The diagnosis of neonatal dengue could eventually be suspected on clinical grounds and then confirmed in the laboratory, but initial presentation may be confused with bacterial sepsis, birth trauma and other causes of neonatal illness. Symptomatic and supportive treatment under close observation is the mainstay of treatment**.**

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CASE REPORT

Congenital Harlequin Ichthyosis: A Rare genetic Disorder

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Introduction

Harlequin Ichthyosis (HI) is an extremely rare genetic disorder. Harlequin baby is a variant of icthyosis which is severe in form and found very rarely. Its incidence is 1 in 300000 child.[1] This is an autosomal recessive disorder.[2,3] Harlequin ichthyosis (HI) is a lethal disease.[4] Affected neonates rarely survive beyond first few days of life but very rare cases may survive for several months or years.[5] This is characterized by thickened, rough, dry and armor like plates of skin. There are deep cracks in between skin. HI appears with severe thickened and scaly skin on the entire body. In addition, ectropion, lack of development of the external parts of the nose and ears, eclabium and open mouth, hypoplastic fingers, anonychia and mobility limitation of the joints are some other clinical features of the HI.[6] Patients with HI are at high risk for hypotermia/ hyperthermia, dehydration, respiratory distress, hypoventilation, malnutrition, hypernatremia, seizure, and skin infection.[7] HI is associated with preterm birth and often leads to death due to neonatal complications such as fluid loss and septicemia.[5] In our country incidence in not known exactly but only few cases were reported. Here we are presenting a severe form of ichthyosis baby born by caesarean section in our hospital

Case report

A 22 years old lady, primi gravida with consenguineous marriage was admitted in Holy Family Red Crescent Medical College and Hospital (HFRCMCH) on 10.10.2017 at her 30 weeks of gestation with the complaints of lower abdominal

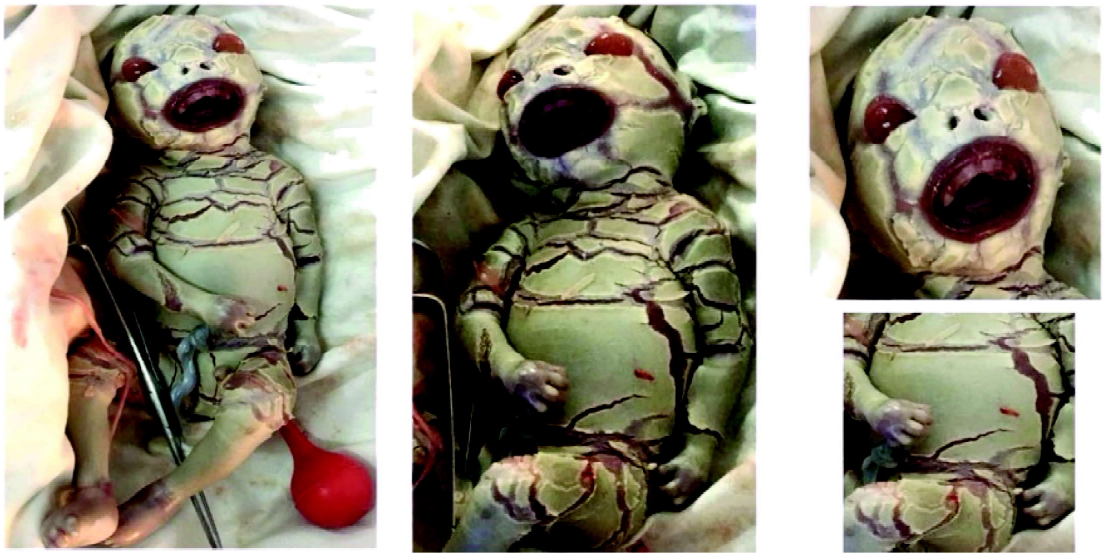

Fig 1 *The patient with deep cracked skin, open wide mouth, abnormal eyes, and flatted nose and ear.*

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pain and per vaginal watery discharge for 4 days. This was her planned pregnancy. During her pregnancy she had regular antenatal checkup at sonargaon health complex. Anomoly scan was done at 20 weeks gestation which was unremarkable. Her pregnancy was uneventful till 30 weeks gestation. She developed lower abdominal pain and per vaginal watery discharge and got herself admitted in HFRCMCH. She had no history of Diabetes Mallitus, Hypertension, Bronchial Asthma, Thyroid disease. Her LMP was on 17.03.2017 and EDD was on 24.12.2017. She was married for 5 years and this was her 1st pregnancy. On examination she was mildly anaemic, non icteric, normotensive. Per abdominally Symphysis-Fundus Height (SFH) was 32 cm. FM was present and FSH was 147/mint. Mild uterine contraction was present. On P/V examination, OS was 3 cm dilated, effacement was 50%, presentatoin was breech, membrane ruptured, show was present. Patient under went CS on 11.10.2017. A male baby was delivered by breech extruction and that was a Harlequin lchthyosis. Apgar score was 7 and weight was 2.5 Kg. Baby died after 3 days due to sepsis.

Discussion

The Harlequin Ichthyosis disorder is a rare genetic condition where an infant is born with a thick yellow, very hard skin. The skin has large diamond shaped plates separated by deep fissures much like a fish. The word Ichthyosis has come from Greek word ikthys and Latin word ichtyos both meaning fish. These skin abnormalities affects the shape of eyelids, nose, mouth, ears and limit the movements of arms and legs. At birth, infants are covered with hard hyperkeratonic armor, composed of large, thick, yellowish brown, and very sticky plates.[3] After birth, deep red fissures occurs on these hard and inflexible plates that extend to the dermis, resulting in a joker-like skin. Infants with Harlequin Ichthyosis might have microcephaly, ectropion, and eclabium.[2] External auditory meatus and nostrils appear rudimentary and immature.[8] In addition, patients with Harlequin Ichthyosis have respiratory failure as a result of restricted chest expansion and skeletal deformities. Feeding problems may result in low blood sugar, dehydration, and kidney failure. In addition, temperature instability and infection is common.[7] Almost all these clinical features were observed in our case.

It is an autosomal recessive condition. There is 25% chance of recurrence in subsequent pregnancy. There is defect in Al2 (ABCA l2) gene on chromosome 2. This gene is responsible for caring information for transport of lipids to keratinocytes in the skin. Hashemzadeh et al[9] also observed Harlequin Ichthyosis in a case of premature baby at 30 weeks gestation in a consanguineous parents. Prenatal diagnosis would be the first step for early detection of the disease. Therefore, obtaining the family history, consanguinity between the parents, and the presence of other skin disorders in offspring would be very helpful for early diagnosis of the disease. Microscopic examination of the amniotic fluid cells and ultrasound for assessment of the shape of fetal mouth at 17 weeks of pregnancy might be useful for the early detection.[10] But in our case anomaly scan at 20 weeks failed to detect any anomaly.

The mortality of HI is high and most of the victims die within a few weeks of birth because of secondary complications such as infection and dehydration.[2] However, survival contributes to the type of mutations; victims with the compound heterozygote mutation survive more than those with the homozygote mutation. In addition, advances in the postnatal treatments and cares improve the prognosis of the disease.[11] The survival rate increases to more than 50% with early prescription of oral retinoids. The patients' quality of life improves with supportive cares. In addition to the routine care such as checking vital signs, patients should be kept in a warm and humid incubator. Hydration should be performed.[12] As accessing to the peripheral vessels can be difficult, an umbilical venous catheter is needed. Taking shower twice per day, saline compresses and gentle emollients must be used to keep the skin soft and to accelerate the desquamation. Water and electrolyte disturbances must be managed as well: Environment must be cleaned up to prevent infection; hence, repeated cultures of the skin is essential to detect the hazardous microorganisms.[2] In this condition there is hyperkeratosis and loss of projective skin barrier.

As a result there is abnormal removal of scales from the skins that leads to deposition of dead skin. So there is hyperkeratosis of skin and the baby is prone to develop skin infection. Our baby survived only 3 days and died due to sepsis.

Conclusion

Harlequin fetus is a rare manifestation of severe congenital icthyosis. It is usually fatal in first few days of life. In this case consanguinity was present. Baby died within 3 day of life. Prenatal diagnosis if possible should be offered to woman with previous affected babies. DNA analysis for ABCA 12 mutation will clinch the diagnosis. Characteristic features on prenatal USG tends to appear late so the scan should be repeated even when the 2nd trimester scan is normal and also helpful when DNA diagnosis is unavailable.

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CASE REPORT

Situs Inversus Totalis with Duodenal Atresia and Preduodenal Portal Vein: A Case Report

Md. Samiul Hasan[1], KM Nurul Ferdous[2]

Introduction

Situs inversus totalis is the mirror image transposition of abdomino-thoracic viscera. Its association with duodenal atresia is very rare.[1] Preduodenal portal vein (PDPV) itself can cause complete or partial obstruction in patients of situs inversus. Presence of PDPV in association of situs inversus and duodenal atresia is extremely rare.[1,2] We report a case, in whom combination of these two anomalies were a management challenges.

Case report

A 3 days old preterm female neonate weighing 2.1 Kg presented with bilious vomiting and failure to pass meconium. Physical examination revealed scaphoid abdomen and dextrocardia. Babygram confirmed situs inversus and duodenal obstruction (Fig 1). Echocardiography revealed with dextrocardia with small ASD and PDA. Laparotomy was planned. On laparotomy stomach was found on right side with type 1 duodenal atresia (Fig 2). Proximal to the atresia there was PDPV, though it was not causing obstruction (Fig 3). An extended duodeno-duodenostomy was made after excising the membrane and bypassing the portal vein, keeping in mind that it may cause obstruction in future. Fortunately the baby recovered well, tolerated oral feed on 6th post operative day (POD) and discharged on 10th POD.

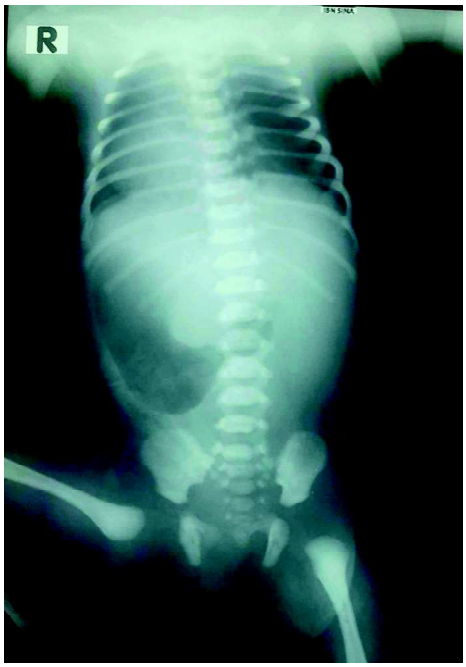

Fig 1 *Situs inversus with double bubble sign*

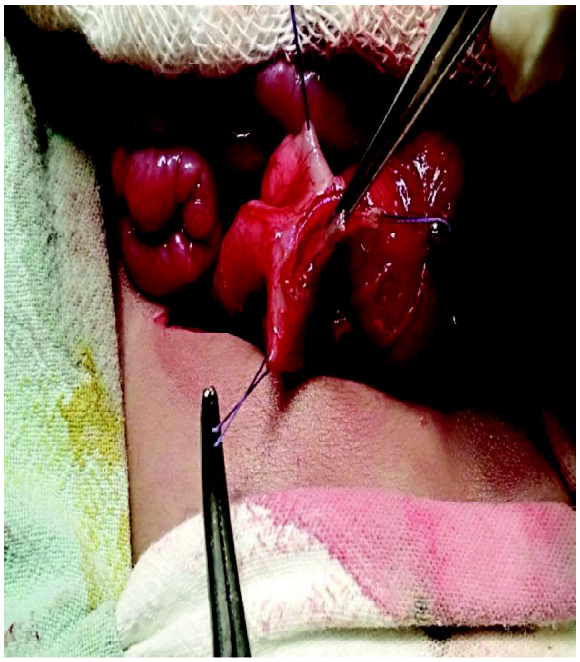

Fig 2 *Type 1 duodenal atresia*

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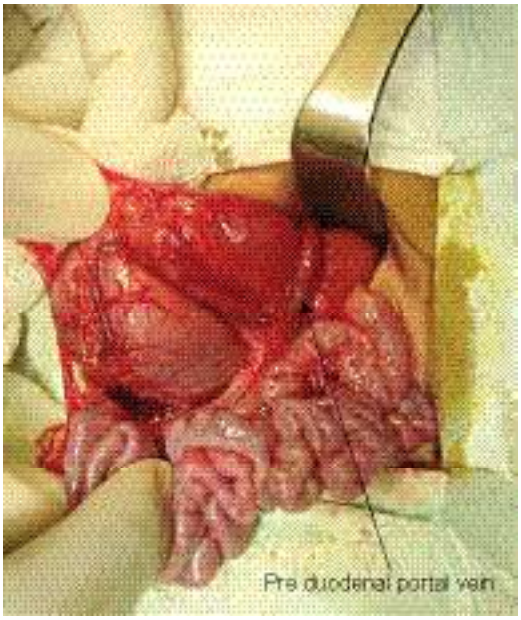

Fig 3 *Pre duodenal portal vein causing incomplete obstruction*

Discussion

Situs inversus results from complex and multifactorial etiology, with a prevalence of 1 in 10000.[3] Incidence of duodenal atresia varies from 1 in 5000 to 1 in 20000 live birth. Association of these two is rare. Around 20 patients have been reported this association.[3,4] PDPV occur usually in patients with situs inversus in which portal vein passes anterior to the duodenum instead of posterior course. Isolated PDPV rarely causes obstruction.[2]

Common associated anomalies of situs inversus are splenic and cardiac anomalies. Other associated anomalies are duodenal atresia and PDPV. In our patient, there was cardiac anomaly but spleen was structurally normal.

Duodenal obstruction in patients with situs inversus is usually due to PDPV, atresia or stenosis. Our patient had both PDPV and atresia in close proximity, which was challenging to correct surgically. The procedure of choice for both conditions is duodenoduodenostomy.[1,2,5] We performed an extended duodenoduodenostomy to bypass both anomalies. Separate anastomosis would be difficult and risky as both the pathologies were in close proximity.

Survival of these patients largely depends on maturity and associated cardiac anomaly.[3] Post operative period of our pati ent was uneventful like most of the reported cases.[1,2,4,5]

Conclusion

Combination of duodenal atresia and PDPV in patients with situs inversus is extremely rare but it should be kept in mind during laparotomy because with appropriate treatment outcome is excellent.

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ABSTRACTS FROM CURRENT LITERATURE

Short Sleep Duration and Later Overweight in Infants

Tuuli Tuohino, B Med Tuuli Tuohino, Isabel Morales-Muñoz, Outi Saarenpää-Heikkilä, Olli Kiviruusu, Tiina Paunio, Petteri Hovi, Kirsi H. Pietiläinen, E. Juulia Paavonen.

The Journal of Pediatrics 2019; 212:13-19.

Objective: To provide further knowledge about the longitudinal association between sleep duration and overweight in infants.

Study design: The data for this study are from the CHILD-SLEEP birth cohort (n = 1679). The sleep data are based on parent-reported total sleep duration collected at 3, 8, 18, and 24 months. For a subgroup of 8-month old participants (n = 350), an actigraph recording was also made. Growth data were derived from the child health clinic records. A logistic regression model was used to study the association between sleep duration and later weight development.

Results: Shorter sleep duration in 3-month-old infants was cross-sectionally associated with lower weight-for-length/height (all *P* values d" .026) and body mass index (all *P* values d" .038). Moreover, short sleep duration at the age of 3 months was associated with greater weight-for-length/height z score at the age of 24 months (aOR 1.56; 95% CI 1.02-2.38) as well as with a predisposition to gain excess weight between 3 and 24 months of age (aOR 2.61; 95% CI 1.75-3.91). No significant associations were found between sleep duration at 8, 18, or 24 months and concurrent or later weight status. Actigraph-measured short night-time sleep duration at the age of 8 months was associated with greater weight-for-length at the age of 24 months (aOR 1.51; 95% CI 1.02-2.23).

Conclusions: Short total sleep duration at the age of 3 months and short night-time sleep duration at the age of 8 months are associated with the risk of gaining excess weight at 24 months of age.

Alternative dosing guidelines to improve outcomes in childhood tuberculosis: a mathematical modelling study

Kendra K Radtke, Kelly E Dooley, Peter J Dodd, Anthony J Garcia-Prats, Lindsay McKenna, Prof Anneke C Hesseling et al.

Lancet Child and Adolescent Health 2019; 3(9): 636-45.

Background: Malnourished and young children are particularly susceptible to severe forms of tuberculosis and poor treatment response. WHO dosing guidelines for drugs for tuberculosis treatment are based only on weight, which might lead to systematic underdosing and poor outcomes in these children. We aimed to assess and quantify the population effect of WHO guidelines for drug-susceptible tuberculosis in children in the 20 countries with the highest disease burden.

Methods: We used an integrated model that linked country-specific demographic data at the individual level from the 20 countries with the highest disease burden to pharmacokinetic, outcome, and epidemiological models. We estimated tuberculosis treatment outcomes in children younger than 5 years following WHO guidelines (children are dosed by weight bands corresponding to the number of fixed-dose combination tablets [75 mg rifampicin, 50 mg isoniazid, 150 mg pyrazinamide]) and two alternative dosing strategies: one based on a proposed algorithm that uses age, weight, and available formulations, in which underweight children would receive the same drug doses as would normal weight children of the same age; and another based on an individualised algorithm without dose limitations, in which derived doses results in target exposure attainment for the typical child.

Findings: We estimated that 57 234 (43%) of 133 302 children younger than 5 years who were treated for tuberculosis in 2017 were underdosed with WHO dosing and only 47% of children would reach the rifampicin exposure target. Underdosing and subtherapeutic exposures were more common

among malnourished children than among age-matched healthy children. The proposed dosing approach improved estimated rifampicin target exposure attainment to 62% and equalised outcomes by nutritional status. An estimated third of unfavourable treatment outcomes might be resolved with this dosing strategy, saving the lives of a minimum of 2423 children in these countries annually. With individualised dosing approaches, almost all children could achieve adequate exposure for cure.

Interpretation: This work shows that a simple change in dosing procedure to include age and nutritional status, requiring no additional measurements or new drug formulations, is one approach to improve tuberculosis treatment outcomes in children, especially malnourished children who are at high risk of mortality.

Unintentional injuries and violence among adolescents aged 12-15 years in 68 low-income and middle-income countries: a secondary analysis of data from the Global School-Based Student Health Survey

Prof Liyuan Han, Prof Dingyun You, Xuping Gao, Shiwei Duan, Prof Guoqing Hu et al.

Lancet Child and Adolescent Health 2019; 3(9): 616-26.

Background: Injuries and violence account for a substantial proportion of the global burden of disease in adolescents, especially among low-income and middle-income countries (LMICs). We aimed to compare the prevalence of unintentional injuries and violence among young adolescents in LMICs.

Methods: We did a secondary analysis of data from the Global School-based Student Health Survey (GSHS) for adolescents aged 12-15 years from LMICs collected between 2009 and 2015. Survey data was collected using a standardised questionnaire. We used survey data to calculate the overall prevalence of serious injuries and violence (eg, physical attack, physical fighting) and bullying per country. We did a random-effects meta-analysis to calculate pooled overall and regional estimates. We also did subgroup analyses stratified by sex, age (12-13 years *vs* 14-15 years), and time period (2009-11 *vs* 2012-15). Logistic regression models adjusted for sex, weights, stratum, and primary sampling unit were used to analyse the differences in prevalence of serious injuries, violence, and bullying.

Findings: We included data from 68 LMICs, including 164 633 young adolescents (77 707 [47·2%] boys; 86 926 [52·8%] girls). The overall prevalence of physical attack, physical fighting, and serious injuries during the past 12 months were 35·6% (95% CI 30·7-40·5), 36·4% (29·9-42·9), and 42·9% (39·0-46·9), respectively. Prevalence varied by WHO region and was higher among boys than girls for injuries (47·8% *vs* 37·5%, p=0·00094), physical attack (41·0% *vs* 29·4%, p=0·001), and physical fighting (45·5% vs 26·9%, p<0·0001). Fractures (22·6%, 95% CI 19·1-26·1) and cuts (21·8%, 16·8-26·8) were the most common types of serious injury, and falling was the main cause of these injuries (33·1%, 30·2-35·9). The overall prevalence of bullying at least once in the past 30 days was 34·4% (27·1-41·7), irrespective of age and sex. The most common types of bullying were physical (18·3%, 13·7-23·0), verbal-sexual (13·2%, 10·2-16·2), and racial-ethnic (11·6%, 9·2-14·0).

Interpretation: The prevalence of unintentional injuries and violence remain high among young adolescents in LMICs. These countries should prioritise the development of anti-violence and anti-injury programmes to improve health in their young adolescent populations.

Funding: National Natural Science Foundation of China, National Key R&D Program of China, Natural Science Foundation of Zhejiang Province, Sanming Project of Medicine in Shenzhen, K.C. Wong Magna Fund in Ningbo University, and Ningbo Scientific Innovation Team for Environmental Hazardous Factor Control and Prevention.

Pre-emptive intervention versus treatment as usual for infants showing early behavioural risk signs of autism spectrum disorder: a single-blind, randomised controlled trial

Prof Andrew J O Whitehouse, Kandice J Varcin, Gail A Alvares, Josephine Barbaro, Catherine Bent, Maryam Boutrus.

Lancet Child and Adolescent Health 2019; 3(9): 605-15.

Background: Great interest exists in the potential efficacy of prediagnostic interventions within the autism spectrum disorder prodrome, but available evidence relates to children at high familial risk.

We aimed to test the efficacy of a pre-emptive intervention designed for infants showing early behavioural signs of autism spectrum disorder.

Methods: In this single-blind, randomised controlled trial done at two specialist centres in Australia, infants aged 9-14 months were enrolled if they were showing at least three early behavioural signs of autism spectrum disorder on the Social Attention and Communication Surveillance-Revised (SACS-R) 12-month checklist. Infants were randomly assigned (1:1) to receive a parent-mediated video-aided intervention (iBASIS-VIPP) or treatment as usual. Group allocation was done by minimisation, stratified by site, sex, age, and the number of SACS-R risk behaviours. Assessments were done at baseline (before treatment allocation) and at the 6 month endpoint. The primary outcome was Autism Observation Scale for Infants (AOSI), which measures early behavioural signs associated with autism spectrum disorder. Secondary outcomes were a range of infant and caregiver outcomes measured by Manchester Assessment of Caregiver-Infant interaction (MACI), Mullen Scales of Early Learning (MSEL), Vineland Adaptive Behaviour Scales, 2nd edition (VABS-2), MacArthur-Bates Communicative Development Inventory (MCDI), and Parenting Sense of Competence (PSOC) scale. This trial is registered with Australian New Zealand Clinical Trials Registry, number ANZCTR126 16000819426.

Findings: Between June 9, 2016, and March 30, 2018, 103 infants were randomly assigned, 50 to the iBASIS-VIPP group and 53 to the treatment-as-usual group. After the intervention, we observed no significant differences between groups on early autism spectrum disorder behavioural signs measured by the AOSI (difference estimate “0·74, 95% CI “2·47 to 0·98). We also observed no significant differences on secondary outcomes measuring caregiver non-directiveness (0·16, “0·33 to 0·65), caregiver sensitive responding (0·24, “0·15 to 0·63), and infant attentiveness (“0·19, “0·63 to 0·25) during parent–child interactions (MACI), as well as on researcher-administered measures of receptive (1·30, “0·48 to 3·08) and expressive language (0·54, “0·73 to 1·80), visual reception (0·31, “0·77 to 1·40), and fine motor skills (0·55, “0·32 to 1·41) using the MSEL. Compared with the treatment-as-usual group, the iBASIS-VIPP group had lower infant positive affect (“0·69, “1·27 to “0·10) on the MACI, but higher caregiver-reported receptive (37·17, 95% CI 10·59 to 63·75) and expressive vocabulary count (incidence rate ratio 2·31, 95% CI 1·22 to 4·33) on MCDI, and functional language use (difference estimate 6·43, 95% CI 1·06 to 11·81) on VABS. There were no significant group differences on caregiver-reported measures of MCDI infant gesture use (3·22, “0·60 to 7·04) and VABS social behaviour (3·28, “1·43 to 7·99). We observed no significant differences between groups on self-reported levels of parenting satisfaction (difference estimate 0·21, 95% CI “0·09 to 0·52), interest (“0·23, “0·62 to 0·16) and efficacy (“0·08, “0·38 to 0·22) on PSOC.

Interpretation: A pre-emptive intervention for the autism spectrum disorder prodrome had no immediate treatment effect on early autism spectrum disorder symptoms, the quality of parent–child interactions, or researcher-administered measures of developmental skills. However, we found a positive effect on parent-rated infant communication skills. Ongoing follow-up of this infant cohort will assess longer-term developmental effects.

DSH NEWS

Fig 1 *Observence of World Premature Day 2019 and giving honor to Prof. MAK Azad Chowdhury, Head of Neonatal Medicine, BICH and Dhaka Shishu Hospital as a pioneer of kangaroo mother care in Bangladesh.*

Fig 2 *Observence of World Cystic Fibrosis Day 2019*

BICH NEWS

BICH is the academic wing of Dhaka Shishu Hospital. It was established in 30th January, 1983. It is affiliated with Dhaka University, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Bangladesh College of Physicians and Surgeons (BCPS). It has been conducting different courses e.g. DCH, FCPS, MD Paediatrics, MS Paediatric surgery & B.Sc in Health technology. It also conducts different sub-specialty courses e.g. FCPS Neonatology, FCPS Haemato-oncology, FCPS Nephrology, MD Neonatology, MD Haemato-oncology and MD Nephrology. It conducts 3 months certificate course in Paediatrics and 15 days Intensive course for MCPS. It organizes IMCI training and Palli Shishu Rural Health Training. Apart from this, the Institute also runs its regular academic activities. It has established Basic Science Department since 2006.

Diploma course of paediatric nursing has been started from 1st January 2012 and Diploma in paediatric physiotherapy under process.

Library facilities

The library of BICH has a rich collection of updated medical texts and reference books and reputed Medical Journals of home and abroad. BICH has introduced Broad Band facilities which are open to all students, teachers/ consultants of hospital for 24 hours. Facilities of library are also improved by HINARI. Students can download 2230 Medical Journals & more than 50 Paediatric Journals.

Present News

A newly formed classroom in BICH has been named as Prof. Sultan Ahmed Chowdhury as a tribute to First Honarary Director of Dhaka Shishu Hospital.

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Postgraduate courses/training in paediatrics and child health

1. FCPS in paediatrics : Twice in a year, in the months of January and July.
2. Recognized center by BCPS for training in FCPS (Paeditric surgery) .
3. Recognized centre for course and training in different subspeciality as: Neonatology, Pediatric Nephrology, Paediatric Haematology and Onchology, Paediatric Pulmonology and Paediatric Neuroscience.
3. MD/MS in paediatrics : Part I: In the month of January every year; 2nd and 3rd parts twice every year.
4. DCH course : Once in a year in the month of July.
5. Three months certificate course : The institute every year runs 3 months certificate course on paediatrics for general practitioners & other post graduate candidates e.g. MCPS.
   (1st August - 31st October)
6. Training programme on IMCI (Integrated management of childhood illness), Essential Newborn Care for doctors and nurses, KMC (Kangaroo Mother Care) traing, ETAT (Emmergency Triage, Assessment and Treatment) training.

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Students Qualified from Bangladesh Institute of Child Health

Undergoing Courses of BICH

Institution	Courses
Bangabandhu Sheikh Mujib Medical University	MD (Pediatrics) MD Pediatrics Nephrology (sub-specialty) MD Neonatology (sub-specialty) DCH MS (Pediatrics Surgery)
Bangladesh College of Physicians and Surgeons (BCPS)	FCPS Part II (Paediatrics) FCPS Neonatology FCPS Pediatric Nephrology FCPS Hematology & Oncology FCPS Pediatric Surgery FCPS Pediatric Neurology & Development FCPS Pediatric Pulmonology
Dhaka University	B.Sc in Health technology (Lab)
Bangladesh Nursing Council	Diploma in Pediatric Nursing

Student Qualified from BICH till July-December 2019

Course	**Number**
DCH	370
MD (Pediatrics)	116
MS (Pediatrics)	109
FCPS (Pediatrics)	28
MD (Neonatology)	13
MD (Pediatrics Nephrology)	5
Total	**641**

Foreign Student Qualified from BICH till January 2013

Country of origin	Course	Number
Nepal	DCH	23
	MS (Ped Surgery)	2
	MD (Ped)	1
India	MD (Ped)	1
Iran	DCH	1
Iraq	DCH	1
Somalia	DCH	1
Sudan	DCH	1
Total		**31**

Present Students (June 2019 to December 2019)

Name of Courses	Number of Students
MD (Paediatrics) Phase - A	25
MD Neonate Phase - A	06
MD Paediatric Nephrology- Phase - A	04
MS (Paediatric Surgery) Phase - A	19
FCPS (Paediatric) - Part-II	0
MD (Paediatric) Part-III	10
MD (Paediatrics) Part-II	0
MS (Paediatric Surgery) Part-III	19
DCH (old)	02
DCH (New)	10
MD (Paediatrics) Phase-B	32
MD (Neonate) Phase-B	06
MD (Nephrology) Phase-B	04
MS (Paediatric Surgery) Phase-B	20
Total	137

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Seminar/Symposium & CME/CPD Programs held at BICH (July- December 2019)

Sl. No.	Topic	Unit	Date
01.	Inborn Errors of Metabolism	MU - III	21.07.2019
02.	Hemolytic Uremic Syndrome	MU - II	29.07.2019
03.	Management of Congenital Anomaly of Kidney	MU - II & PNSB	18.08.2019
04.	Dengue fever: Issues and controversies	MU - VI	08.08.2019
05.	Movement Disorder in Children	MU - III	25.08.2019
07	Identification of Neonatal Shock & Management	MU - IV	22.09.2019
06.	Talipes Equinovarus (TEV): An Update	SU - I	27.10.2019
07.	Respiratory sounds	MU - V	24.11.2019
08.	Influenza : A Forgotten Pandemic	MU - VI	29.12-2019

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INSTRUCTIONS FOR AUTHORS

Dhaka Shishu Hospital Journal is the official organ of BICH which is the academic wing of DSH. It is published twice a year since 1984. The present editorial board has decided that the cover design will be in accordance with the subject of editorial in each issue. The editor welcome articles to be published in the journal as leading article, original article, review article, case report, current issues of child health, short report and junior's page where trainee doctors are encouraged to publish their topic of interest.

Original papers written in *english* will be considered for publication provided these have not been published previously and are not under consideration for publication elsewhere.

Conditions for manuscript submission:

- All manuscripts will be subjected to peer and editorial review.
- Accepted manuscripts become the property of the *Dhaka Shishu Hospital Journal*. Any reproduction in whole or part will require written permission from the editorial board of the journal.
- The author should obtain written permission from appropriate authority if the manuscript contains any table; data or illustration from previously published in other journals. The letter of permission should be submitted with the manuscript.
- If the photographs are not disguised, permission from the patient or parents/ guardians to print should accompany the manuscript. Otherwise identity will be blackened out.
- Rejected manuscripts/electronic copies/ illustrations/photographs will not be returned to the authors.
- Editors are not responsible for courier/postal failure.

Manuscript preparation: The format of the Dhaka Shishu Hospital Journal complies with *"Uniform Requirements for Manuscripts Submitted to Biomedical Journals"* published by the International Committee of Medical Journal Editors in Vancouver, British Columbia in 1979 (the widely accepted ***"Vancouver style"***)' published in the Annals of Internal Medicine 1982; 96: 766-71. All scientific units should be expressed in *System International (SI) units*. Authors are referred to Annals of Internal Medicine 1987; 106: 114-29 for guidance in the use of SI units. All drugs should be mentioned in their generic form.

- Should be typed in english and on one side of A4 (290 x 210cm) size white paper, using *Times New Roman* font size 12, with single space.
- There should be one original and two paper copies and one IBM compatible electronic copy. (CD or Pen drive)
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2. Semi Auto Biochemistry analyzer - Routine biochemical tests
3. Electrolyte analyzer - Na, K, Cl, TCO_2
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Director
Dhaka Shishu (Children) Hospital

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