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Initial Inotrope in Preterm Neonatal Shock Based onAetiology: A Prospective Cohort Study

Dr Sachin Dubey[1], Dr Anumodangupta[2], Dr Aditi Saini[3], Dr Tushar Parikh[4]
[1,2,4] *Division of Neonatology Department of Pediatrics,*[3] *Department of Gynecology and obstetrics KEM hospital Pune .*

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ABSTRACT
Purpose: The objective of the study is to study theInitial Inotrope in Preterm Neonatal Shock Based on Aetiology in level 3 NICU in India.
Materials And Methods: This was prospectivecohort study which analysed preterm neonates with shock admittedto our NICU from JANUARY 2017 toMARCH 2018.After diagnosing a shock as per predefined criteria, little preterm babies were categorised on aetiological basis of shock and then accordingly different inotropes were started for treatment purpose as per cause-based effect.
Statistical Methods: Descriptive analyses were used to study the parameters.
Results: A total of 119preterm babies less than 34 week GA wereevaluated.The most common etiology of shock present in our study was LOS present in 34.4% of our babies followed by transient circulatory compromise which was present in 22.6% babies,hsPDA, PPHN and hypovolemia were uncommon causes and were present in 10%, 5% and 1.7% babies respectively. Accordingly, the most common inotrope used in our unit was dobutamine which was started in 41.1% of the babies. Dopamine in combination with dopamine was started in 34.4% of the babies. Dopamine as a single drug was started in 19.3% of the babies. Most of the patients were started the drug for late onset sepsis. NS bolus was given as a initial support in only 5% of the babies.
KEYWORDS: Low birth weight, Dopamine, late onset sepsis, shock,

I. INTRODUCTION

Our approach to managing shock and cardiovascular deterioration in neonates has conventionally been based on limited information and remains a challenging aspect of neonatal care. The problem is further enhanced by the dynamic nature of cardiovascular physiology and its impact on cellular and metabolic mechanisms. A necessary part of our understanding comprises of the outcomes of shock and more specifically how different etiologies affect the outcomes.Aetiology factors leading to development of shock in neonates includes hypovolemia, myocardial dysfunction, abnormal peripheral vasoregulation or combination of all these factors. Enhanced cardiovascular monitoring, and earlier therapeuticionotropic intervention based on the exact pathophysiological change may prove to be an imperative step toward improving survival further and minimizing adverse neurodevelopmental sequelae.

In Indian settings, shock is an important contributor to mortality and morbidity in the NICU and therefore a study which throws alight on use of inotropes based on the etiological factors of shock and the complications associated with them will help in treating shock more appropriately and complications associated with shock.This study focussed on use of appropriate inotropesby clinician to effectively treat hemodynamic condition of sick neonates

II. MATERIAL AND METHODS

It was a Single centre prospective observational cohort study conducted at King Edward Memorial hospital NICU which is located at Pune, Maharashtra conducted from 1st January 2017 to 31st March 2018. This hospital is a 550 bedded multispeciality teaching institute with a 41 bedded level III A NICU. It caters to both intramural and extramural babies and serves around 1000 neonates every year. All preterm neonates < 34 weeks developing shock during NICU stay.New-borns with structural heart disease, surgical anomalies, out born and syndromic babies were excluded. Calculated sample size was 115(92x1.25). Written informed consent was obtained from either of the parents after explaining them about the study.Approval of institutional scientific and ethical committee were taken before starting the study.
The presence of shock was decided based on the following clinical and lab criteria.

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Clinical[1]

1) Heart rate > 2 SD for age and gestation
2) Blood pressure < 3rd centile for that gestational age
3) Capillary refill time >3 seconds
4) Core-periphery temperature difference > 3 degree centigrade
5) Urine output < 1.0 ml/kg/hour

Lab parameters

1) Arterial blood gas- The normal values for pH and HCO3 are as follows[2]

	pH	HCO3
Term	7.32-7.38	24-26
30-36 Weeks	7.30-7.35	22-25
<30 Weeks	7.27-7.32	19-22

2) Base excess levels more than 10[1]
3) Lactate levels > 4.0 mmol[91]

The following criteria were used for defining shock before starting therapy

1) Either a mean BP < 3rd centile below threshold **or**
2) Combination of 2 of the clinical criteria **or**
3) A Capillary Refill Time > 4 seconds and a lactate value > 4 mmol[1] **or**
4) Low cardiac output or contractility on echo

INTERVENTION:

All preterm babies <34 weeks presenting with shock based on predefined criteria were treated as per established treatment protocols. Interventions included

- volume administration
- inotropic support
- vasopressor support
- hydrocortisone

The starting and maximum doses for the medications is mentioned below

INTERVENTION	Starting Dose	Maximum Dose
Volume	10 ml/kg	20 ml/kg
Dobutamine	10 µg/kg/min	20 µg/kg/min
Dopamine	5 µg/kg/min	15 µg/kg/min
Adrenaline	0.05 µg/kg/min	1 µg/kg/min
Milrinone	75 µg/kg over 1 hour	0.5-0.7 µg/kg/min
Hydrocortisone	2 mg/kg Loading	1 mg/kg 8 hourly
Ibuprofen (for hsPDA)	10 mg/kg on I day	5 mg/kg X 2 days

Following the intervention, the baby was monitored for improvement of the shock. The duration for the intervention was documented. The end point of stopping of therapy was improvement in the clinicaland lab parameters. The complications arising were investigated and documented. The diagnostic criteria used for each of the complications are as follows:

The grading of IVH was per Papile grading system[3].Modified Bell's Staging[4] was used for Acute Kidney Injury was evaluated. Any neonate with oliguria/ increased serum creatinine levels within 72 hours of developing shock was labelled as developing acute kidney injury. The reference serum creatinine was as per GA and day of life[5].Baby was evaluated for the development of bronchopulmonary dysplasia. The disease was classified as per NICHD classification[6] ROP- Was identified and classified as per ICROP classification [7]All the data was compiled in a predesigned Performa and further statistical analysis was done.

III. STATISTICAL ANALYSIS

Data was entered in Microsoft excel and was analysed by SPSS software (version 13.1). We used proportion for categorical variables

IV. RESUTS

Total inborn babies born at <34 weeks were 412 and Babies developing shock during NICU stay were144.Similarly babies going discharge against medical advice/declined treatment were 15 Babies not documented at the beginning of study were 05.Out of all, Babies with structural heart disease were 02, Syndromic babies were 03 and total babies enrolled in the study were119.

Baseline Maternal Clinical and Demographic Variables are shown in table 1. 53 %

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mothers had pregnancy induced hypertension. Gestational diabetes mellitus was present in only around 1 % of the mothers. A complete course of antenatal steroids was received by 82.3 % mothers. Preterm premature rupture of membranes was present in 40.3 % of the mothers. Urinary tract infection was present in 1,6 % of the mothers. Fever was present in 3.3 % of the mothers and chorioamnionitis was present in only 0.8 % of the mothers. 34.4 % mothers received antibiotics. Antepartum haemorrhage was present in 6.7 % mothers. USG and Dopplers were normal in 56.3 %. Abnormal USG and Dopplers included decreased umbilical artery flow in 24.4 %, absent flow in 10.9 %, reversal of flows in 0.8 % and oligohydramnios in 7.6 % of the mothers. 64.8 % deliveries were caesarean section. This was probably because our hospital is tertiary care referral centre for high risk deliveries.

Table 1. Baseline Maternal Clinical and Demographic Variables

	PRESENT	ABSENT
PIH	63(53%)	56(47%)
GDM	01(0.08%)	118(99.2%)
ANS(COMPLETE COURSE)	98(82.3%)	21(17.7%)
PPROM	48(40.3%)	71(59.7%)
UTI	02(1.6%)	117(98.4%)
Fever	04(3.3%)	115(96.7%)
Chorioamnionitis	01(0.8%)	118(99.2%)
Antibiotics Received	41(34.4%)	78(65.6%)
APH	08(06.7%)	111(93.3%)
USG/DOPPLERS	67=Normal (56.3%)	52=Abnormal (43. 7%)
Mode Of Delivery	Vaginal=42(35.2%)	LSCS=77(64.8%)

Table 2 shows that 32% babies were extremely premature i.e less than 28 weeks, 45.3% babies were between 28-30 weeks and 22.7 % babies were between 31-33 weeks. 5 babies were in the periviablei.e between 20-25 weeks. 7.6 % babies were less than 750 gms, 39.4 % babies were between 750-1000 gms, 52.2% babies were between 1000-1500 gmas and 0.8 % were more than 1500 gms. There were 40.3 % female babies and 59.7 % male babies in the study. 40.3% babies were small for gestational age and the rest were appropriate for age. During delivery 41 % required resuscitation and the apgarscores at 1 minute were <4 in 39.2 % of babies, between 4-7 in 59.7 % of babies and 8 or more in 1.1% of babies.

Table 2. Baseline Study Population Characteristics

GESTATIONAL AGE	<28weeks	38(32%)
	28-30 weeks	54(45.3%)
	31-33weeks	27(22.7%)
BIRTH WEIGHT	<750 gms	09(7.6%)
	750-999gms	47(39.4%)
	1000-1500gms	62(52.2%)
	>1500gms	01(0.8%)
SEX	Female	48(40.3%)
	Male	71(59.7%)
WEIGHT FOR AGE	AGA	71(59.7%)

	SGA	48(40.3%)
APGAR SCORES	0-3	45(39.2%0
	4-7	71(59.7%)
	8-10	03(1.1%)
RESUSCITATION REQUIRED	Yes	49(41%)
	No	70(59%)
MULTIPLICITY	Singleton	84(70.6%)
	Twin	32(27..1%)
	Triplets	03(2.3%)

Table 3 shows the clinical and lab variables which were used by the primary care physicians to start inotropes/vasopressors. Hypotension, which is generally the most common parameter used for defining shock was present in 61.3 % of the babies. Tachycardia was present in 60.5 % of the babies. The most common deranged parameter in the babies was an increase in the core-periphery temperature difference more than 3 degree centigrade which was present in 93.2 % of the babies. Capillary refill time was deranged in almost half i.e 49.5% of the babies. Oliguria defined as reduced urine output as per the day of life was present in 20% of the babies. A deranged pH which was adjusted for gestational age was present in 37% of the babies. Increased lactate values were present in 54.6 % of the babies.

Table 3: Baseline Clinical And Lab Parameters

	Present	Absent
Hypotension	73(61.3 %)	46(38.7%)
Tachycardia	72(60.5%)	47(39.5%)
Core-Periphery Temp Difference >3° centigrade	111(93.2%)	08(6.8%)
Capillary Refill Time>3 sec	59(49.5%)	60(50.5%)
Oliguria	24(20%)	95(80%)
Abnormal Blood Ph	44(37%)	75(63%)
Base excess > 10	41(34.5%)	78(65.5%)
Arterial Lactate > 4mmol/ltr	65(54.6%)	54(45.4%)

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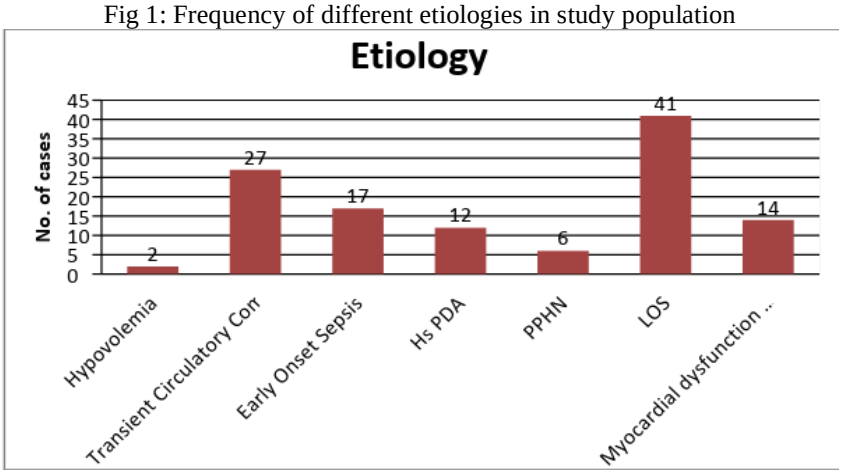
Figure 1 shows the distribution of etiology in the study population. The etiology was defined on history, clinical and lab parameters and was supported by functional ECHO. The most common etiology of shock present in our study was LOS present in 34.4% of our babies followed by transient circulatory compromise which was present in 22.6% babies. Early onset sepsis contributed to shock in 14.2% of babies followed by myocardial dysfunction secondary to hypoxia ischaemia which was present in 14.2% of babies. hsPDA, PPHN and hypovolemia were uncommon causes and were present in 10%, 5% and 1.7% babies respectively.

Fig 1: Frequency of different etiologies in study population



Specific inotropes started in the babies were based on the etiology as shown in Table 5 All babies with hypovolemia were NS bolus initially. 26/27(96.2 %) babies with transient circulatory compromise were started on dobutamine. 13/17(76.4%) babies with EOS were started on dopamine with dobutamine, 3/17(17.6%) babies on dopamine alone and one baby on dobutamine. All babies with hsPDA were started on dobutamine. All babies with PPHN were started on dopamine with dobutamine. 19/41(46.3%) with LOS were started on dopamine while 17(41.4%) of them were started on dopamine with dobutamine. 4(10%) of them were given NS bolus initially and one baby received dobutamine, 9/14(64.3%) babies with myocardial dysfunction received dobutamine initially while the rest received dopamine with dobutamine.

TAB 5: ETIOLOGY AND INITIAL INOTROPE

		Initial Inotrope / Vasopressor				Total
		No Bolus=0	Dobutamine	Dopamine	Dopamine + Dobutamine	
Etiology	Hypovolemia	2	0	0	0	2
	Transient Circulatory Compromise	0	26(96.2%)	1	0	27
	Early Onset Sepsis	0	1(5.8%)	3(17.6%)	13(76.4%)	17
	Hs PDA	0	12(100%)	0	0	12
	PPHN	0	0	0	6(100%)	6
	LOS	4(10%)	1(2.5%)	19(46.3%	17(41.4%)	41

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	Myocardial dysfunction Secondary to hypoxia ischaemia	0	9(64.3%)	0	5(35.7%)	14
Total		6	49	23	41	119

Table 6 shows the most common initial inotrope/vasopressor used in our unit.Accordingly, the most common inotrope used in our unit was dobutamine which was started in 41.1% of the babies. Dobutamine as a single inotrope was started mostly in the initial 72 hours of life. Dopamine in combination with dopamine was started in 34.4% of the babies. Dopamine as a single drug was started in 19.3% of the babies. Most of the patients were started the drug for late onset sepsis. NS bolus was given as a initial support in only 5% of the babies.

Table 6: Frequency Of Initial Inotrope

	FREQUENCY
INITIAL THERAPY	
NS BOLUS	6(5%)
DOBUTAMINE	49(41.1%)
DOPAMINE	23(19.3%)
DOBUTAMINE+DOPAMINE	41(34.4%)
TOTAL	119

V. DISCUSSION

Use of inotropes in any NICU is imperative based on some inadequate amount of literature only. Although Preventive measures like antenatal glucocorticoids, delayed cord clamping, early surfactant administration, and reducing mechanical ventilation were all effective in reducing cardiovascular compromise in preterm babies. However, if cardiovascular compromise does occur and leads to shock, it is unlikely that targeting 1 hemodynamic parameter using a 1-size-fits-all approach is recommendable, thus an approach toward individualized tailored use of inotropes would be of immediate benefit to the patients and the treating physicians, John Dryden,quoted that “first we make our habits, and then our habits make us.” Newborn units in india have been using dopamine as first-line treatment in almost any clinical situation with hemodynamic compromise, even though it has been abandoned by mostNICU in western countries. It seems old habits are hard to break.Seri et al. found an increased BP and urinary output in preterm infants (<2 days) following dopamine administration, but no change in mesenteric and cerebral perfusion indices[11]. Contradictive results have been reported on the effect of dopamine on cerebrovascular autoregulation in infants. Wong et al. found an increased potential for cerebral flow and metabolism coupling, suggesting an improved blood supply in response to demand [12]. Contrary to these findings, Eriksen et al. found dopamine had an adverse effect on cerebrovascular autoregulation in preterm infants8.Burns et al. reported that dopamine was the most commonly used vasoactive agent with a median duration of administration of 46 h and a median maximum dose of 10 µg/kg/min, followed by epinephrine (33 h and 0.3 µg/kg/min,

respectively) and dobutamine (22 h and 8.3 µg/kg/min, respectively), with the increasing use of milrinone, norepinephrine, and vasopressin[69]. There are multiple recent reviews or meta-analyses of dopamine use as an antihypotensive agent for premature neonates[9]. Dobutamine, when compared to dopamine, may have better CO or SVC flows in hypotensive preterm neonates. Interestingly, dobutamine (9.1 ± 1.1 µg/kg/min) improved stroke volume and CO of preterm neonates within 20 min, whereas increases in flow velocities at the cerebral, mesenteric, and renal arteries were observed 8–10 h later. No difference was found in mortality, intraventricular or periventricular hemorrhage, morbidities at term-corrected age, and outcomes at early childhood.[71]

Perhaps, given the comparative studies of dopamine and dobutamine which show that dopamine increases the readily accessible measurement of BP, while dobutamine may increase CO or SVC flows, a measurement often requiring echocardiography, a recent study in the trend of antihypotensive use indicates that dobutamine has decreased from second to fourth most commonly used medication in the treatment of neonatal hypotension [10]

In our study dobutamine was used initially in 41.1% of the babies, dopamine in 19.3% of the babies and combination of dopamine and dobutamine in 34.4% of babies. The difference in our study was that we assessed the haemodynamic derangements and used dobutamine with low cardiac output states and decreased myocardial contractility and dopamine in babies with low BP and high/normal CO. A combination of both the drugs were used in cases with low BP and CO.

VI. CONCLUSION

Low BP should trigger evaluation of the infant's status, including a spectrum physiologic parameters, clinical status, and more objective assessments of the hemodynamic status and deciding about inotrope should be based on etiology based not as one shoe fits for all

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Informed Consent: Informed consent was obtained from all Parents/guardians included in the study

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