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Original Research Article

Mortality and morbidity of neonatal shock in premature babies in a tertiary care neonatal intensive care unit

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ABSTRACT

Background: Despite advances in understanding of pathophysiological changes in neonatal shock, its effect on morbidity and mortality is still an ongoing process. The primary objective was to study etiology-specific mortality and the secondary objective was to study the short-term morbidities of neonatal shock in premature babies born less than 34 weeks of gestation.
Methods: This single centre prospective cohort study was conducted from 01 January 2017 to 31 March 2018. Neonatal shock was defined on clinical and laboratory criteria. Outcomes in terms of mortality and short-term morbidities like intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), acute kidney injury (AKI), chronic lung disease (CLD) and retinopathy of prematurity (ROP) were recorded for analysis.
Results: A total of 119 preterm neonates with shock were enrolled. The most common etiology of neonatal shock was late-onset-sepsis (LOS: 34.4%; n=41) followed by transient circulatory compromise (22.6%; n=27) and early-onset-sepsis (EOS: 14.2%, n=17). The overall mortality of neonatal shock was 15.9% (n=19) out of which 36.8% (n=7) had EOS, 26.3% (n=5) had myocardial dysfunction and 21% (n=4) had LOS ($p<0.05$). On logistic regression, none of the independent variables were significant for mortality. Neonatal morbidities of IVH (> Grade 2), NEC, CLD, AKI and ROP developed in 4.2% (n=5), 11.7% (n=14), 15% (n=18), 27.7% (n=33) and 33. 6% (n=40) respectively.
Conclusions: LOS was the commonest etiology of neonatal shock in preterm neonates. Neonatal shock due to EOS was the major cause of mortality in preterm neonates thus highlighting the need for preventing EOS to improve survival and to reduce neonatal morbidities.

Keywords: Neonatal shock, Morbidity, Mortality, Preterm babies, Early-onset-sepsis

INTRODUCTION

Our approach to hemodynamic monitoring and cardiovascular decision making in neonates has conventionally been based on limited information. There is a lack of readily available information that provides a clear insight into physiology of cardiovascular health and its influence on end organ performance. The problem is further enhanced by the dynamic nature of cardiovascular physiology and its impact on cellular and metabolic mechanisms.[1] A necessary part of our understanding comprises of the outcomes of shock and more specifically how different etiologies affect the outcomes. Enhanced cardiovascular monitoring and earlier therapeutic interventions based on the exact pathophysiological derangements may prove to be an imperative step towards improving survival further and minimizing adverse neurodevelopmental outcome. Advances in neonatology have led to a radical change in our understanding of shock in neonates. The emerging evidence about definition,

diagnosis and management has led to newer guidelines in managing shock in neonates. Despite all this shock continues to be a major cause of morbidity and mortality in the neonatal intensive care units (NICU) across the world.

The primary objective was to study etiology-specific mortality and the secondary objective was to study the short-term morbidities of neonatal shock in babies born less than 34 weeks of gestation.

METHODS

This single centre prospective observational cohort study was conducted over a period of 12 months from 01 January 2017 to 31 December 2017. It was carried out in the neonatal intensive care unit of King Edward Memorial Hospital Pune, a tertiary care teaching hospital in Maharashtra, India after getting institutional scientific and ethical committees approval and written consent from parents. The hospital mainly caters to high-risk pregnancies with approximately 2000 births per year.

The study population comprised of all inborn preterm babies born less than 34 weeks of gestation who developed shock during NICU stay. Babies with structural heart diseases, surgical anomalies, major congenital defects and those who were transferred in from other units, were excluded from this study.

Neonatal shock was defined on the basis of following clinical and laboratory criteria

Clinical criteria included: heart rate >2 SD for age and gestation; blood pressure <3rd centile for that gestational age; capillary refill time >3 seconds; core-periphery temperature difference >3 degree centigrade; and urine output <1.0 ml/kg/hour.[2]

Laboratory criteria included: arterial blood gas for babies born at 30-36 weeks of gestation, normal pH is 7.30 to 7.35 and normal HCO_3 is 22 to 25 and for babies less than 30 weeks, normal pH is 7.27 to 7.32 and normal HCO_3 is 19 mmol/l to 22 mmol/l; base excess >10 mmol/l; and lactate >4.0 mmol/l.[3]

The following criteria was used for defining shock before starting therapy: either a mean BP <3rd centile below threshold or; combination of 2 of the clinical criteria **or; a** capillary refill time >4 seconds and a lactate value >4 mmol/l.[2]

All the enrolled babies were treated as per established treatment protocols depending on the underlying etiology.

Statistical analysis

Baseline data were recorded in a predesigned case record form and a master chart was prepared in Microsoft Excel sheet. Standard statistical methods were used and a descriptive analysis of the study population was done. A univariate analysis was conducted to study the relationship between mortality and the etiology of neonatal shock. To identify the variables significantly and independently associated with the mortality, we performed a multivariate analysis including all the factors with $p<0.05$ on univariate analysis. We used SPSS for Windows 20.0 for analysing the data. P value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 412 preterm babies born before 34 completed weeks of gestation were admitted in our neonatal intensive care unit (NICU) during the study period, out of which 144 developed shock. Out of these 144 eligible babies, 15 declined treatment or were discharged against medical advice, 5 babies had structural heart diseases while 5 babies were syndromic, thus excluded from the study, leaving 119 babies to be enrolled. While calculating the baseline characteristics, we found that 82.3% (n=98) of mothers had received a complete course of antenatal steroids, 53% (n=63) had pregnancy induced hypertension, 40.3% (n=48) had preterm premature rupture of membranes, 6.7% (n=8) of the mothers had antepartum hemorrhage and 54.8% (n=65) delivered by caesarean section. Among the neonates, 77.3% (n=92) were ≤30 weeks of gestation, 47% (n=56) were <1000 grams at birth, 40.3% (n=48) were small for gestational age and 59.7% (n=71) were male babies. Hypotension was present in 61.3% (n=73), tachycardia in 60.5% (n=72), 93.2% (n=111) had a core-periphery temperature difference >3 ^{o}C, 49.5% (n=59) had a capillary refill time of >3 seconds, 20% (n=24) had oliguria while abnormal arterial blood pH (adjusted for gestational age), base excess >10 mmol/l and arterial lactate more than 4mmol/lit was found in 37% (n=44), 34.5% (n=41) and 54.6% (n=65) respectively.

Late-onset-sepsis (LOS: 34.4%, n=41) followed by transient circulatory compromise (22.6%, n=27), early-onset-sepsis (EOS: 14.2%, n=17), myocardial dysfunction secondary to hypoxic-ischemic insult (14.2%, n=14) and hemodynamically significant patent ductus arteriosus (hsPDA) (10%, n=12) were the commonest causes of neonatal shock while persistent pulmonary hypertension of new-born (PPHN) and hypovolemia as a cause of neonatal shock were found in 5% (n=) and 1.7% (n=2) respectively (Figure 1).

The overall mortality of neonatal shock in preterm babies in this study was 15.9% (n=19). Most of these deaths were because of the shock due to EOS (36.8%, n=7; $p<0.05$) followed by shock due to myocardial dysfunction secondary to hypoxic-ischemia insult (26.3%, n=5; $p<0.05$) and shock due to LOS (21%, n=4; $p<0.05$) (Table 1). Logistic regression model showed 13.4-22% variation (Naeglerkerke r^2) in mortality which was not significant when applied to ascertain the effect of gestational age, birth weight, small for gestational age, pregnancy induced

hypertension, antenatal steroids and resuscitation at birth on the likelihood of mortality.

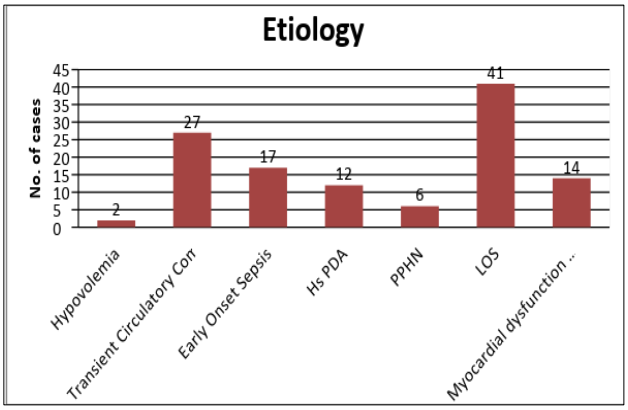

Figure 1: Causes of neonatal shock in premature babies.

The total incidence of IVH in neonatal shock in preterm neonates in this study was 20.1% (n=24) while 4.2% (n=5) babies developed IVH of >grade 2. Neonatal shock due to LOS contributed 37.5% (n=9) of IVH cases, 33.3% (n=8) of IVH cases were because of neonatal shock due to myocardial dysfunction secondary to hypoxic-ischemic insult, 25% (n=6) of the cases were contributed by neonatal shock due EOS while 4.2% (n=1) were because of the shock due to hsPDA. Out of the 5 babies who developed IVH >grade 2, 40% (n=2), 40% (n=2) and 20% (n=1) was in babies who developed shock because of LOS, myocardial dysfunction secondary to hypoxic-ischemic insult and EOS respectively. None of the babies developed grade 4 IVH (Table 2).

Overall incidence of NEC in our cohort was 11.7% (n=14), out of which 2.5% (n=3) had stage 1 NEC, 6.7% (n=8) had stage 2 and 2.5% (n=3) developed stage 3 NEC. Majority of the cases of NEC were seen in babies who developed shock due to LOS (71.4%, n=10), 21.4% (n=3) of NEC cases were in babies developing shock due to myocardial dysfunction secondary to hypoxic-ischemic insult while 7.1% (n=1) of NEC cases were in babies who developed shock due to hsPDA (Table 3).

CLD developed in 23.6% (n=28) of these premature infants with shock out of which 7.6% (n=9) had mild CLD, 12.6% (n=15) had moderate CLD and 3.4% (n=4) developed severe CLD. Neonatal shock due to transient circulatory compromise (28.6%, n=8) and LOS (28.6%, n=8) were the commonest causes of CLD in our cohort followed by shock due to EOS (14.3%, n=4), shock due to hsPDA (10.7%, n=3), shock due to myocardial dysfunction secondary to hypoxic-ischemic insult (10.7%, n=3) and shock due to PPHN (7.1%, n=2) (Table 4).

The incidence of AKI in neonatal shock in premature babies born before 34 weeks of gestation in this study was 27.7% (n=33). The commonest cause of AKI was shock due to LOS (39.4%, n=13) followed by shock due to EOS (30.3%, n=10), shock due to myocardial dysfunction secondary to hypoxic-ischemic insult (21.2%, n=7), shock due to hsPDA (3%, n=1) and shock due to PPHN (3%, n=1) (Table 5).

The incidence of ROP in the cohort was 33.6% (n=40), out of which 15% (n=6) required treatment as shown in table 6. Maximum cases of ROP developed in babies with shock due to LOS (37.5%, n=15) followed by shock due to EOS (20%, n=8), shock due to transient circulatory compromise (15%, n=6), shock due to myocardial dysfunction secondary to hypoxic-ischemic insult (15%, n=6), shock due to hsPDA (7.5%, n=3) and shock due to PPHN (5%, n=2).

Table 1: Mortality of neonatal shock in premature babies.

Etiology	Outcome		P value
	Discharged (%)	Expired (%)	
Early onset sepsis (n=17)	64.7 (n=11)	35.2 (n=6)	<0.05
Late onset sepsis (n=41)	78 (n=32)	22 (n=9)	<0.05
Hypovolemia (n=2)	100 (n=2)	0 (n=0)	<0.05
hs patent ductus arteriosus (n=12)	100 (n=12)	0 (n=0)	<0.05
Transient circulatory compromise (n=27)	100 (n=27)	0 (n=0)	<0.05
Persistent pulmonary hypertension of newborn (n=6)	100 (n=6)	0 (n=0)	<0.05
Myocardial dysfunction secondary to hypoxic-ischaemic insult (n=14)	71.5 (n=10)	28.5 (n=4)	<0.05

hs- hemodynamically significant

Table 2: Incidence of IVH.

Etiology	IVH		
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Early onset sepsis (n=17)	5.9 (n=1)	23.5 (n=4)	5.9 (n=1)
Late onset sepsis (n=41)	12.2 (n=5)	4.9 (n=2)	4.9 (n=2)
Hypovolemia (n=2)	0 (n=0)	0 (n=0)	0 (n=0)

Continued.

Etiology	IVH		
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
hs patent ductus arteriosus (n=12)	8.3 (n=1)	0 (n=0)	0 (n=0)
Transient circulatory compromise (n=27)	0 (n=0)	0 (n=0)	0 (n=0)
Persistent pulmonary hypertension of newborn (n=6)	0 (n=0)	0 (n=0)	0 (n=0)
Myocardial dysfunction Secondary to hypoxic-ischaemic insult (n=14)	21.4 (n=3)	21.4 (n=3)	14.3 (n=2)

hs- hemodynamically significant

Table 3: Incidence of NEC.

Etiology	NEC		
	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)
Early onset sepsis (n=17)	0 (n=0)	0 (n=0)	0 (n=0)
Late onset sepsis (n=41)	4.9 (n=2)	14.6 (n=6)	4.9 (n=2)
Hypovolemia (n=2)	0 (n=0)	0 (n=0)	0 (n=0)
hs patent ductus arteriosus (n=12)	8.3 (n=1)	0 (n=0)	0 (n=0)
Transient circulatory compromise (n=27)	0 (n=0)	0 (n=0)	0 (n=0)
Persistent pulmonary hypertension of newborn (n=6)	0 (n=0)	0 (n=0)	0 (n=0)
Myocardial dysfunction secondary to hypoxic-ischaemic insult (n=14)	0 (n=0)	14.3 (n=2)	7.1 (n=1)

hs- hemodynamically significant

Table 4: Incidence of CLD.

Etiology	CLD		
	Mild (%)	Moderate (%)	Severe (%)
Early onset sepsis (n=17)	5.9 (n=1)	11.8 (n=2)	5.9 (n=1)
Late onset sepsis (n=41)	4.9 (n=2)	9.7 (n=4)	4.9 (n=2)
Hypovolemia (n=2)	0 (n=0)	0 (n=0)	0 (n=0)
hs patent ductus arteriosus (n=12)	8.3 (n=1)	16.7 (n=2)	0 (n=0)
Transient circulatory compromise (n=27)	18.5 (n=5)	11.1 (n=3)	0 (n=0)
Persistent pulmonary hypertension of newborn (n=6)	0 (n=0)	16.7 (n=1)	16.7 (n=1)
Myocardial dysfunction secondary to hypoxic-ischaemic insult (n=14)	0 (n=0)	21.4 (n=3)	0 (n=0)

hs- hemodynamically significant

Table 5: Incidence of AKI.

Etiology	AKI	
	Yes (%)	No (%)
Early onset sepsis (n=17)	58.8 (n=10)	41.2 (n=7)
Late onset sepsis (n=41)	31.7 (n=13)	68.3 (n=28)
Hypovolemia (n=2)	50 (n=1)	50 (n=1)
hs patent ductus arteriosus (n=12)	8.3 (n=1)	91.7 (n=11)
Transient circulatory compromise (n=27)	0 (n=0)	100 (n=27)
Persistent pulmonary hypertension of newborn (n=6)	16.6 (n=1)	83.4 (n=5)
Myocardial dysfunction secondary to hypoxic-ischaemic insult (n=14)	50 (n=7)	50 (n=7)

hs- hemodynamically significant

Table 6: Incidence of ROP.

Etiology	ROP		
	Prethreshold (%)	Threshold (%)	Aggressive posterior (%)
Early onset sepsis (n=17)	17.7 (n=3)	17.7 (n=3)	11.7 (n=2)
Late onset sepsis (n=41)	26.8 (n=11)	4.9 (n=2)	4.9 (n=2)

Continued.

Etiology	ROP		
	Prethreshold (%)	Threshold (%)	Aggressive posterior (%)
Hypovolemia (n=2)	0 (n=0)	0 (n=0)	0 (n=0)
hs patent ductus arteriosus (n=12)	16.6 (n=2)	8.3 (n=1)	0 (n=0)
Transient circulatory compromise (n=27)	7.4 (n=2)	7.4 (n=2)	7.4 (n=2)
Persistent pulmonary hypertension of newborn (n=6)	0 (n=0)	16.7 (n=2)	0 (n=0)
Myocardial dysfunction secondary to hypoxic-ischaemic insult (n=14)	21.4 (n=3)	14.2 (n=2)	7.3 (n=1)

hs- hemodynamically significant

DISCUSSION

The study was carried out to study the etiology based outcomes of neonatal shock in babies born before 34 completed weeks of gestation. The etiology was formulated based on the history and clinical parameters in the baby and was confirmed based on laboratory criteria. There was no mortality when the etiology of shock was transient circulatory compromise, hsPDA, PPHN or hypovolemia. Our study observed a mortality rate of 35.2% when the etiology of neonatal shock was EOS. In a study by Francis et al the mortality was 18.5% while a study by Brodshka et al observed a mortality of 40% in this cohort.[4-5] Neonatal shock due to myocardial dysfunction secondary to hypoxic-ischemic insult was responsible for 28.5% of the deaths in the cohort. In a study by Frauenschuh et al the mortality was 12.5% in cases with intrauterine hypoxia.[6]

IVH is a common injury in preterm babies. The predisposition is due to having a pressure passive circulation because of lack of auto regulation of blood flow.[7] The overall incidence of IVH in our study was 18.5% out of which 4.2% developed severe IVH (grade 3) while none had grade 4 IVH. In the EPIPHAGE II study the incidence of severe IVH was 14% (OR=3.4; CI: 1.07-9.4).[8] Faust et al observed that 20.3% of babies with neonatal shock developed IVH during first three days of life.[9] A study by Satar et al found no association between EOS and IVH while a study by Viscardi et al observed that the babies with EOS had 2.3 fold chances of developing severe IVH (OR=2.5; CI: 1.06-5.89).[10-11]

NEC is one of the most severe complications of preterm birth occurring in 5–10% of very low birth weight infants[12-13]. The overall incidence of severe NEC (stage II/stage III) in our study was 11.7%. Gephart et al found that neonatal shock requiring inotropic treatment and LOS were associated with an increased risk of NEC.[14] Youn et al observed that hypotension within a week of life is an independent risk factor for NEC.[15]

CLD is a common pulmonary morbidity in premature infants. As more premature infants survive, its incidence is increasing especially in extremely low birth weight babies. In our study, the overall incidence of CLD was 23.3% out of which 7.5% cases were of mild CLD, 12.5% cases of moderate CLD and 3.3% cases of severe CLD. The incidence of CLD in EPIPHAGE II study was 22.4%.[8]

ROP is a leading cause of childhood blindness and the main cause of visual impairment in premature infants, posing an increasing concern due to advances in neonatal care and increased survival of extremely preterm infants.[16] In our study total babies developing ROP were 33.3% and babies developing severe ROP were 16.7%. Melissa et al in their study observed 65% of preterm babies with shock developed ROP.[17] In a study by Yau et al the incidence of ROP and severe ROP was 53.4 and 14.5%, respectively.[18]

The limitations of this study are the heterogeneity of the gestational age and birth weight of our cohort ranging from 23 weeks to 33 weeks and 630 grams to 1700 grams, respectively, limited number of babies with certain etiologies such as hypovolemia, hsPDA and PPHN which could prove to be a hindrance in applying the results on large population.

CONCLUSION

Late-onset-sepsis was the commonest etiology of neonatal shock in preterm neonates. Neonatal shock due to early-onset-sepsis was the major cause of mortality in preterm neonates thus highlighting the need for preventing EOS to improve survival and to reduce neonatal morbidities.

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