ORIGINAL ARTICLE

CORRELATION OF SEVERITY OF METABOLIC ACIDOSIS AT ADMISSION AND OUTCOME IN ASPHYXIATED NEONATES

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Background: Blood gases can provide information about the perinatal, natal and postnatal condition of newborn. Severity of metabolic acidosis has deleterious effect on the outcome of babies. When the cord blood gases are not available the arterial blood gases are used for interpreting the status of newborn. The purpose of study was to determine the relationship between severity of metabolic acidosis at admission with the stage of hypoxic ischemic encephalopathy, and its outcome in asphyxiated neonates. **Methods:** This was descriptive cross-sectional study of 384 neonates born at ≥35 weeks to <42 weeks from June to December 2018, admitted in Neonatology department of the Children's hospital & the Institute of Child Health, Lahore within first 6 hours of birth. The neonates with history of delayed cry at birth and arterial pH ≤7.30 and base deficit ≥10 were included in the study. The pH and base deficit of babies was analyzed in relation to the stage of HIE, duration of stay and death or discharge of the babies using SPSS-20. The *p*-value was calculated using chi-square test. **Results:** Total of 470 neonates were eligible. Eighty-four neonates were excluded. Finally, 384 neonates were included and analyzed for the outcome variables. With severe metabolic acidosis pH <7.01, all the babies developed HIEII/III. Majority (82.1%) of the babies expired and 27.9% had prolonged hospital stay. **Conclusion:** Increasing severity of metabolic acidosis at admission increases the likelihood of adverse outcome in asphyxiated neonates.

Keywords: HIE; Metabolic acidosis; Base deficit; Adverse outcome

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INTRODUCTION

Neonatal mortality is very high globally and of the estimated 140 million infants born every year 2.7 million die in the neonatal period which accounts for 45% of under-five years deaths.[1,2]

Pakistan is one of the countries with highest neonatal mortality rate (NMR) in the world. According to PDHS survey 2017–18, NMR of Pakistan is 42 per 1000 live births.[3] Among the causes of neonatal deaths in Pakistan, asphyxia accounts for 25% of total neonatal mortality.[4]

The best indicator of intrapartum asphyxia is severe metabolic acidosis (pH<7.0, base deficit ≥12 mmol/L) in umbilical cord arterial blood at delivery. The umbilical cord blood pH<7.0 or base deficit ≥12mmol/L are threshold beyond which the risk of adverse outcome is considered to be increased.[5,6]

The relationship between severity of metabolic acidosis at birth and immediate condition of the infant and risk of subsequent encephalopathy is not well characterized. A study of infants born at 35 weeks of gestation and more shows significant association between severity of acidosis at the time of birth and adverse neonatal and long term neurodevelopment outcome.[7] Other studies have shown uncertainty about the prognostic value of the degree of acidosis at birth, despite cord pH being used as an outcome measure in obstetric clinical trials.[8]

The neonatal data regarding the effect of severity of acidosis on neonatal outcome is lacking. This study is aimed to describe correlation between severity of metabolic acidosis at admission and the risk of severe neonatal encephalopathy and its outcome. The results shall help in early identification of neonates with HIE who most likely to benefit from therapeutic interventions, in rationalizing resources for their management, their long term follow up and counseling of parents.

MATERIAL AND METHODS

This descriptive cross-sectional study was done at Neonatology department of The Children's Hospital and The Institute of Child Health, Lahore from June to December 2018 after taking approval from institutional review board. This is a tertiary care hospital and receives babies from Punjab as well as other parts of the country. The department of Neonatology is 40 bed unit with 8 bed NICU. All the babies admitted here are out born. It has facilities of intensive care, total body hypothermia as well as conventional and high frequency ventilation. The unit attends outpatient clinic three times a week and

manages independent neonatal emergency which functions 24/7. Our study included all babies with gestational age of ≥35 weeks to <42 weeks with history of delayed cry at birth, pH≤7.30, base deficit of 10 or more and received in emergency within first 6 hours of birth. Birth aphyxia is defined as failure to initiate and sustain breathing at birth.[9] So we took asphyxiated neonates as those neonates who presented with history of delayed cry at birth. Hypoxic ischemic encephalopathy was defined as signs and symptoms of neurological dysfunction due to lack of oxygen or blood supply to brain resulting from asphyxia, when other causes of neonatal encephalopathy have been excluded.[10] It was classified into three stages, HIE I, II and III based on Sarnat staging.[11] Arterial blood gases were taken at the time of admission and analyzed using cobas b 121 blood gas analyzer system. Details of neonates including gender, birth weight, gestational age, age at admission, arterial blood gases, stage of HIE using Sarnat staging, duration of stay, discharge and death were entered on predesigned proforma after taking consent from parents or guardian. Babies with hypothermia, hypoglycemia, suspected IEM, pulmonary hypertension, congenital heart disease, sepsis, surgical problems, syndromes, brain malformations, incomplete data and treatment received from other hospital and those receiving therapeutic hypothermia were excluded. The objective of study was to see the correlation of severity of acidosis at admission and the stage of HIE, duration of stay, discharge from hospital or death in asphyxiated neonates.

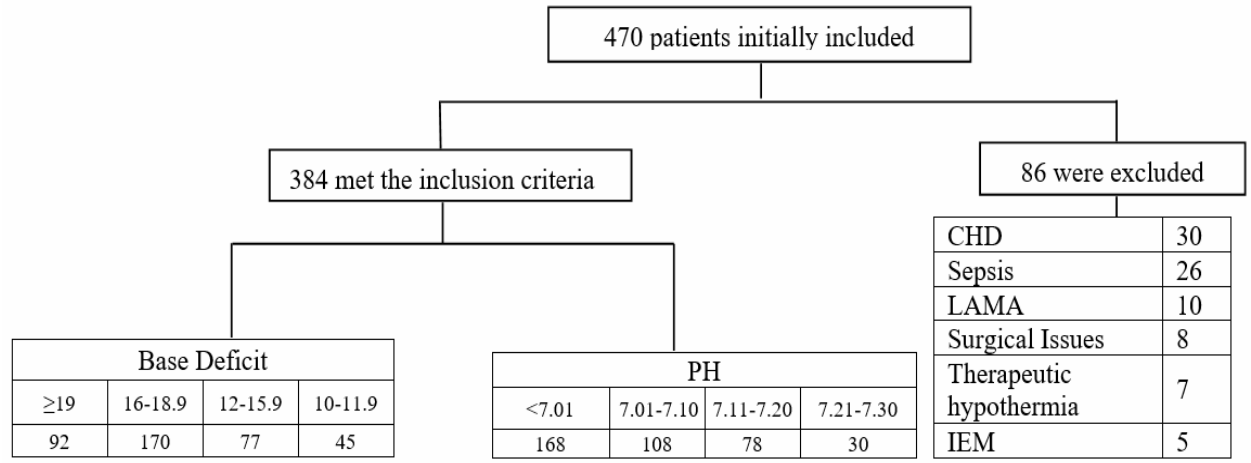

Figure-1: Flow chart of study sample for analysis

Table-1: Demographic data and outcome

Demographic Data		HIE n (%)			Duration of Stay n (%)			Death n (%)
		I	II	III	<4 Days	4-7 days	>7 days	
Gender	Male	46 (11.9)	77 (20.0)	93 (24.2)	91 (23.7)	61 (15.8)	64 (16.6)	154 (40.1)
	Female	45 (11.7)	61 (15.8)	62 (16.1)	91 (23.7)	47 (12.2)	30 (7.8)	62 (16.1)
Age at presentation (hours)	<1	31 (8.0)	61 (15.9)	31 (8.0)	46 (11.9)	47 (12.2)	30 (7.8)	31 (8.0)
	1-<3	15 (3.9%)	77 (20.0)	124 (32.3)	91 (23.7)	61 (15.9)	64 (16.6)	185 (48.2)
	3-6	45 (11.7%)	0	0	45 (11.7)	0	0	0
Weight (Kg)	2.2-<2.5	31 (8.0)	16 (4.2)	15 (3.9)	46 (11.9)	16 (4.2)	0	15 (3.9)
	2.5-3.5	45 (11.7%)	91 (23.7)	124 (32.3)	105 (27.3)	77 (20.0)	78 (20.3)	154 (40.1)
	>3.5	15 (3.9)	3 1(8.0)	16 (4.2)	31 (8.0)	15 (3.9)	16 (4.2)	47 (12.2)

Table-2: Significance of HIE Stage II and III in relation to pH

PH	HIE stage		*p*-value
	II	III	
7.11–7.20	16 (20.5%)	16 (20.5%)	0.009
7.01–7.10	47 (43.5%)	46 (42.6%)	<0.001
<7.01	75 (44.6%)	93 (55.4%)	0.0012

Table-3: Significance of HIE stage II and III in relation to base deficit

Base Deficit	HIE stage		*p*-value
	II	III	
12-15.9	31(40.3%)	0	<0.001
16-18.9	91(53.5%)	79(46.5%)	<0.001
>19	16(17.4%)	76(82.6%)	0.005

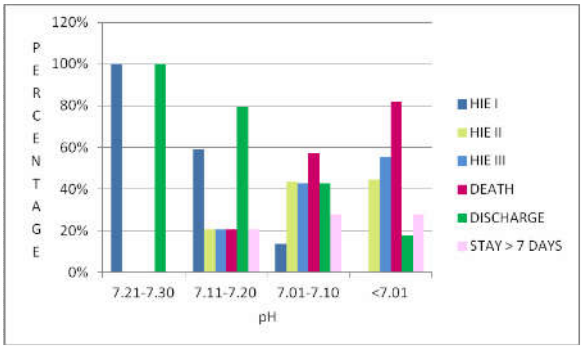

Figure-2: pH and outcome of asphyxiated neonates

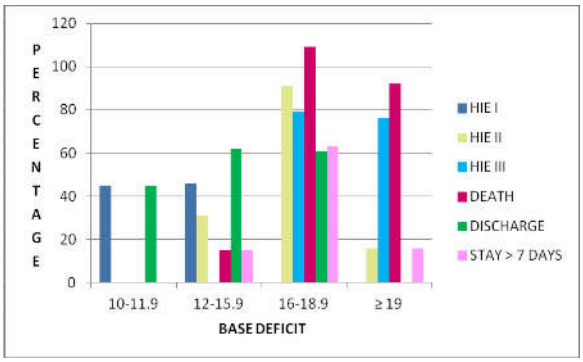

Figure-3: Base Deficit and outcome of asphyxiated neonates

Statistical Analysis: There were 470 newborns initially recruited in the study. Sample size was calculated using 80% power of test, 5% level of significance and neonatal mortality due to asphyxia as 25%. Eighty-six neonates were excluded due to various reasons (Figure-1). Finally, 384 neonates were analyzed for the outcome variables using SPSS version 20.0. Significance of stage II/III encephalopathy with metabolic acidosis using pH and base deficits independently was calculated by applying chi-square test. *p*-value less than 0.05 was taken as significant.

RESULTS

Of the 384 neonates who were continued into the study, 216 (56.3%) were males and 168 (43.8%) were females. Among the study group 16.1% weighed <2.5 kg, 67.7% from 2.5–3.5 kg and 16.1% were >3.5 kg of weight. 32% babies presented within 1hour of life, 56.3% in 1–3 hours and 11.7% presented in 3–6 hours of life. Death occurred in 216 (56.3%) neonates and 168 (43.8%) survived to discharge. Most of the asphyxiated neonates 182 (47.3%) stayed in hospital for less than 4 days. While 108 (28.1%) babies stayed from 4–7 days and 94 (24.5%) remained in hospital for more than 7 days.

pH: This included 168 (43.7%) babies with the lowest pH <7.01, out of them none had HIE stage I, 75 (44.6%) developed HIE II and 93 (55.3%) had HIE III. Death occurred in 138 (82.1%) neonates in the same group and 47 (27.9%) babies remained in hospital for more than 7 days. One hundred and eight neonates had pH 7.01–7.10, 15(13.9%) of them had HIE I, 47 (43.5%) HIE II, 46 (42.6%) HIE III, while 62 (57.4%) died and 31 (28.7%) had hospital stay of more than 7 days. There were 78 (20.3%) babies with pH 7.11–7.20, 46 (59%) of them developed HIE I while 16 (20.5%) developed each stage HIE II and III. In this pH range 62 (79.5%) were discharged home and 16 (20.5%) stayed in hospital for more than 7 days. Thirty babies were admitted having pH 7.21–7.30, all had HIE Stage I, none of them died and all were discharged in less than 4 days. Figure-2 shows the admitted neonates with different pH range and their outcome. Table-II shows significance of HIE II and HIE III with respective pH ranges.

Base Deficit: Of the total 384 patients, 92 (24%) neonates had severe base deficit >19 and of them all developed Stage II 16 (17.3%), and Stage III 76 (82.6%) hypoxic ischemic encephalopathy. All of the babies in the same group died. Duration of stay was more than 7 days in 16 (17.3%) such babies. There were 45 neonates with lowest base deficit in the study of 10–11.9, all of them had HIE I and all were discharged to home within 4 days. Figure-3 describes neonates with different base deficit and their respective outcome. Table-3 shows significance of HIE II and HIE III with base deficit.

Duration of stay: Most of the asphyxiated neonates 182 (47.3%) stayed in hospital for less than 4 days. While 108 (28.1%) babies stayed from 4-7 days and 94(24.5%) remained admitted for more than 7 days.

DISCUSSION

World-wide neonatal mortality is very high. Pakistan is one of the countries with highest neonatal mortality rate (NMR). Among the causes of neonatal deaths in Pakistan, asphyxia contributes to 25% of total neonatal mortality.[4] Early identification of newborns who are most likely to benefit from therapeutic interventions for hypoxic-ischemic encephalopathy is important to reduce the high mortality and morbidity associated with it.

Umbilical cord blood is usually taken in high risk deliveries especially in intrapartum asphyxia for blood gas analysis to detect metabolic acidosis. We receive babies which are out born and cord blood pH and lactate analysis record is not available for these babies. Due to same reason we have taken arterial blood sample for blood gas analysis. So our study provides the predictive value of acidosis for the outcome in such settings and also includes babies whose umbilical cord values may not reflect the degree of acidosis at the time of delivery; example cases of cord obstruction. It is also the fact that although strongly correlated with adverse

outcome, cord gas analysis is neither very sensitive nor specific for adverse outcomes.[12–14]

Males have been receiving the medical attention more than females and various studies in asphyxiated neonates show the male predominance over females.[15–17] Similarly in our study males are dominating however, there was no major difference, male to female ratio of 1.28:1.

The acidosis in asphyxiated neonates has been studied in term and preterm babies independently as the preterm babies have many other contributing factors for their morbidity and mortality.[16,18,19] Our study population also included babies 35–0/7 weeks or more due to same reasons. Majority (67.7%) of our neonates weighed 2.5–3.5 kg, which is similar to study of asphyxiated neonates in Karachi, where 57% of the newborns weighed more than 2.5 kg.[18] This is because we have included only late preterm and term babies.

In our study we have analyzed pH and base deficit independently and correlated them with the stage of HIE, duration of stay and death. However, whether base deficit adds any additional information than that provided by the pH was not analyzed. Most of the previous studies used either pH or base deficit to correlate the outcome. Low et al showed increasing umbilical arterial base deficit correlated with complications however arterial pH were not studied.[20] Another study by Andres et al showed that increasing base deficit was associated with greater risk of complications including encephalopathy. In this study also it was not excluded that arterial pH was lower in neonates with greater base deficit.[21] Yeh *et al* in a cohort study showed increased risk of adverse neurological outcome at a pH<7.0 and that above a pH of 7 neonatal acidemia is weakly associated with adverse outcome. Base deficit was not analyzed for the outcome in this cohort.[12] A cohort study in term neonates showed that pH is a significant predictor of adverse outcome, encephalopathy grade II/III and or death. However, it showed that the base deficit did not improve the prediction of outcome.[22]

In our study stage II/III encephalopathy was significantly higher. All the neonates with pH <7.01 developed HIE II/III (p=0.0012) and 82.1% of them died. Similarly, majority 86.4% developed HIE Stage II/III with base deficit >12 mmol/L and 63.7% died. A systematic review and meta-analysis conducted by Malin *et al* to find association between umbilical cord pH and outcome showed that low pH is associated with neonatal mortality, HIE, intraventricular hemorrhage, periventricular leukomalacia and cerebral palsy. However, the study population included both term and preterm infants and the variables and threshold used to define significant acidosis varied among papers.[23] There is sparse data available that relates base deficit to the outcome in term infants. A study of cord blood base deficit showed that 40% of the newborns developed complications with base deficit >16 mmol/L.[20] Another study in term newborns with arterial blood gases taken between 30th and 45th minutes of life showed that moderate or severe encephalopathy occurred in 26% of patients with base deficit greater than 10 mmol/L and in 79% with base deficit higher than 18mmo/L.[24] Therefore, our study is in accordance with previous studies which show the predictive importance of pH and base deficits in asphyxiated infants.

Another important consideration is that the duration of stay was shorter in many of the asphyxiated neonates because 70.3% of the deaths occurred within 7 days of life. Thus, fewer survived beyond 7 days. This might also be because the critically sick neonates are referred to our hospital and hence have higher chances of mortality.

Limitation of this study is that since the hospital receives the sickest newborns it is likely that there may be other acidotic infants who had acidosis but remained well and not referred to us. Thus, the extent to which acidosis may predict the adverse outcome may be overestimated. We also did not examine the babies with only high base deficit so we are limited in interpretation of importance of base deficit in non-acidemic neonates and thus cannot comment on which measure of arterial blood gases, whether pH or base deficit, is most useful for prediction of outcome. Arterial pH was found to be the best predictor of outcome by Gergieva *et al*.[25] We also need further studies to further understanding as why neonates with similar arterial blood gases have different outcome as it involves different mechanisms of injury and also obstetrical insults are multifactorial.

CONCLUSION

This study defines a clear relationship between degree of acidosis and outcome. Increasing severity of metabolic acidosis at admission increases the likelihood of adverse outcome in asphyxiated neonates. It may help in rationalizing resources for the management of such babies in resource restricted settings, decreasing the future burden of morbidity and for counseling of parents and follow up of patients.

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AUTHORS' CONTRIBUTION

JY: Conception of study design, acquisition, analysis and interpretation of data, drafting and revising, final approval. SH, FH, KAIW, MUK, MQK: Conception of study design, collection, analysis, data interpretation, drafting, proof reading, final approval.

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