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Original Article

Correlation between umbilical venous blood gas at birth and comorbidities in preterm babies - A cohort study

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ABSTRACT

Background: Umbilical cord blood gas analysis is a useful tool in predicting short-term outcomes in term infants. The value of umbilical venous blood gas analysis in predicting short-term outcomes in preterm infants is less clear. **Objectives:** The study was carried out to determine the correlation between venous blood gases and various antenatal and natal characteristics as well as short term comorbidities in preterm infants born before 34 weeks of gestation. **Methods:** In a cohort study, 74 preterm infants born before 34 weeks of gestation were enrolled, and umbilical venous blood gas analysis was performed within 1 h of birth. All preterm infants with pH <7.20, lactate >4 mmol/L and bicarbonate <15 mmol/L were compared with those with pH ≥7.20, lactate ≤4 mmol/L, and bicarbonate ≥15 mmol/L. Antenatal and natal characteristics such as steroid administration, gestational diabetes, pregnancy-induced hypertension (PIH), birth weight, gestational age, APGAR score, and need for resuscitation were recorded and compared between the two groups. Various neonatal comorbidities were also analyzed in the two groups. **Results:** Lactate >4 mmol/L and bicarbonate <15 mmol/L showed a significant association (p=0.03 and 0.02, respectively) with PIH. Lactate >4 mmol/L showed a significant association with neonatal death (p=0.01) and thrombocytopenia was significantly associated with bicarbonate <15 mmol/L (p=0.01). All comorbidities were higher in the group with abnormal blood gases although statistically insignificant. **Conclusion:** Venous blood gas analysis is an important tool in predicting mortality in preterm babies.

Key words: *Preterm, Short term co morbidities, Umbilical venous blood gas*

Umbilical cord blood gas analysis can provide very important information about the preceding hypoxic stress, the present condition and can possibly predict the future condition of the baby [1]. The umbilical cord blood gas analysis is now recommended in all high-risk deliveries by both the British and American Colleges of Obstetrics and Gynecology [2]. Several studies have shown the association between low pH and short-term morbidities as well as adverse long-term neurological outcomes. Some have studied pH 7.2, whereas most of the studies are on lower pH values [3]. Goldaber et al. recommended that a realistic value for defining pathological acidemia is pH <7.004 [4]. In a study of 4045 cord samples, Westgren et al. showed that lactate was similar to both pH and base excess in its ability to predict low APGAR scores, and other selected short-term morbidities [5]. The value of umbilical venous blood obtained in the neonatal ICU for predicting morbidity and mortality in preterm infants is less clear. Studies demonstrating the relationship between low pH, high lactate, low bicarbonate levels, and various short-term adverse outcomes are also limited. Therefore, we planned this study to find the correlation between venous blood gas measurements taken within 1 h of birth and the comorbidities in the neonatal period in preterm babies <34 weeks of gestation. The association with various antenatal and natal characteristics was also studied.

METHODS

This cohort study was conducted over 6 months from November 2014 to April 2015 at a tertiary care centre in North Kerala after obtaining approval from the Institutional Ethics Committee. Preterm babies born at or before 34 weeks of gestation during the study, who required umbilical venous catheterization for venous access in the neonatal intensive care unit, were included in the study. Babies with major congenital anomalies were excluded from the study. Umbilical venous blood gases were obtained within 1 h of delivery by umbilical venous catheterization. All samples were sent in pre-heparinized syringes and prepared under the aseptic condition and occupational safety. The samples were analyzed by arterial blood gas analyzer. Infants with blood pH <7.20, lactate levels >4 mmol/L, and bicarbonate levels <15 mmol/L were compared with those with pH ≥7.20, lactate ≤4 mmol/L, and bicarbonate ≥15 mmol/L.

Antenatal and natal characteristics such as sex, antenatal steroid administration, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), birth weight categorized

into less than 1000 g and more than 1000 g, gestational age categorized into less than28 weeks and more than 28 weeks, APGAR score at 1 min and 5 min and need for resuscitation in the form of bag and mask or bag and tube ventilation were recorded.

The infants were followed up during the neonatal period. The outcome variables recorded include hyaline membrane disease (HMD) (clinical features of respiratory distress in a preterm with chest X-ray showing reticulogranular pattern with air bronchograms and blood gases showing hypoxia and respiratory acidosis), patent ductus arteriosus (PDA) (hemodynamically significant PDA diagnosed based on the clinical features and confirmed by echocardiography), pulmonary hemorrhage (oozing of blood from nose and mouth or endotracheal tube with worsening of respiratory status and chest X-ray showing patchy infiltrates to complete opacification of lung fields), necrotizing enterocolitis (NEC) (diagnosed based on Bell staging), hypotension (mean blood pressure lower than the gestational age of the baby), pneumothorax (diagnosed by chest X-ray), intraventricular hemorrhage (IVH) (diagnosed by neurosonogram in babies with clinical suspicion, sepsis, (culture proven), seizures, feed intolerance, hypoglycemia (plasma glucose <45 mg/dl), hyperglycemia (plasma glucose >145 mg/dl), hypocalcemia (total serum calcium <7 mg/dl), anemia (hemoglobin <14 g/dl at birth), polycythemia (venous hematocrit ≥65%), thrombocytopenia (platelet count ≤1.5 lakhs/mm^3), retinopathy of prematurity, bleeding manifestations and death.

Data were entered into the Microsoft Excel 2010 and analyzed using Epi info 7 software applying the Chi-square test. The value of p<0.05 was considered statistically significant.

RESULTS

Over 6 months, venous blood gases were obtained within 1 h of birth from 74 preterm babies below 34 weeks of gestation. The various characteristics such as GDM, PIH, reception of antenatal steroids, extremely low birth weight, extreme prematurity, male gender and a low APGAR of <7 at 1 and 5 min and need for resuscitation were more in neonates with pH <7.20 but were not statistically significant. The relation between the above characteristics and lactate levels were analyzed in 64 preterm babies, and a significant association (p=0.03) was obtained between lactate >4 mmol/L and PIH. The relation between venous bicarbonate levels and the perinatal parameters in 73 babies were analyzed. PIH was found to have a significant association with bicarbonate levels ≤15 mmol/L (p=0.02).

Comparison of various short-term outcomes such as HMD, pulmonary hemorrhage, sepsis, NEC, seizures, IVH, anemia, polycythemia, thrombocytopenia, pneumothorax, hypotension, hypoglycemia, hyperglycemia, hypocalcemia, bleeding manifestations, neonatal death, and pH <7.20 were analyzed, but none of these outcomes had a significant association (Table 1). Similarly, comparison between various neonatal complications and lactate levels >4 mmol/L and bicarbonate levels <15 mmol/L were performed as shown in Tables 2 and 3, respectively. Neonatal death was found to be significantly associated with high lactate levels (p=0.01) and thrombocytopenia showed significant association with low bicarbonate levels (p=0.01).

Table 1: Difference in incidence of neonatal complications at pH<7.20 or pH≥7.20 (N=74)

Neonatal complications	N (%)		p value
	pH≥7.20	pH>7.20	
HMD	34 (63.0)	10 (50.0)	0.4
PDA	4 (7.4)	2 (10.0)	0.7
Pulmonary hemorrhage	1 (1.9)	0 (0.0)	0.9
NEC	1 (1.9)	1 (5.0)	0.4
Hypotension	6 (11.1)	0 (0.0)	0.1
Pneumothorax	2 (3.7)	0 (0.0)	0.6
IVH	3 (5.6)	0 (0.0)	0.5
Sepsis	15 (27.8)	5 (25.0)	0.9
Seizures	0 (0.0)	1 (5.0)	0.3
Feed intolerance	7 (13.0)	5 (25.0)	0.3
Hypoglycemia	1 (1.9)	2 (10.0)	0.2
Hyperglycemia	5 (9.3)	1 (5.0)	0.6
Hypocalcemia	4 (7.4)	3 (15.0)	0.4
Anemia	1 (1.9)	1 (5.0)	0.4
Polycythemia	1 (1.9)	0 (0.0)	0.9
Thrombocytopenia	6 (11.1)	1 (5.0)	0.7
ROP	3 (5.6)	2 (10.0)	0.6
Bleed	2 (3.7)	0 (0.0)	0.9
Died	6 (11.1)	0 (0.0)	0.2

HMD: Hyaline membrane disease, PDA: Patent ductus arteriosus, NEC: Necrotizing enterocolitis, IVH: Intraventricular hemorrhage, ROP: Retinopathy of prematurity

Table 2: Difference in incidence of neonatal complication and mortality at UVB lactate level≤4 and >4 mmol/L (n=64)

Neonatal complications	N (%)		p value
	Lactate≤4 mmol/L	Lactate>4 mmol/L	
HMD	28 (65.1)	12 (57.1)	0.6
PDA	4 (9.3)	1 (4.8)	0.7
Pulmonary hemorrhage	0 (0.0)	1 (4.8)	0.3
NEC	1 (2.3)	1 (4.8)	0.9
Hypotension	4 (9.3)	2 (9.5)	0.9
Pneumo thorax	2 (4.7)	0 (0.0)	0.5
IVH	1 (2.3)	1 (4.8)	0.9
Sepsis	9 (20.9)	6 (28.6)	0.5
Apnea	7 (16.3)	4 (19.0)	0.9
Seizures	1 (2.3)	0 (0.0)	0.9
Feed intolerance	8 (18.6)	3 (14.3)	0.9
Hypoglycemia	3 (7.0)	0 (0.0)	0.5
Hyperglycemia	3 (7.0)	1 (4.8)	0.9
Hypocalcemia	5 (11.6)	1 (4.8)	0.6
Anemia	1 (2.3)	1 (4.8)	0.9
Thrombocytopenia	2 (4.7)	4 (19.0)	0.08
ROP	3 (7.0)	1 (4.8)	0.9
Bleed	0 (0.0)	2 (9.5)	0.1
Died	1 (2.3)	5 (23.8)	0.01

HMD: Hyaline membrane disease, PDA: Patent ductus arteriosus, NEC: Necrotizing enterocolitis, IVH: Intraventricular hemorrhage, ROP: Retinopathy of prematurity, UVB: Ultraviolet B

Table 3: Incidence of neonatal complication and mortality at UVB bicarbonate level<15 and ≥15 mmol/L (N=73)

Neonatal complications	N (%)		p value
	Bicarbonate<15 mmol/L	Bicarbonate≥15 mmol/L	
HMD	27 (67.5)	17 (51.5)	0.2
PDA	4 (10.0)	2 (6.1)	0.6
Pulmonary hemorrhage	1 (2.5)	0 (0.0)	0.9
NEC	2 (5.0)	0 (0.0)	0.5
Hypotension	4 (10.0)	2 (6.1)	0.4
Pneumothorax	2 (5.0)	0 (0.0)	0.5
IVH	3 (7.5)	0 (0.0)	0.2
sepsis	13 (32.5)	7 (21.2)	3
apnea	6 (15.0)	9 (27.3)	0.2
seizures	0 (0.0)	1 (3.0)	0.4
Feed intolerance	8 (20.0)	4 (12.1)	0.5
Hypoglycemia	0 (0.0)	3 (9.1)	0.09
Hyperglycemia	4 (10.0)	2 (6.1)	0.6
Hypocalcemia	3 (7.5)	4 (12.1)	0.7
Anemia	1 (2.5)	1 (3.0)	0.9
Polycythemia	1 (2.5)	0 (0.0)	0.9
Thrombocytopenia	7 (17.5)	0 (0.0)	0.01
ROP	2 (5.0)	3 (9.1)	0.4
bleed	2 (5.0)	0 (0.0)	0.4
Died	3 (7.5)	3 (9.1)	0.9

HMD: Hyaline membrane disease, PDA: Patent ductus arteriosus, NEC: Necrotizing enterocolitis, IVH: Intraventricular hemorrhage, ROP: Retinopathy of prematurity, UVB: Ultraviolet B

DISCUSSION

This study showed that neonatal death was significantly associated with high lactate levels while thrombocytopenia was significantly associated with low bicarbonate levels. Preterm babies born to mothers with PIH were also found to be related to high lactate and low bicarbonate levels at birth. Other parameters such as HMD, pulmonary hemorrhage, NEC, sepsis, seizures, IVH, hypoglycemia, hyperglycemia, hypocalcemia, anemia, and polycythemia were not found to be associated with abnormal pH, lactate, and bicarbonate levels. The previous study, carried out to demonstrate the relationship between placental histological features and cord blood gases in preterm neonates, found that lesions related to poor blood gas values were significantly more frequent in preterm preeclampsia [6]. This study also proved a similar relationship between maternal PIH and abnormal blood gases.

Another study found no significant relation between birth weight, and medical disease of mothers including PIH with acidosis (p=0.05) [7]. Although our study did not show a relationship between acidemia and PIH, abnormal lactate, and bicarbonate levels were significantly related to PIH. PIH was determined as one of the risk factors of fetal distress and acidemia at birth which was demonstrated in a study on fetal distress after hydralazine therapy for PIH [8].

In a study on 93 neonates, no correlation could be demonstrated between the umbilical cord PCO_2, PO_2, pH, bicarbonate, and base deficit with death, need of resuscitation, convulsions, respiratory distress syndrome, PDA, NEC, intrauterine growth retardation, sepsis, and hypoxic ischemic encephalopathy (HIE) [9]. Perlman and Risser showed that a combination of cord pH <7.0, requirement for intubation and a 5-min APGAR score of ≤5 had an 80% positive predictive value for the development of seizures in the term, singleton babies [10]. Several studies, mostly on umbilical arterial blood and few on venous blood have been able to show that death was more likely at pH <7 and seizures at pH<7.05. The recommended cut-off for defining pathological acidemia was pH <7.00 according to some researchers [4]. In our study, we have taken a cut-off of 7.20 and we could not demonstrate any significant association.

Umbilical cord pH <7.20 has also been studied as a prognostic factor for birth asphyxia and other short-term outcomes. In a systematic review, low arterial cord pH was significantly associated with perinatal and long-term neonatal outcomes such as mortality, HIE, IVH, or periventricular leukomalacia and cerebral palsy [11]. However, similar studies on venous blood are not available. The sex predilection of fetal and neonatal academia has also been studied by the researchers. Perinatal acidemia was more common in male neonates, and they were more prone to fetal distress and low APGAR score [12]. This finding corresponds with our study, which showed a mild predominance of perinatal acidemia in male newborns. Ahmadpour-Kacho et al. found that an umbilical cord pH <7.20 immediately after birth can be used

as a prognostic factor for unfavorable short-term outcome in newborns [13].

Victory et al. studied the relationship between fetal acidemia and adverse outcomes in a large cohort of preterm and very preterm infants (32-36 weeks and 25-32 weeks, respectively) and found that there is no discrimination between umbilical artery and vein as the acidosis worsens [14]. This study showed an increased incidence of adverse outcomes in preterm babies with low umbilical cord pH, but the association was not statistically significant. Hibbard et al. studied umbilical cord blood gas values and morbidity and mortality in 191 very low birth weight infants. The mean umbilical arterial pH and base excess differed significantly between survivors and non-survivors. The presence of at least moderate acidosis (arterial pH 7.15 or lower) was related significantly to mortality, particularly in infants younger than 26 weeks. The mean cord blood gas values did not predict the presence or severity of HMD or IVH, but APGAR scores did. Bronchopulmonary dysplasia, neurologic sequelae, NEC, and sepsis also did not correlate with mean cord gas values [15].

The fact that pH or base excess cannot be used as proxy measures for blood lactate and the importance of measuring lactate independently as a prognostic factor in babies has been demonstrated by researchers long back in 1997 [16]. The association of high lactate with mortality has also been demonstrated by several researchers [17,18]. Tuuli et al. have demonstrated, in a study on 7741 babies, that umbilical venous lactate strongly predicts arterial lactic acidemia and is comparable with arterial lactate for predicting neonatal morbidity at term. They have suggested the cut-off as 3.4 mmol/L [19]. The authors have also suggested that umbilical venous lactate can be used as a measure of neonatal morbidity when arterial blood is not available. Our study also was able to find a significant association between high lactate levels and mortality in preterm babies.

This study highlights the importance of blood gases in predicting the outcome in preterm babies thus adding to the limited data available in preterm babies. The major limitation of this study is the small sample size. Second, we obtained the venous blood gas which may not be reflecting the exact arterial picture. We suggest similar studies to be conducted on a larger population group to get significant results so that venous blood gas can be used as a tool to predict mortality in preterm babies.

CONCLUSION

In the present study, we tried to find out the correlation between umbilical venous blood gases taken at birth with the various short term comorbidities in preterm babies. We could demonstrate a higher incidence of death in babies with high lactate levels (lactate >4 mmol/L) and thrombocytopenia in babies with low bicarbonate levels (<15 mmol/L). Although it failed to find a significant association with other adverse outcomes, the number of babies with adverse outcomes was higher in the group with abnormal blood gases.

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