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Original Article

pH Prodigy: Predicting early Neonatal Destiny in Perinatal Asphyxia through cord Blood's Crystal ball

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Abstract

Introduction: Perinatal asphyxia, a condition affecting blood flow or gas exchange during birth, is a major contributor to neonatal morbidity and mortality. It adversely impacts various body systems, including renal, CNS, cardiac, and pulmonary functions. Common assessment methods, like Apgar scores, have limitations in subjectivity and sensitivity. Advanced technologies like aEEG and MRI, while more predictive, may lack universal accessibility. Studies exploring cord blood gas analysis as a link to short-term outcomes show promise in addressing perinatal asphyxia-related morbidity and mortality, particularly in resource-constrained settings such as ours.

Methods: This one-year prospective cohort study at B.P. Koirala Institute of Health Sciences, Dharan, Nepal included 150 inborn newborns of 37 weeks or more who exhibited either failure to initiate and sustain breathing or an Apgar score of less than 7 at 5 minutes of life. They were subjected for estimation of umbilical cord blood pH, APGAR score, and outcome looked were NICU admission, seizure incidence, hypoxic ischemic encephalopathy assessment by Sarnat and Sarnat score, neurological status, duration of hospital stay, and final outcome (Discharge, LAMA, death).

Results: Neonates with lower pH values have a higher likelihood of NICU admission, seizures, and hypoxic ischemic encephalopathy, extended hospital stays and increased mortality rates. A strong negative correlation between pH and hypoxic ischemic encephalopathy was observed, with a correlation coefficient of - 0.8112 ($p < 0.001$). Notably, pH emerged as the most significant independent predictor for hypoxic ischemic encephalopathy and abnormal neurologic examination (hypotonia).

Conclusion: Umbilical cord blood pH is valuable predictor of early neonatal outcome in perinatal asphyxia.

Introduction

Perinatal asphyxia, a condition marked by insufficient blood flow or gas exchange during the peripartum period, significantly contributes to neonatal morbidity and mortality.[1] In Nepal, it constitutes up to 30% of neonatal deaths, with an estimated incidence of 6 per 1000 term live births.[2]

Perinatal asphyxia adversely affects major body systems, leading to renal, CNS, cardiac, and lung dysfunction in term infants.[3] Hypoxic ischemic encephalopathy (HIE) is a common consequence, characterized by CNS dysfunction due to inadequate oxygen and blood flow to the brain. Accurate assessment of cerebral function in at-risk newborns is vital, considering the limited therapeutic window for neuroprotective interventions.[4]

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While strategies like Apgar scores are widely used, their subjectivity and insensitivity to neurological outcomes pose limitations.[5] Technologies like aEEG and MRI offer better prediction but may not be widely available. Therefore, studies associating umbilical cord blood gas analysis with short-term outcomes provide practical insights for reducing morbidity and mortality associated with perinatal asphyxia

Methods

This prospective cohort study, conducted at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal with ethical clearance from the Institutional Review Committee, spanned one year. The sample size was determined based on the basis of study by Singh et al[6] which found a minimum prevalence of 10.2% for HIE Stage 2 among perinatal asphyxia cases in relation to pH. The sample size calculation used formula, $n = (Z^2 PQ) / L^2$, where Z at 5% level = 1.96, P = 10.2% and considered a permissible error (L) of 20% and accounted for potential non-responses, resulting in a corrected sample size of 143. However, all neonates meeting the inclusion criteria during the study period were enrolled, making the sample size 150. Inclusion criteria encompassed inborn newborns of 37 weeks or more who exhibited either failure to initiate and sustain breathing or an Apgar score of less than 7 at 5 minutes of life.[7] Neonates with major congenital anomalies and those who did not provide consent were excluded. 1 ml of blood was collected in heparinised syringe from doubly clamped segment of umbilical cord (either arterial or venous) for ABG within one hour after birth of asphyxiated new born. All babies were monitored for Apgar score at 1, 5 and 10 minutes. Outcome looked were NICU admission, seizure incidence, HIE assessment by Sarnat and Sarnat score,[8] neurological status by Dubowitz neurological examination, duration of hospital stay, and final outcome (discharge, LAMA, death). The chi-square test was used to compared categorical variables. Bivariate and logistic regression identified potential predictors for early neonatal outcomes, with a multivariate model using predictors with $p < 0.2$.

Results

Of 150 cases enrolled, majority of mothers were in the 20 - 35 years age group and were primiparous. Common maternal risk factors included gestational hypertension and diabetes. Thick meconium-stained amniotic fluid was the most prevalent risk factor for perinatal asphyxia. Caesarean sections were more frequent, and there was a higher proportion of male babies falling in the 2500 - 4000 gm weight category as shown in Table 1.

Table 1: Baseline characteristics of mothers / newborns with perinatal asphyxia

Baseline characteristics of mothers		Frequency (%) (N = 150)
Maternal age in years	15 – 19 years	12 (8.0%)
	20 – 35 years	133 (88.7%)
	> 35 years	5 (3.3%)
Parity	Primiparous	117 (78%)
	Multiparous	33 (22%)
Maternal risk factors	GHTN	23 (15.3%)
	GDM	8 (5.3%)
	Hypothyroidism	4 (2.7%)
	Others (UTI, PROM, PV leaking)	13 (8.7%)
Perinatal risk factors	Meconium stained liquor	28 (18.7%)
	Oligohydraminos	8 (5.3%)
	Cord entanglement	5 (3.3%)
Mode of delivery	NVD	61 (40.7%)
	LSCS	80 (53.3%)
	Vacuum assisted delivery	9 (6.0%)
Baseline characteristics of newborns		
Gender	Male	84 (56.0)
	Female	66 (44.0)
Gestation	Term	127 (84.7%)
	Post dated / Post term	23 (15.3%)
Birth weight	2500 - 4000gm.	147 (98)
	> 4000gm.	3(2)

NVD (Normal Vaginal Delivery), LSCS (Lower section Caesarian section), GHTN (Gestational hypertension), GDM (Gestational diabetes mellitus), UTI (Urinary Tract Infection), PROM (Premature rupture of membrane), PV (per vaginal)

Regarding the mode of resuscitation, the majority of neonates (78.7%) received bag and mask ventilation exclusively, while only 21.3% required intubation, as illustrated in Figure 1.

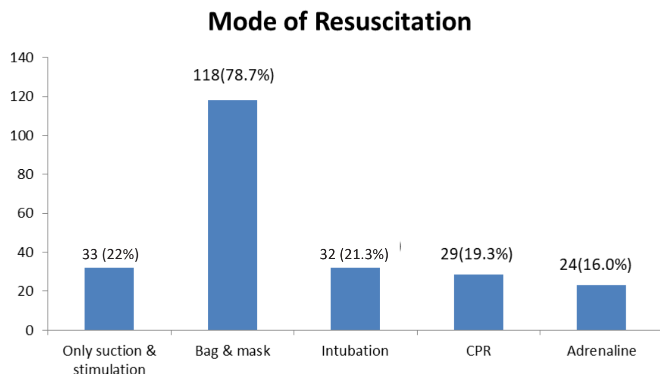

Figure 1: Bar diagram showing different mode of resuscitation

Table 2: Short term outcome of neonates with perinatal asphyxia

Clinical characteristics (N = 67)		Frequency (%)
Admission	NICU	78 (52.0%)
	Nursery / Neonatal ward	72 (48.0%)
Seizure	Yes	67 (44.7%)
	No	83 (55.3%)
Hours of seizure	< 6 hours	43 (64.2%)
	6 – 24 hours	23 (34.3%)
	24 – 48 hours	1 (1.5%)
Persistent	Yes	25 (37.3%)
	NO	66 (44.0%)
HIE	Stage I	17 (11.3%)
	Stage II	29 (19.3%)
	Stage III	38 (25.3%)
Tone at the time of discharge or before LAMA / Death	Normal tone	100 (66.7%)
	Abnormal tone	50 (33.3%)
Final outcome	Discharge	128 (85.3%)
	Death	11 (7.3%)
	LAMA	11 (7.3%)

There was a negative correlation between pH and HIE with correlation coefficient -0.8112 ($p < 0.001$), indicating that as pH decrease, the risk of HIE increases as shown in Table 3 and Figure 2.

Table 3-Correlation of cord blood pH and HIE

Parameter	Correlation coefficient (r)	P value
Cord blood pH	-0.8112	< 0.001

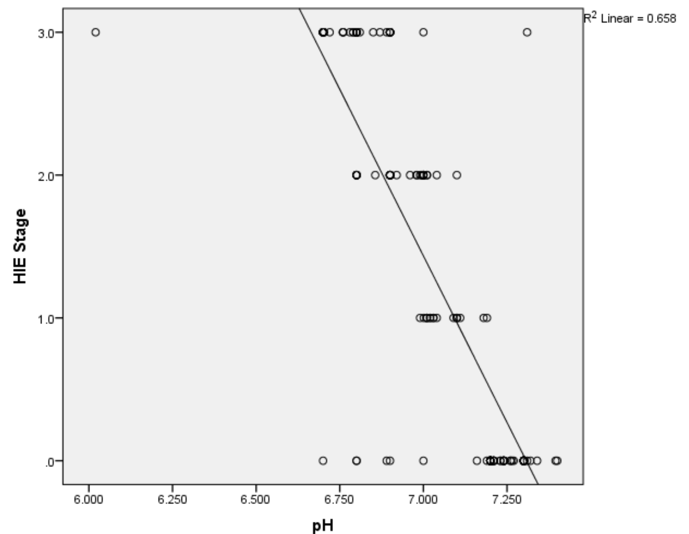

Figure 2: Illustration of correlation of umbilical cord blood pH with HIE

Neonates with pH < 7 faced higher NICU admission (85.2% vs. 29.2%, $p < 0.001$, OR 14), more seizures (90.2% vs. 13.5%, $p < 0.001$, OR 58.819), increased HIE risk (91.8% vs. 31.5%, $p < 0.001$, OR 24.4), and greater likelihood of abnormal neurologic status. pH ≥ 7 had a 21.28 times higher discharge probability ($p < 0.001$), while pH < 7 had more leaving against medical advice (LAMA) (14.8% vs. 2.2%, $p = 0.001$, OR 7.529). All deaths occurred in the pH < 7 group as shown in Table 4.

Table 4: Comparison of short term outcome between pH < 7 and pH ≥ 7 umbilical cord pH Groups

Outcome Variables		pH < 7 (N = 61)	pH ≥ 7 (N = 89)	p-value	OR (95% CI)
Need of being admitted to NICU		52 (85.2%)	26 (29.2%)	< 0.001#	14 (6.03 - 32.503)
Seizure		55 (90.2%)	12(13.5%)	< 0.001#	58.81 (20.805 - 1066.293)
Hypoxic ischaemic encephalopathy		56 (91.8%)	28 (31.5%)	< 0.001#	24.4 (8.81 - 67.555)
Anormal neurologic status		42 (68.9%)	4 (4.5%)	< 0.001#	46.97 (15.026 - 146.85)
Final outcome	Discharge	41 (67.2%)	87 (97.8%)	< 0.001#	0.04 (0.011- 0.211)
	LAMA	9 (14.8%)	2 (2.2%)	0.001#	7.52 (1.566-36.196)
	Death	11 (18.6%)	0		

#:chi square test

Neonates with cord blood pH less than 7 had a significantly longer hospital stay (8.53 ± 7.91 days) compared to those with pH of 7 or higher (5.09 ± 3.98 days), indicating a statistically significant difference with a p-value of 0.001 as shown in Table 5.

Table 5: Comparison of duration of hospital stay Between pH < 7 and pH ≥ 7 Umbilical Cord pH Groups

Outcome variables		pH < 7	pH ≥ 7	p-value
Duration of Hospital stay	Mean ± SD	8.53 ± 7.91	5.09 ± 3.98	0.001#
	Median	6	4	
	Interquartile range	2.63 - 11.5	2-7	

#:chi square test

Multivariate analysis identified pH, Apgar score at 5 minutes, and maternal risk factors as independent predictors of HIE, with pH being the most significant (AOR = 21.298) as shown in Table 6.

Table 6: Univariate and multivariate analysis of predictors of HIE

	Univariate odds ratio		P value	Multivariate odds ratio		P value
	COR	95% CI		AOR	95% CI	
Sex of the neonates versus HIE						
Female	1		0.181	1		.847
Male	0.64	.33-1.23		1.094	0.44-2.74	
Gestational age of the neonates versus HIE						
37 – 40 wks	1		0.333	NA		
> 40 wks	1.58	0.62 - 3.98				
APGAR score at 5 min of the neonates versus HIE						
≥ 7	1		< 0.001	1		.013
0 - 6	5.31	2.44 -11.58		3.686	1.32-10.26	
Mode of delivery versus HIE						
NVD	1			1		
LSCS	0.342	0.169 -0.693	0.003	0.483	0.156 -1.520	0.215
Vacuum assisted	0.523	0.126 -2.176	0.373	0.293	0.19 -4.65	0.384
Meconium aspiration syndrome versus HIE						
No MAS	1		.068	1		.808
MAS	2.27	0.93-5.54		1.162	0.35-3.91	

Maternal age versus HIE						
20 - 35 years	1		.114	1		.054
15 - 19 and > 35 years	2.033	0.68 - 6.09		4.181	0.98 -17.89	
Parity of the Mother versus HIE						
Primi	1		.317	NA		
Multi	1.5	0.68 - 3.33				
pH group of the category of the neonates versus HIE						
≥ 7	1		<0.001	1		< 0.001
< 7	24.4	8.81 - 67.56		21.298	6.93- 65.41	
Risk factors in mother versus HIE						
No risk factor	1		.192	1		0.017
Risk factor Present	1.601	.79- 3.26		3.136	1.22-8.04	

In our multivariate logistic regression, both 5-minute Apgar score (AOR = 9.327, 95% CI = 1.58-55.24, p < 0.014) and pH (AOR = 46.535, 95% CI = 12.9-167.9, p < 0.001) independently predicted abnormal neurologic examination in perinatal asphyxia neonates, with pH identified as the most significant predictor as shown in Table 7.

Table 7: Univariate and multivariate analysis of predictors of abnormal neurologic examination (hypotonia)

Sex of the neonates versus abnormal neurologic examination (hypotonia)						
	Univariate Odds Ratio		P value	Multivariate Odds Ratio		P value
	COR	95% CI		AOR	95% CI	
Female	1		.325	NA		
Male	.705	.35 - 1.42				
Gestational age of the neonates versus abnormal neurologic examination (hypotonia)						
37 – 40 wks	1		.052	1		.119
> 40 wks	2.410	0.97 - 5.96	3.102	.75-1.58		
APGAR score at 5 min of the neonates versus abnormal neurologic examination (hypotonia)						
≥ 7	1		< 0.001	1		.014
0 - 6	14.32	3.29 - 62.31	9.327	1.58 - 55.24		
Mode of delivery vs abnormal neurologic examination (hypotonia)						
NVD	1			1		.249
LSCS	.480	.23 - .99	0.45	1.259	.42 -3.76	.680
Vacuum assisted	.180	.02 - 1.53	0.116	.128	.01 -1.79	.126
Meconium aspiration syndrome vs abnormal neurologic examination (hypotonia)						
No MAS	1		.045	1		.945
MAS	2.33	1.01 - 5.43	1.045	.3-3.7		
Maternal age vs abnormal neurologic examination (hypotonia)						
20 - 35 years	1		0.905	NA		
15 - 19 and > 35 years	.935	.31- 2.83				
Parity of the mother versus abnormal neurologic examination (hypotonia)						
Primi	1		.422	NA		
Multi	1.395	.62 - 3.15				

pH group of the category of the neonates versus Abnormal neurologic examination (hypotonia)							
≥ 7	89	1		< 0.001	1		< 0.001
< 7	61	46.974	15.03 - 146.85		46.535	12.9 - 167.9	
Risk factors in mother versus HIE							
No risk factor	1		.325	NA			
Risk factor Present	1.446	0.694-3.012					

Discussion

In the study involving 150 neonates, the predominant age group for mothers (88.7%) was 20 to 35 years. This pattern, which is similar to other studies emphasizes the inclination of women to give birth during their peak fertility years.[9-11] Notably, 78% of mothers were primiparous, a trend reflected in other similar studies suggesting challenges faced by first-time mothers, possibly linked to delayed prenatal care and reduced awareness of maternal responsibilities.[10,11]

Common maternal risk factors identified included gestational hypertension (15.3%), gestational diabetes mellitus (5.3%), oligohydramnios (5.3%), cord entanglement (3.3%), and hypothyroidism (2.7%), aligning with findings by Sunil et al.[9] The primary perinatal risk factor for perinatal asphyxia was thick meconium-stained amniotic fluid (18.7%) which is similar to observations of other studies.[10,12-15] In our study, the majority of births occurred through LSCS, which is similar to findings from other studies.[9,16] Among 150 neonates diagnosed with perinatal asphyxia, males constituted 56%, maintaining a 1.27:1 male-to-female ratio, consistent with the 2022 Nepal Demographic Health Survey and Nutan et al.[6,17]

In our study 78.7% neonates received bag and mask ventilation. The requirement of bag and mask ventilation during resuscitation as observed by various studies in Nepal ranges from 56% to 74.4%.[9,14,18] The higher use of bag mask ventilation in our study, initiated promptly per NRP guidelines, may stem from avoiding delays and excessive tactile stimulation.

In our study, 21.3% of newborns underwent intubation, a lower rate compared to other similar studies.[16,19] Our institution's strict adherence to NRP guidelines contributed to more effective resuscitation, resulting in a reduced need for neonatal intubation and mechanical ventilation.

Out of 150 studied neonates, 52% with perinatal asphyxia were admitted to the Neonatal Intensive Care Unit (NICU) whereas Nutan et al reported a NICU admission rate of 71.4%.[6] Our lower rate is attributed to effective resuscitation by skilled professionals. Vigilant post-resuscitation monitoring and careful categorization resulted in NICU admission for severe cases only.

In our study, neonates with a pH < 7 had a significantly higher NICU admission rate (85.2%) compared to the pH ≥ 7 group (29.2%) (p < 0.001). Victory et al too observed that the risk for NICU admission increased with worsening of acidemia at birth in term neonates.[20] Mousa et al[12] and Umamahesh et al[21] observed more NICU admission even at pH < 7.2 and pH < 7.25 respectively. Despite pH cutoff variations, the consistent trend of higher admission rates in neonates with lower pH emphasizes the need to address the specific needs of these infants in neonatal health management. The occurrence of seizures was notably high at 44.7%, more common in the pH < 7 group (90.2%) than pH ≥ 7 (13.5%) (p < 0.001). This aligns with Goldaber et al, indicating that low pH levels below 7.05, even 7.00, are associated with increased likelihood of seizures.[22] Williams et al noted that low umbilical artery pH, particularly below 7, had higher sensitivity (73.8%) in predicting neonatal seizures than a base excess of -16 (52.5%).[23] In a meta-analysis by Malin et al, the odds ratio for the association between arterial cord pH and seizures was 8.1 (95% confidence interval 3.0 to 21.9), highlighting a strong link between pH levels and neonatal seizures.[24]

In our study of 150 neonates with perinatal asphyxia, 56% developed HIE, distributed across stages: 11.3% in stage I, 19.3% in stage II, and 25.3% in stage III. Incidence variations were observed compared to Nutan et al (51.8%) and Sunil et al (68%).[6,9] The distribution of neonates in HIE stages varied across studies, reflecting differences in definitions and inclusion criteria. A significant association was found between a pH below 7 and HIE (91.8%), which is similar to results of Mousa et al.[12] A meta-analysis supported this association (OR 13.8, 95% CI 6.6-28.9). Negative correlation between pH and HIE (r = -0.8112) was consistent with Nutan et al (r = -0.926) and studies by Joseph et al and Gemma L Malin.[6,16,24]

Among 84 neonates with HIE, 56 had a pH below 7, consistent with various studies.[24-26] Multivariate analysis identified pH, Apgar score at 5 minutes, and maternal risk

factors as independent predictors of HIE, with pH being the most significant (AOR = 21.298). Zamzami et al supported pH as a potent predictive variable, with OR for pH at 4.2 (95% CI 1.5 - 11.8) and for Apgar scores at 5.1 (95% CI 2.2 - 11.6).[27] Joseph et al emphasized the relevance of pH, noting that pH < 7.2 significantly associated with HIE development. Other factors linked to severe HIE included male gender, endotracheal intubation, instrumental delivery, severe acidemia (pH < 7), and moderate acidemia (pH < 7.2).[16] Victory et al explored the relationship between cord blood pH and adverse outcomes, finding significant inverse associations with Apgar scores, NICU admission, and the need for assisted ventilation.[20] While pH consistently emerges as a significant independent predictor, variability in other identified predictors can be attributed to differences in study populations, variations in risk factors analyzed, and disparities in inclusion criteria.

In our study, 33.3% of neonates with perinatal asphyxia exhibited abnormal tone at discharge, aligning with Nutan et al.[6] Low pH (< 7) significantly correlated with abnormal neurologic status (hypotonia) (68.9%), with an odds ratio of 46.974 (95% CI 15.026 - 146.85). Gilstrap's study also noted a link between pH < 7 and hypotonia (17%) with an odds ratio of 10.3.[28]

In our multivariate logistic regression, both 5-minute Apgar score (AOR = 9.327, 95% CI = 1.58-55.24, p < 0.014) and pH (AOR = 46.535, 95% CI = 12.9 - 167.9, p < 0.001) independently predicted abnormal neurologic examination, with pH identified as the most significant predictor. This aligns with Silva et al who highlighted metabolic acidemia as the predominant factor associated with hypotonia and depression (odds ratio 2.3, 95% CI 1.64 - 2.85, p < 0.001).[29] Newborns with cord blood pH below 7 had a longer hospital stay (8.53 ± 7.91 days) compared to those with a pH of 7 or higher (5.09 ± 3.98 days, p = 0.001), which is similar to Mousa et al's findings.[12]

In our study, 85.3% of neonates were discharged, 7.3% died, and 7.3% opted for Leave Against Medical Advice (LAMA). This is similar to Sunil et al's 4.3% mortality rate, while Dongol et al and Nutan et al documented higher mortality rates of 15.7% and 19.44%, respectively.[6,9,10] Notably, the exclusion of LAMA cases from the mortality count might have contributed to the lower mortality rate. All mortalities in our study occurred in the pH < 7 group, with no deaths in the pH ≥ 7 group, consistent with other studies.[6,12] This pattern underscores a strong association between lower umbilical cord blood pH and adverse outcomes, specifically mortality at discharge, which is similar to findings in other study and a meta-analysis.[24,30]

Ours is a single centric study with limited population. Further research are required to substantiate our results and clinical application of these findings can contribute to better neonatal care in the future.

Conclusion

Neonates with lower pH values have a higher likelihood of NICU admission, seizures, and HIE, extended hospital stays and increased mortality rates.

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