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Original Article

Paediatrics Section

Effect of Hypoxic Ischaemic Encephalopathy on Coagulation Profile in Neonates in a Tertiary Care Center, Agra- A Prospective Clinical Study

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ABSTRACT

Introduction: Perinatal asphyxia is very common in developing countries. Coagulopathy occurs as a part of spectrum of multiorgan dysfunction following hypoxic insult. In asphyxiated neonate, bleeding due to coagulation abnormality is common and potentially life threatening. There are very few studies done on coagulation profile with perinatal asphyxia in last few decades.

Aim: To evaluate the coagulation profile in neonates with hypoxic ischaemic encephalopathy in a tertiary care center, Agra.

Materials and Methods: This was a prospective clinical study undertaken in Neonatal Intensive Care Unit (NICU) FH Medical College Agra, a tertiary care center catering rural and urban population. Total 60 neonates admitted with history of birth asphyxia between January 2022 to June 2022 were enrolled. Neonates were classified into Hypoxic Ischaemic Encephalopathy (HIE) stage 1, 2 and 3 (according to Sarnat and Sarnat staging). Parameters such as Prothrombin Time (PT)/ International Normalised Ratio (INR) and platelet count was analysed. For describing continuous variables means and standard deviations and for comparison Analysis of Variance (ANOVA) test and Chi-square test were used.

Results: In this study, total 60 neonates were enrolled. Out of these 43 (71.61%) were male and 17 (28.33%) female. Highest number of cases 34 (56.7%) were from HIE stage 3 followed by 22 (36.7%) HIE stage 2 and 4 (6.7%) from HIE stage 1. Among them 14 newborns with HIE stage 3 were died. PT and INR was significantly deranged in HIE stage 3 and 2 (p-value <0.05). HIE stage 3 has highest mortality and morbidity. Platelet count were normal in HIE stage 1 followed by decreased in HIE stage 2 and 3 and also statistically significant.

Conclusion: Coagulation derangement is very common in babies with HIE and evident before clinical bleeding and this derangement is associated with poor outcome. Hence, timely intervention and appropriate management can improve the clinical outcome.

Keywords: Birth asphyxia, Coagulopathy, Haemostasis, Platelets, Prothrombin time

INTRODUCTION

Birth asphyxia is defined as the failure to establish breathing at birth. Approximately, 9 lac babies every year died of perinatal asphyxia and is one of the leading causes of early neonatal mortality [1].

Birth asphyxia affects most of the organ systems in the body due to hypoxic injury. Haemostasis is being very delicately balanced system does get deranged during birth asphyxia [2]. The deranged coagulation in these babies can be caused by a variety of mechanism, including liver dysfunction and consumption of coagulation factors, many studies have shown this [3,4].

American Academy of Pediatrics (AAP) has given recommendation for single stat dose of vitamin K in newborns at birth since 1961. The AAP recommends 1 mg vitamin K to all neonates with birth weight >1500 grams and 0.3 mg/kg to 0.5 mg/kg vitamin K to all neonates with birth weight <1500 grams after birth to prevent haemorrhagic disease of newborn [5].

It has been observed that the response to vitamin K in elevating the coagulation factors is reduced in asphyxiated babies, which could be one of the mechanisms of developing coagulation profile abnormalities [2,6,7]. Birth asphyxia and different other causes of respiratory failure causes derangement of coagulation cascade, shown by many other studies as well done for other purposes [8,9].

Perinatal asphyxia may result in coagulopathy as part of a spectrum of multiple organ dysfunction [10]. As compared to normal term newborns, asphyxiated term newborns are at higher risk of Disseminated Intravascular Coagulation (DIC) [11-13]. Coagulation profile abnormalities are common in birth asphyxia and manifest with prolonged PT/INR, Activated Partial Thromboplastin Time (APTT) and low fibrinogen levels [14,15]. In term babies with birth asphyxia, plasma level of D-dimer, thrombin-anti-thrombin complexes, soluble fibrin monomer complexes and fibrin degradation products are higher same as in DIC [11-13]. From the perspective of coagulation, moderate decrease in platelet is also reported in asphyxiated babies but none of study showed any statistical significance [16,17]. The most important mechanism of thrombocytopenia in birth asphyxia is increased destruction of platelets [18].

There are very few published studies on correlation of coagulation profile abnormalities with various stages of HIE and its outcome [2,6,18]. Forman KR et al., found that all neonates with HIE, treated with therapeutic hypothermia had coagulopathy, while 54% of them developed bleeding [19]. Coagulation dysfunction due to birth asphyxia is well known, hence the bleeding. Very few studies done on this important problem, some with very few subjects and other with hypothermia intervention [2,6,19]. Hence, present study was done to relook this important issue and to evaluate coagulation profile in neonates with HIE.

MATERIALS AND METHODS

This study was prospective clinical and conducted in NICU of Paediatric Department of FH Medical College Agra, a tertiary care unit

catering both urban and rural population between 1st January 2022 to 30th June 2022. Study was approved by Ethical Committee of FH medical college Agra (Reference No-FHMC/IEC/R.Cell/2022/20). All newborns within study duration were enrolled in the study after taking informed consent from the parents.

Inclusion criteria: Term or preterm neonates with birth asphyxia were included. The diagnosis of birth asphyxia was considered if-

a. APGAR score of <5 at 1 minute and later developed HIE or renal failure or necrotising enterocolitis or respiratory distress. In all the cases, blood culture was done to exclude the sepsis.

b. APGAR score <7 at 5 minutes

c. If history of fetal distress was there, bag and mask ventilation needed during resuscitation [2,6].

Within one hour of birth arterial blood gas was done and revealed metabolic acidosis/hypoxia/hypercarbia or both. Or in infants who developed features of asphyxia as mentioned in criteria 'a'. Most of the babies referred from other hospital without documented APGAR score, hence this criteria was considered.

Exclusion criteria: Congenitally malformed neonates and who developed bleeding within six hours of life were excluded.

Procedure

Total 65 newborns with perinatal asphyxia were admitted during study period, and five of them did not gave consent for enrollment. So, 60 newborns were enrolled during study period by convenient sampling. All the study subjects were divided in 3 stages of HIE according to Sarnath and Sarnath staging [Table/Fig-1] [20].

	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
Level of consciousness	Hyperalert	Lethargic/obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch	Overactive	Overactive	Decreased/ Absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak/Absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/Absent
Tonic neck	Slight	Strong	Absent
Autonomic function			
Pupil	Mydriasis	Miosis	Variable
Heart Rate	Tachycardia	Bradycardia	Variable
Bronchial/ salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/ Decreased	Increased/ Diarrhoea	Variable
Seizures	None	Common/Focal or multifocal	Uncommon
Electroencephalogram (EEG)	Normal/ Decreased	Early low voltage continuous delta and theta, later periodic seizures focal 1-1.5 Hz spike wave	Early periodic pattern with isopotential phases, later isopotential
Duration	<24 hour	2-14 days	Hours to weeks

[Table/Fig-1]: Sarnath and Sarnath Staging [20].

Collection of samples: Approximately, 1.8 mL of blood was collected in citrated vial for PT/INR and 0.5 mL in microtainer Ethylenediaminetetraacetic acid (EDTA) vial for platelet count. Blood sample was taken from arterial or central line if present otherwise peripheral venous sample was taken. Sample was taken and sent to Pathology laboratory and tested on Tulip haemostasis analyser.

Normal values of PT/INR were defined in [Table/Fig-2] [21]. Thrombocytopenia was defined as a platelet count less than 1.5 lac [22]. Values outside these limits were taken as abnormal. The outcome at discharge was also assessed.

	Preterm (30-36 week)	Term (>36 weeks)	
	Day 1 of life	Day 1 of life	Day 3 of Life
Prothrombin Time	13 (10.6-16.2)	15.6 (14.4-16.4)	14.9 (13.5-16.4)
INR		1.26 (1.15- 1.35)	1.2 (1.05-1.35)

[Table/Fig-2]: Normal value of Prothrombin Time (PT) and International Normalised Ratio (INR).

STATISTICAL ANALYSIS

All statistical analysis was done using Statistical Package For Social Sciences (SPSS) version 22.0. Data were expressed as table and charts and appropriate statistical test were applied to analyse the data. For describing continuous variables means and standard deviations and for comparison ANOVA test and Chi-square test were used. Coagulation parameters between various stages of HIE were compared using ANOVA test. A p-value<0.05was considered to be significant.

RESULTS

Total of 65 newborns were included, among which 4 were HIE stage 1, 22 and 34 were HIE stage 2 and 3, respectively. A total of 43 (71.67%) were male and 17(28.33%) females. In study population, 52 were term delivered and 8 preterm. Most of the neonates (n=46) were delivered vaginally and rest (n=14) by caesarean section, which was statistically significant. Among total 60 neonates, 18 and 26 babies from HIE stage 2 and 3, respectively were vaginally delivered (obstructed labour). Mean birth weight is also comparable in all 3 groups. The p-values for gender, gestation and mode of delivery were non significant (p-value >0.05). But p-value for birth weight (0.001) was significant [Table/Fig-3].

Variables		Stage 1 (n=4)	Stage 2 (n=22)	Stage 3 (n=34)	Total (N=60)	p-value
Gender	Male	2	17	24	43 (71.67%)	0.5
	Female	2	5	10	17 (28.33%)	
Gestation	Preterm	2	3	3	8 (13.33%)	0.07
	Term	2	19	31	52 (86.67%)	
Mode of delivery	LSCS	2	4	8	14 (23.33%)	0.38
	VD	2	18	26	46 (76.67%)	
Birth weight	Mean ±SD	2.457 ±0.635	2.565 ±0.307	2.88 ±0.312	2.634 ±0.12	0.001

[Table/Fig-3]: Demographic profile of patient.
Chi-square test, ANOVA test; HIE: Hypoxic ischaemic encephalopathy; LSCS: Lower segment caesarean section; VD: Vaginal delivery; A p-value <0.05 was considered to be significant

In HIE stage 3, PT was highest (23.02±5.829) followed by HIE stage 2 (18±4.8) and normal in HIE stage 1 (14.05±1.236) and statistically

significant. So, the INR was highest in HIE stage 3 (1.813±0.519) followed by stage 2 (1.33±0.356) and normal in stage 1 (0.99± 0.519), this was also statistically significant. On complete blood count, platelets were normal in HIE stage 1 followed by decreased in HIE stage 2 and 3 [Table/Fig-4]. This was also statistically significant.

	HIE			p-value
	Stage 1	Stage 2	Stage 3	
Prothrombin time (Mean±SD)	14.05±1.236	18±4.8	23.02±5.829	0.0003
INR	0.99±0.519	1.33±0.356	1.813±0.519	0.00007
Platelet count (lac/mm^3)	2.4±0.33	1.4±0.27	1.05±0.05	0.005

[Table/Fig-4]: Derangement in Prothrombin Time (PT), International Normalised Ratio (INR) and Platelet count in different stages of Hypoxic Ischaemic Encephalopathy (HIE).
A p-value <0.05 was consideredto be significant

Out of 60 neonates, 10 died after bleeding episode and the remaining 4 died due to HIE, where all were HIE stage 3. Poor neurological examination (in terms of neonatal reflexes viz., tone, moro reflex, rooting, sucking and swallowing) was found in total 32 newborns (14 in HIE stage 2 and 18 from stage 3). All 4 newborns were normal in HIE stage 1 [Table/Fig-5]. Proportion of normal neurological examination at discharge was highest (100%) in HIE stage 1 and lowest in HIE stage 3 [2 (10%) out of 20 surviving babies].

HIE	Expired+LAMA	Surviving neonates		p-value
		Poor neurological examination at discharge	Normal neurological examination at discharge	
Stage 1	0	0	4 (100%)	<0.001
Stage 2	0	14 (63.6)	8 (36.4%)	
Stage 3	14	18 (90%)	2 (10%)	

[Table/Fig-5]: Outcome at discharge.
p-value calculated using Chi-square test; LAMA: Left against medical advice; A p-value<0.05was considered to be significant

DISCUSSION

Coagulation profile abnormalities after birth asphyxia have multiple mechanisms. Both oxygen and blood supply altered to bone marrow and liver, which negatively impact the synthesis of platelet and clotting factors respectively [18]. DIC is also common in neonates suffering from birth asphyxia [19,23].

Birth asphyxia is an acute event, may lead to many changes to maintain haemodynamics. Most significant change is diving reflex, in which normal circulation to vital organ and compromised circulation to less vital organ. In this haemodynamic cascade, liver get less perfused so liver function deranged and synthesis of clotting factors decreased. Because of this, normal blood haemostasis system gets adversely affected. Thus, more chances of abnormal coagulation parameters and bleeding in neonates with perinatal asphyxia.

In present study, more males were affected with birth asphyxia, this may be because more health seeking practices for male babies for regional and ethnicity area which is similar to other studies done in birth asphyxia patients. This is consistent with the report from Solayman M et al., in Bangladesh (60.8%), Aslam HM et al., in Karachi (61.3%), and Aliyu I et al., in Nigeria 60.3% [24-26]. This could be explained by the protective effect of the additional "x" chromosome [27].

Mode of delivery is an important risk factor in birth asphyxia. In present study, most common route of delivery was vaginal (76.67%) followed by Lower Segment Caesarian Section (LSCS) (23.33%), which was similar to Behera A et al., they reported birth asphyxia in 73.5% neonates delivered vaginally [28]. This study corroborates with the study of Kapur S et al., who reported higher incidence of neonatal asphyxia in vaginal delivery [29]. Due to abnormal labour and delivery, 60% babies were asphyxiated, as reported by Dweck HS et al., [30]. Chaturvedi P and Shah N reported vaginal breech deliveries highly associated with birth asphyxia [31].

PT is a good indicator of synthetic function of liver. In hepatic dysfunction PT gets prolonged due to defective synthesis of factors I, II, V, VII, X. In adults, the PT is compared to a normal control sample and given as a ratio called the INR which allows that all results are standardised irrespective of which analytical system is used to measure the PT. In newborns, the actual PT is quoted and the INR is less commonly used [32]. In present study, both PT and INR prolonged in HIE stage 2 and 3 and statistically significant which is similar to Jha R and Verma N [6]. These neonates may require fresh frozen plasma and platelet transfusion in cases of severe bleeding. In birth asphyxia thromboxane levels are also increased, which in turn causes platelet activation.

It has been observed in-vitro that under acidic environment platelet aggregation becomes defective. This altered physiological property of platelets in acidosis may be an additional factor contributing to haemorrhagic and thrombotic complications in neonates with birth asphyxia. Higher oxygen concentration used during resuscitation of asphyxiated babies negatively affects platelet aggregation. Megakaryocytic production, maturation and stimulation is mediated by thrombopoietin, a growth factor. Thrombopoietin is increased during hypoxia. During asphyxia platelet count negatively correlated with thrombopoietin levels. At day 7 of life thrombopoietin levels correlated with the clinical severity of asphyxia, however, neither platelet count nor thrombopoietin levels were predictors of death in birth asphyxia [18].

Platelet count was much deranged in severe and moderate birth asphyxia than in mild birth asphyxia, which similar to other studies with birth asphyxia. This may be due to increased destruction of platelet rather than decreased synthesis of platelet because normal overall bone marrow cellularity. Along with this, abnormal platelets functions due to hypoxemia and acidosis may contribute to bleeding [33]. Outcome was poorer with higher stages of HIE, which was similar to Behera A et al., [28]. Dixon G et al., reported that 62% neonates with severe encephalopathy and 25% neonates with moderate encephalopathy had poor developmental outcome [34].

Limitation(s)

Major limitation was sample size taken by convenient sampling. Other parameters of coagulation like PTT, Fibrinogen level, FDP etc., were not assessed.

CONCLUSION(S)

This study shows birth asphyxia was more common in vaginal delivery than in caesarean delivery. Mostly males were affected. As per the grade of HIE, more severe grade has more derangement in PT and INR. Platelets count was most severely affected in higher grade of HIE. Only HIE stage 3 had mortality. In conclusion, Coagulation derangement and thrombocytopenia in asphyxiated babies is very common. This in turn may lead to severe bleeding and increased mortality, so coagulation profile should be done in all neonates with perinatal asphyxia. Further studies are required to assess the role of prophylactic administration of fresh frozen plasma on the basis of abnormal coagulation profile.

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