

Full Length Research Paper

Coagulation profile in term of Nigerian infants with birth asphyxia

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Birth asphyxia may predispose to haemostatic failure. The objective of this study was to evaluate coagulation profile of babies with birth asphyxia and correlate these values with their clinical characteristics. Clinico-laboratory characteristics and coagulation profiles of 41 consecutive full term babies who had birth asphyxia were evaluated. Their coagulation profiles were compared to another 41 suitably-matched controls. The mean prothrombin time, activated partial thromboplastin time, thrombin time and clotting time were significantly higher among cases than the controls [18.4 ± 3.6 s; 54.4 ± 2.3 s; 12.4 ± 0.9 s and 11.2 ± 1.7 min, respectively compared to 11.5 ± 3.9 s; 50.2 ± 6.1 s; 9.1 ± 1.8 s and 6.9 ± 0.3 min ($p = 0.001$)]. The mean platelet count of the cases was however lower, that is, $130.5 \pm 37.9 \times 10^3/\mu\text{l}$ vs. $167.8 \pm 22.3 \times 10^3/\mu\text{l}$ respectively, $p = 0.001$. Among babies with asphyxia, coagulation parameters were prolonged in those with hypothermia or erythrocytosis ($p < 0.001$). Dyscoagulation and or haemostatic failure should be considered in all asphyxiated babies especially those with hypothermia and or erythrocytosis. This is important for appropriate anticipatory care such as transfusion of fresh frozen plasma to maintain their coagulation status.

Key words: Birth asphyxia, coagulation tests, newborn, Nigerian.

INTRODUCTION

Spontaneous coagulopathies occur more frequently in the neonatal period than any other time in healthy individuals (Peter et al., 1984). This is because, newborns, especially those with perinatal asphyxia, sepsis, infants of mothers with preeclampsia, preterm and small for gestational age infants tend to experience haemostatic alterations resulting from hepatic or platelets dysfunctions, and or derangement in clotting factors (Monagle et al., 2006).

World Health Organisation defined birth asphyxia as

the failure of a newborn to initiate and sustain spontaneous respiration at birth (WHO, 2007). It accounts for about 23 per cent of the four million newborn deaths worldwide. In most developing nations, it is the single most important cause of neonatal death, occurring singly or in combination with other morbidities (Ogunfowora and Ogunlesi, 2011; WHO, 2007; Olowu and Azubuike, 1999).

Asphyxia predisposes to coagulopathy by enhancing consumption of platelets and some clotting factors as a result of the associated severe hypoxaemia, acidaemia and sepsis (Monagle et al., 2006). Some reports in developed countries have shown that the levels of vitamin K dependent clotting factors are significantly lower in

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babies with birth asphyxia than healthy ones (Kuhle and Massicotte, 2005; Puckett and Offringa, 2000). However, these abnormalities in the coagulation tests do not usually manifest with clinically evident bleeding. Bleeding and or thrombosis accentuate morbidity and neonatal mortality in this group of babies (Bauman and Cheung, 2011).

To our knowledge, no known study has examined the coagulation profiles of babies with birth asphyxia in Nigeria. The present study therefore evaluated the effect of birth asphyxia on the haemostatic status of babies at birth before administration of Vitamin K. We also correlated the clinical characteristics of these asphyxiated babies with their haemostatic profile.

SUBJECTS AND METHODS

This prospective case-control study was undertaken at the Maternity and Special Care Baby Unit (SCBU) of the Wesley Guild Hospital, Ilesha (One of the tertiary units of Obafemi Awolowo University Teaching Hospitals' Complex), Osun State, Nigeria, from October, 2012 to April, 2013. The hospital is a major referral health institution that provides a specialist and maternity services to many states in the south-western part of Nigeria.

Cases were consecutive term babies (37 - 41 weeks gestation) delivered in the labour ward of the hospital who suffered birth asphyxia and were subsequently admitted into the SCBU of the hospital. The controls were apparently healthy babies delivered in the labour ward of the hospital with APGAR score of ≥ 7 at first and fifth minutes of life. Written consent was obtained from the parents of the babies before enrollment into the study. The study protocols were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Babies with birth asphyxia were those with APGAR score of less than 7 at five minute and did not cry immediately after delivery (Olowu and Azubuike, 1999; Ibe, 1990). Birth asphyxia was graded based on the APGAR score at five minutes, resuscitative efforts and presence of neurologic symptoms (Mcgil-Ugwu et al., 2012; Ibe, 1990). Those with mild asphyxia had APGAR score of 6 at five minutes, and the baby required only stimulation and suctioning to establish a cry. For moderate asphyxia, the APGAR score at five minutes was 4 or 5 and stimulation, suctioning and intranasal oxygen administration were required before establishing a cry. Severe birth asphyxia occurred when the APGAR score was 0 – 3 and the baby required major intervention(s) such as endotracheal intubation or when there was associated neurologic symptoms such as seizure and coma.

Excluded from the study were babies whose mothers were on antihypertensive, antiretro-viral, antituberculous and anticoagulant drugs as well as those whose mothers

had hepatitis, eclampsia and bleeding disorders. Also, ineligible for the study were preterms (babies delivered before 37 completed weeks of gestation from the first day of the mother's last menstrual period); low birth weight babies (birth weight <2500 g), babies who had intravenous infusion of drugs, blood or plasma transfusion, babies with clinical and or laboratory evidence of sepsis or with conditions predisposing to sepsis and those who had received intramuscular Vitamin K.

Maternal data including age, date of last menstrual period (LMP), parity, record of antenatal care, gestational age at delivery; maternal illness during pregnancy especially pregnancy induced hypertension, bleeding disorders, diabetes mellitus were recorded into a proforma for the study. Mother's educational status was also documented. All the neonates had a complete physical examination. The gestational age (GA) in weeks was determined using mother's LMP. Anthropometric data such as weight and occipitofrontal circumference were also taken.

Before administration of Vitamin K, 4.5 ml of venous blood was obtained from each baby into a specimen bottle containing 3.2% sodium citrate (in a proportion of 9:1). Part of the blood was used for haematocrit determination and the other was centrifuged immediately after collection at 2500 g for 10 min at 22°C (Mitsiakos et al., 2009). The citrated plasma was then stored at -20°C in polypropylene tubes and thawed with water at 37°C for five minutes before serial analysis. In order to prevent activation of the intrinsic pathway of the clotting cascade, glass tubes were not used.

Platelet count, prothrombin time (PT); activated partial thromboplastin time (aPTT) and thrombin time (TT) were measured by standard procedures (Mitsiakos et al., 2009; Salonvaara et al., 2003). PT and aPTT were measured with Thrombolyzer (Behnk Elektronik, Norderstedt, Germany) using Thrombotest and Cephotest reagents (Nycomed, Oslo, Norway). Prothrombin time was expressed as the international normalised ratio (INR). Platelet count was measured with a Coulter STKS analyzer (Coulter Corporation, Miami, Florida, USA). Clotting time (CT) was also estimated for all the babies. All the coagulation tests were done by the same laboratory scientist within an hour of sample collection.

Other laboratory tests such as haematocrit, serum bicarbonate and serum glucose were carried out by standard methods (Dacie and Lewis, 1991), and their results documented. Pulse oximetry for the babies was also recorded. Hypoxaemia was defined as $\text{SaO}_2 < 90\%$, acidosis as serum bicarbonate $< 20 \text{ mmol/l}$, hypoglycaemia as serum glucose $< 2.2 \text{ mmol/l}$, anaemia and polycythaemia as venous haematocrit $< 45\%$ and $> 65\%$, respectively (Bauman and Cheung, 2011; Basnet et al., 2006). There was however, no facility for blood gas measurement.

Data analysis

Data were fed into a computer and analysed using SPSS 17.0. Means of normally distributed data were compared using the independent sample t-test. As indicated, Pearson's chi-square tests, with or without Yates' continuity correction or Fisher's exact tests were used to compare categorical variables. *P* values <0.05 were considered significant.

RESULTS

Sociodemographic characteristics and birth weight of the babies

A total of 82 babies (41 cases and 41 controls) were enrolled. The asphyxiated babies comprised 22 males and 19 females (M: F = 1.2: 1). Their birth weight ranged from 2.5 to 4.1 kg, with a mean of 3.04 ± 0.53 kg. Males were significantly heavier, the mean weight of the males was 3.22 ± 0.14 kg compared to 3.00 ± 0.18 kg for females, $t = 4.4$, $p = 0.001$. Of the 41 controls, 20 were males, M: F = 1: 1. Table 1 compares the sociodemographic characteristics of the babies with birth asphyxia and the controls. There was no significant difference between the subjects and the controls as regards to gestational age, gender, age at presentation, mode of delivery and birth weight, $p > 0.5$.

Coagulation parameters

Table 2 compares coagulation profiles among the asphyxiated babies and the controls. PT, aPTT, TT and clotting time were significantly higher in the asphyxiated babies ($p < 0.001$). Platelet count was however significantly lower ($130.5 \pm 37.9 \times 10^3/\mu\text{l}$) compared to $167.8 \pm 22.3 \times 10^3/\mu\text{l}$ among the controls, $p = 0.001$.

Also, the mean aPTT for the controls (50.2 s) was slightly prolonged than the 45 s upper limit of the reference range for older children and adults in our laboratory. PT, TT, Platelet counts and bedside clotting time however, did not differ from the reference values in our laboratory. For the asphyxiated babies, all the coagulation tests were deranged when compared with the reference values.

Severity of birth asphyxia and coagulation profiles.

Thirty-two (78.0%) had severe birth asphyxia and the remaining nine (22.0%) had moderate birth asphyxia, none had mild asphyxia. PT, aPTT, TT and bedside clotting time were significantly more prolonged among the 32 babies with severe asphyxia than the nine with moderate asphyxia. However, platelet counts were statistically similar between the two groups. Using

Pearson correlation analysis, APGAR score positively, though non-significantly correlated with PT ($r = 0.21$, $p = 0.135$); aPTT ($r = 0.62$, $p = 0.855$); TT ($r = 0.29$, $p = 0.745$) and clotting time, $r = 0.16$, $p = 0.071$).

Relationship of patients' clinico-laboratory parameters and coagulation tests

Table 3 compares coagulation profiles in relation to the presence of clinically evident bleeding, hypothermia, anaemia, erythrocytosis and hypoglycaemia among asphyxiated babies. Only three (7.3%) of the 41 asphyxiated babies had clinical bleeding, that is, two (4.9%) had petechiae haemorrhages and one (2.4%) had gastrointestinal bleeding. Clotting profiles were significantly prolonged among asphyxiated babies with hypothermia than those without hypothermia. The mean PT, aPTT and TT were 18.4 ± 0.8 , 56.3 ± 0.7 and 13.1 ± 1.4 s, respectively compared to 13.7 ± 0.3 , 51.1 ± 2.1 and 10.3 ± 1.0 s among non-hypothermic asphyxiated babies ($p < 0.001$). This is similar to what was obtained in erythrocytosis.

DISCUSSION

The clinical diagnosis of perinatal asphyxia is based on several criteria, however, the two that are commonly considered by American Academy of Pediatrics and American Congress of Obstetricians and Gynecologists (Leuthner and Gas, 2004) reflect evidence of cardiorespiratory and neurological depression. These include APGAR score that is less than 7 at fifth-minute of life and evidence of acute hypoxic compromise with acidaemia, that is, an arterial blood pH of less than 7 or base excess greater than 12 mmol/L. Definition of birth asphyxia in this study was however based on the former, since assessment of fetal or neonatal acidaemia is not currently available in our facility.

In this study, platelet count, PT, TT and bedside clotting time for the controls (apparently healthy babies) were similar to those previously reported in adults and healthy babies by Okunade and Essien (1998) in the University College Hospital, Ibadan, Nigeria. However, aPTT of these apparently healthy babies was slightly prolonged than the values expected for older children and adults in our environment. This may indeed reflect a relative hypocoagulable state in healthy newborn babies, and may justify the continued routine use of Vitamin K for all newborn babies.

In this prospective case-control analysis, although estimation of antithrombin III, protein C, protein S, factor V Leiden and individual clotting factors were not done, there were ample laboratory evidences of impaired haemostasis among babies with birth asphyxia, despite the fact that only three (7.3%) of them had clinically evident bleeding. All the coagulation screening tests done

Table 1. Sociodemographic characteristics of the cases and controls.

Sociodemographic variable	Cases (n = 41)	Controls (n = 41)	Overall	P value
Gestational age in weeks, (Mean ± SD)	39.51 ± 1.17	39.56±1.38	39.54± 2.01	0.86*
Male, n(%)	22 (53.7)	20 (48.8)	42 (51.2)	0.67#
Female, n(%)	19 (46.3)	21 (51.2)	40 (48.8)	
Age at presentation in hours (Mean ± SD)	31.22± 28.66	31.66±28.20	31.44±28.26	0.94*
Birth weight (in kilogram) Mean ± SD	3.04± 0.53	3.00±0.55	3.02 ± 0.54	0.74*
Mode of delivery:				
CS, n(%)	25 (61.0)	21 (51.2)	46 (56.1)	0.39#
SVD, n(%)	16 (39.0)	20 (48.8)	36 (43.9)	

CS = Cesarean section; SVD = Spontaneous vaginal delivery; * Done with independent sample t-test; # Done with Pearson's chi-square test.

Table 2. Comparison of the coagulation parameters of the cases and controls.

Coagulation parameter	Reference values	Moderate asphyxia	Severe asphyxia	Total asphyxia	Controls	t	p value
Number		9	32	41	41		
PT (s)	10–12	15.1±0.3	21.3±1.4	18.4±3.6	11.5±3.9	8.32	0.001
aPTT (s)	35–45	52.0±6.4	56.5±1.6	54.4±2.3	50.2±6.1	4.13	0.001
TT (s)	8–11	11.8±0.3	12.9±3.1	12.4±0.9	9.1±1.8	10.50	0.001
INR		1.3±0.4	1.4±0.1	1.3±0.8	1.3±0.5	0.00	1.00
Clotting time (min)	5–10	10.6±1.5	11.8±3.7	11.2±1.7	6.9±0.3	15.95	0.001
Platelet count*	150-450	141.1±43.5	129.5±36.8	130.5±37.9	167.8±22.3	5.50	0.001
Haematocrit (%)	45–65	59.6±3.4	56.1±3.8	58.1±0.6	57.3±8.8	0.58	0.563

*Platelet count was expressed in $\times 10^3/\text{mm}^3$; PT = Prothrombin time; aPTT = activated Partial Thromboplastin time, TT = Thrombin time, INR = International Normalised Ratio, s = seconds, min = minutes.

Table 3. Comparison of coagulation profiles in some associated clinico-laboratory factors among babies with birth asphyxia.

Variable		No (%)	PT Mean±SD	aPTT Mean±SD	TT Mean±SD	Platelet count Mean ± SD
Clinical bleeding	YES	3 (7.3)	15.8±0.1	52.1±0.1	11.9±0.3	134±14
	NO	38 (92.7)	16.1±1.4	53.7±1.3	12.1±0.5	132±17
Hypothermia	YES	18 (43.9)	18.4±0.8*	56.3±0.7*	13.1±1.4*	133±22
	NO	23 (56.1)	13.7±0.3	51.1±2.1	10.3±1.0	129±19
Anaemia	YES	5 (12.2)	16.1±2.2	55.0±2.7	12.2±0.7	130±27
	NO	36 (87.8)	15.9±0.5	54.8±2.8	12.6±0.3	130±15
Erythrocytosis	YES	7 (17.1)	17.7±2.7*	54.4±2.2*	12.7±0.8*	128±10*
	NO	34 (82.9)	14.0±1.1	50.1±0.1	10.0±0.1	143±32
Hypoglycaemia	YES	10 (24.4)	16.0±0.3	53.4±0.7	13.8±1.2*	132±11
	NO	31 (75.6)	16.7±1.0	53.8±0.3	10.5±1.0	133±16

*P < 0.001 with independent sample t-test; clinical bleeding: petechiae haemorrhage (2) and gastrointestinal bleeding (1); hypothermia = rectal temperature <36.5°C; anaemia = venous haematocrit <45%; erythrocytosis = venous haematocrit >65%; hypoglycaemia = serum glucose <2.2 mmol/L.

were significantly prolonged among the asphyxiated babies. This is because, birth asphyxia is known to alter the balance between bleeding and clotting cascades, including coagulation, fibrinolysis and impairment in platelets interactions (Bauman and Cheung, 2011). Several pathophysiological mechanisms have been proposed for derangement in coagulation by these groups of babies. They tend to have decreased platelet survival and impaired platelet activation as well as aggregatory functions, because of hypoxaemia and acidosis associated with asphyxia (Bauman and Cheung, 2011; Castle et al., 1986). Anoxic tissue damage in birth asphyxia may possibly contribute to intravascular coagulation by releasing tissue thromboplastin into the circulation (Christensen, 2000; Monagle et al., 2006). In spite of this, clinically evident bleeding is rare in newborn, even among ill babies. When present, they may be life-threatening especially when associated with disseminated intravascular coagulopathy. In this study, it is however possible for few other babies to have concealed haemorrhage such as mild intraventricular or subdural haemorrhage which could have been missed.

Abnormalities in the clotting tests were more prominent among asphyxiated babies with erythrocytosis and hypothermia in the present study. The high haematocrit levels in babies with erythrocytosis has been linked with prolongation of coagulation times (Bauman and Cheung, 2011). The elevated haematocrits and the subsequent increased blood viscosity leads ultimately to platelet aggregation and eventual consumption of the clotting proteins. Hypothermia, in this study, appears to be related to prolongation of coagulation times; possibly by impairing coagulation factors and accelerating microvascular thrombosis (Dirkmann et al., 2008). Interestingly, therapeutic hypothermia for babies with severe perinatal asphyxia has not been associated with an increased incidence of haemostatic complications (Azzopardi et al., 2009).

Asphyxia has been noted as a cause of thrombocytopenia in the newborn, although there are inconsistencies in the degree of thrombocytopenia in these babies from previous studies (Jeremiah and Oburu, 2010; Phelan et al., 2007). Increased destruction of platelets is the most plausible pathophysiological mechanism of thrombocytopenia in asphyxia. This decreased platelet survival occur despite normal overall bone marrow cellularity. Castle et al. (1986) reported destructive thrombocytopenia in 22% of critically ill neonates, most of whom had birth asphyxia.

In conclusion, dyscoagulation should be considered in all severely asphyxiated babies especially those with hypothermia and or erythrocytosis, even when there is no clinically evident bleeding. They may therefore require fresh frozen plasma to restore and or maintain their coagulation status. In environments such as ours, where coagulation screening, as well as blood and blood

products transfusion may not be readily available, the best approach to haemostatic complications of asphyxia is to prevent the asphyxiating events.

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