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Gestational age, prematurity and birth asphyxia on platelet indices in neonates

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Abstract
Platelets in newborn demonstrate several activities, including hemostasis and maintaining integrity of blood vessels. Hemostasis of a neonate is a dynamic system that gradually evolves throughout gestation and early infancy. The newborn physiological status affects the risk for and the presence of acquired hemostatic disorders. Prematurity, birth asphyxia (BA) and small for gestational age (SGA) babies have been associated with hemostatic abnormalities. The present study was planned to evaluate the effect of gestational age, prematurity and birth asphyxia on platelet indices in neonates.
The present study was planned in the Upgraded Department of Paediatrics (Neonatology) in Patna Medical College and Hospital, Patna from June 2018 to Dec 2018. Total 100 neonates were enrolled in the present study and divided in four study groups of controls, Small Gestational Age (SGA), preterm and Birth Asphyxia (BA).
Platelet indices may represent easy and early biomarker for identification of thromboembolic status in neonates, and thus improves the neonatal outcome. Platelet count & plateletcrit was decreased, mean platelet volume & platelet distribution width was significantly increased in SGA and premature newborns due to platelet activation.

Keywords: birth asphyxia, neonates, platelet indices, prematurity, small for gestational age

Introduction
Perinatal asphyxia, neonatal asphyxia or birth asphyxia is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. Hypoxic damage can occur to most of the infant's organs (heart, lungs, liver, gut, kidneys), but brain damage is of most concern and perhaps the least likely to quickly or completely heal. In more pronounced cases, an infant will survive, but with damage to the brain manifested as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity.
It results most commonly from a drop in maternal blood pressure or some other substantial interference with blood flow to the infant's brain during delivery. This can occur due to inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation. Perinatal asphyxia happens in 2 to 10 per 1000 newborns that are born at term, and more for those that are born prematurely [1]. WHO estimates that 4 million neonatal deaths occur yearly due to birth asphyxia, representing 38% of deaths of children under 5 years of age [2].
Perinatal asphyxia can be the cause of hypoxic ischemic encephalopathy or intraventricular hemorrhage, especially in preterm births. An infant suffering severe perinatal asphyxia usually has poor color (cyanosis), perfusion, responsiveness, muscle tone, and respiratory effort, as reflected in a low 5 minute Apgar score. Extreme degrees of asphyxia can cause cardiac arrest and death. If resuscitation is successful, the infant is usually transferred to a neonatal intensive care unit.
There has long been a scientific debate over whether newborn infants with asphyxia should be resuscitated with 100% oxygen or normal air [3]. It has been demonstrated that high concentrations of oxygen lead to generation of oxygen free radicals, which have a role in reperfusion injury after asphyxia [4]. Research by Ola Didrik Saugstad and others led to new international guidelines on newborn resuscitation in 2010, recommending the use of normal air instead of 100% oxygen [5].
There is considerable controversy over the diagnosis of birth asphyxia due to medicolegal reasons [7 8]. Because of its lack of precision, the term is eschewed in modern obstetrics [6].
There are number of tests that can confirm perinatal asphyxia. These tests include a CT scan, an MRI, and an Electroencephalogram (EEG). These may not be specific enough, so other more thorough tests include the SPECT tests, a form of CT scan that checks areas of the brain for blood flow and metabolism, and evoked potential tests, tests that evaluate the visual, auditory, and sensory pathways.
Birth asphyxia could be very severe. Your baby might have stopped breathing for only a few seconds, causing hypoxia, or your baby could have birth asphyxia, could stop breathing for minutes, causing anoxia, and lead to other birth injuries such as Hypoxic Ischemic Encephalopathy (HIE) and cerebral palsy –two conditions that could affect your baby for the rest of his or her life.
Gestational age is a measure of the age of a pregnancy which is taken from the beginning of the woman's last menstrual period (LMP), or the corresponding age of the gestation as estimated by a more accurate method if available. Such methods include adding 14 days to a known duration since fertilization (as is possible in *in vitro* fertilization), or by obstetric ultrasonography. The popularity of using such a definition of gestational age is that menstrual periods are essentially always noticed, while there is usually a lack of a convenient way to discern when fertilization occurred.

The initiation of pregnancy for the calculation of gestational age can be different from definitions of initiation of pregnancy in context of the abortion debate or beginning of human personhood.

As a general rule, the official gestational age should be based on the actual beginning of the last menstrual period, unless any of the above methods gives an estimated date that differs more than the variability for the method, in which case the difference cannot probably be explained by that variability alone [7]. For example, if there is a gestational age based on the beginning of the last menstrual period of 9.0 weeks, and a first-trimester obstetric ultrasonography gives an estimated gestational age of 10.0 weeks (with a 2 SD variability of ±8% of the estimate thereby giving a variability of ±0.8 weeks), the difference of 1.0 weeks between the tests is larger than the 2 SD variability of the ultrasonography estimate, indicating that the gestational age estimated by ultrasonography should be used as the official gestational age [7].

Once the estimated due date (EDD) is established, it should rarely be changed, as the determination of gestational age is most accurate earlier in the pregnancy [8].

Platelets in newborn demonstrate several activities, including hemostasis and maintaining integrity of blood vessels. Hemostasis of a neonate is a dynamic system that gradually evolves throughout gestation and early infancy. The newborn physiological status affects the risk for and the presence of acquired hemostatic disorders. Prematurity, birth asphyxia (BA) and small for gestational age (SGA) babies have been associated with hemostatic abnormalities. The present study was planned to evaluate the effect of Gestational Age, Prematurity and Birth Asphyxia on Platelet Indices in Neonates.

Methodology

The present study was planned in the Upgraded Department of Paediatrics (Neonatology) in Patna Medical College and Hospital, Patna from June 2018 to Dec 2018. Total 100 neonates were enrolled in the present study and divided in four study groups of controls, Small for Gestational Age (SGA), Preterm and Birth Asphyxia (BA).

Data regarding the neonatal physiological status with respect to prematurity, gestational age and BA were collected. Newborns in gestational age 25-32 weeks and weighing 1000-2150 g and Apgar score of 4-8 points at 1 min were considered preterm. Newborns in gestational age 38-41 weeks, but weighing <10th percentile were considered as SGA. Newborns whose Apgar score at 5th min was <5 and arterial blood pH during birth or a few hours after birth below 7.2 and had the findings of hypoxic ischemic encephalopathy were accepted as having BA. Platelet indices from full term, AGA without BA were taken as controls.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

It was observed that average platelet count in preterm and SGA neonates was found to be decreased as compared with full term AGA newborns. Hemostasis in neonate is a dynamic entity which evolves gradually throughout the fetal period and early infancy. Platelets first appear in human fetus at the gestational age of 5 weeks after conception, it gradually increases during the fetal life, reaching a mean of 150×100 /L by the end of first trimester and reach the adult value by gestational age of 22 weeks.

The fetal platelet count increases linearly with gestation from a mean of 187,000/mcL at 15 weeks to 274,000/mcL at 40 weeks. Normal platelet counts in preterm infants are in the identical range (150,000/mcL to 450,000/mcL) as that of adults. Thus, at any age, a platelet count less than 150,000/mcL is abnormally low, so by definition, all 3 infants in the preceding scenarios are thrombocytopenic. The clinical significance of platelet counts in the 100,000-150,000/mcL range is unclear. Although abnormal, these counts may not convey an increase in bleeding risk.

Table 1: Age & Weight

Platelet indices	Controls	Small Gestational Age (SGA)	Preterm	Birth Asphyxia (BA)
Total Cases	25	25	25	25
Age	38 - 41 week	38 - 41 week	25 - 32 week	36 - 41 weeks
Weight gm	2550 - 3160 gm	1470 - 2130 gm	1210 – 2090 gm	2420 –2840gm

Table 2: Comparison of Platelets

Platelet indices	Controls	Small Gestational Age (SGA)	Preterm	Birth Asphyxia (BA)
Total Cases	25	25	25	25
Platelet count x 10^2/µl	183 – 325	143-197	168-294	164 – 283
Mean platelet volume (fL)	7.3 – 8.7	7.6 – 8.8	7.5 – 9.1	7.8 – 9.1
Plateletcrit (%)	0.15 – 0.24	0.13 – 0.23	0.12 – 0. 24	0.11 – 0.25
Platelet distribution width (fL)	10.2 – 16.1	11.2 – 17.3	11.5 – 17.6	12.4 – 18.6

Laboratory evaluations can provide clues to the kinetic mechanism of an infant's thrombocytopenia. Mean platelet volume (MPV) is a measure of the average size of circulating platelets. MPV is normal (7.5-9.5 fL) when thrombocytopenia is caused by reduced production, and elevated (> 10-12 fL) when caused by accelerated destruction. Larger platelets are evident when the bone marrow is stimulated to produce more immature platelets in response to increased platelet utilization. MPV is measured by automated analyzers and is reported along with the platelet count or can be obtained by calling the laboratory. The percentage of reticulated platelets (RPs) is another indicator of the kinetic mechanism. RPs are newly produced platelets that have a higher ribonucleic acid content than do older platelets [9].

An important factor in stimulating the formation of platelets is thrombopoietin, whose principal place of synthesis is liver in newborns and fetuses. Thrombopoietin acts through the c-MPL receptor present on platelets, megakaryocytes and precursor cells of megakariopoiesis, and its plasma

concentration depends on the amount of free receptor cMPL [10]. When the platelet count increases, a significant proportion of circulating TPO binds to the receptor c-MPL, resulting in a decrease of free TPO, and inhibits thrombopoiesis. When the platelet count falls, more freely circulating plasma thrombopoietin stimulates thrombopoiesis. Wasiluk *et al*. found higher levels of TPO in SGA suggesting the role of impaired thrombopoiesis [11].

The evolution of neonatal coagulation system has been stated to be independent of maternal side due to placental barrier for large coagulation proteins between the two blood circulations. Most of hemostatic indices gradually evolve during early life and reach their adult levels by 6 month. Available studies show immature coagulation system in association with lower GA and neonatal immaturity at the time of birth [12].

The functions of platelets are found to be related to the gestational age [13]. Lower platelet counts observed in preterm neonates is mostly due to developmental limitation in the ability to increase megakaryocyte size and placental dysfunction may also be responsible for the alteration of platelet count in newborns at birth [14-15]. The reduced platelet count and their function in relation to gestational age may result in higher risk of bleeding tendency in preterm neonates [13].

Studies by Wasiluk *et al*. demonstrated that platelet indices are altered by prematurity and GA [16, 17]. Although, platelet changes in premature neonates have been already contributed to GA and birth weight [18], these authors concluded that decreased platelet count and increased distribution width occurs in relation with low GA and dysfunction of placenta. Further study also confirmed these findings with more emphasis on the effect of intrauterine growth retardation on thrombopoiesis and subsequent platelet impairments.

Conclusion

Platelet indices may represent easy and early biomarker for identification of thromboembolic status in neonates, and thus improves the neonatal outcome. Platelet count & plateletcrit was decreased, mean platelet volume & platelet distribution width was significantly increased in SGA and premature newborns due to platelet activation.

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