Patent Ductus Arteriosus: Looking for the Right Approach of Management

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In majority of healthy preterm neonates, ductus arteriosus closes spontaneously by 3-7 days after birth [1]. However, three-fourth of very preterm neonates with respiratory distress may continue to have a patent ductus arteriosus (PDA) at end of first week of life. Persistent patency of ductus arteriosus increases blood flow through pulmonary vascular bed and decreases blood flow through cerebral, mesenteric and renal vascular beds. PDA has been associated with decreased survival and increased incidence of pulmonary hemorrhage and bronchopulmonary dysplasia. Ever since initial reports of effect of indomethacin in inducing ductal closure were published in 1970s, impact of prophylactic and therapeutic administration of prostaglandin inhibitors on short- or long-term outcomes of preterm neonates has been an active research issue [2]. During the last decade, acquisition of basic echocardiographic skills by neonatologists has led to earlier recognition and treatment of PDA before the associated clinical features make their appearance. However, questions on selecting appropriate biomarker of hemodynamic significance, optimal timing (prophylactic, pre-symptomatic or symptomatic) of administration of prostaglandin inhibitors, and even necessity of inducing PDA closure remain largely unanswered.

In this issue of *Indian Pediatrics*, Popat, *et al.* [3] present their data on closure rate of PDA with indomethacin. PDA was treated on appearance of clinical symptoms and up to three course of indomethacin were administered. Two-thirds of neonates born at less than 29 weeks gestation had significant PDA. Although, 90% responded to multiple courses of indomethacin, treatment of PDA was not associated with improved neonatal morbidities. Neonates who did not respond to multiple courses of indomethacin were more likely to be females, born at earlier gestation, and tended to have higher sickness severity scores and culture-proven sepsis.

Indomethacin is the drug of choice for inducing PDA closure in preterm neonates. However, non-response or reopening of PDA after single course of indomethacin administration is not uncommon. Lack of exposure to antenatal steroids, small-for-gestation status, significant respiratory distress, lower gestation age, liberal fluid intake and a shorter duration of indomethacin treatment are associated with a decreased probability of treatment response [4]. Once indomethacin treatment fails to induce ductal closure, options include ductal ligation, repeated courses of indomethacin or conservative management waiting for spontaneous closure. Surgical ligation of PDA has its own set of associated morbidities (vocal cord paralysis, pneumothorax, chylothorax, scoliosis and infection) and may lead to impaired lung growth and increased incidence of BPD [4]. Indomethacin administration has not only been unsuccessful in improving survival or decreasing incidence of BPD and pulmonary hemorrhage, its infusion induces vasoconstriction in different vascular beds leading to decreased end-organ perfusion. Repeated courses may have cumulative detrimental effect. As a result, advocacy for investigating the third option of conservative watch of PDA is now gaining more voice [5].

Prophylactic administration of indomethacin within 24 h of birth has been associated with decreased incidence of intraventricular or pulmonary hemorrhage and risk of developing symptomatic PDA [6]. Although no improvement in survival without disability was reported at 18 months, gender-specific effect on neurological outcome has been proposed [1]. The need and length of subsequent courses of therapeutic indomethacin may also influence the neurological outcome.

Preterm neonates constitute a heterogenous group in which PDA may close spontaneously, respond to prostaglandin inhibitors or remain open despite multiple attempts of medical closure. Search continues for a select subgroup of neonates, who, identified through a suitable biomarker, will benefit from prophylactic, early therapeutic or repeated administrations of prostaglandin inhibitors.

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Point of Care Estimation of Blood Glucose in Neonates

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Prolonged hypoglycemia in newborn infants is associated with adverse neurodevelopmental consequences. Therefore, in 1996, the American Academy of Pediatrics recommended routine screening in newborn units which take care of infants at risk for hypoglycemia [1]. The optimum method for measuring blood glucose is laboratory estimation of plasma glucose. Laboratory analyzers use a number of different enzymes to measure glucose eg, glucose oxidase, hexokinase or glucose dehydrogenase. These measure plasma glucose and are less affected by interference by metabolites, are not affected by hematocrit and are considered the gold standard for clinical measurement of glucose levels. The major issues with laboratory based testing are need of a larger volume of blood, non availability of results quickly enough for timely appropriate treatment and errors associated with delayed estimation [2].

Therefore 'point of care' (POC) testing is often used for measurement of whole blood glucose concentration in neonatal intensive care units. Point of care testing is defined as any analytic testing done outside a designated laboratory space. It has several advantages like rapid turnaround time, reduced blood volume requirements, and clinical utility over traditional laboratory-based testing and is especially well suited for acute care settings such as the neonatal intensive care unit. Accuracy studies have shown that their results correlate well with laboratory measured plasma glucose in the normoglycemic and hyperglycemic range, but are not satisfactory in the lower range. This is understandable as the currently used glucometers were initially developed for glucose monitoring in adult patients with diabetes. However, our main concern in newborn babies is the low blood glucose range [3].

As there are accuracy issues with the simple convenient bedside POCT devices, many workers have tried to compare these with the gold standard laboratory estimation. When analyzing the performance of glucometers in the hypoglycemic range, glucometers are required to perform to the standards of the US National Committee for Clinical Laboratory Standards (NCCLS) or the American Diabetic Association (ADA). In 1994, the ADA recommended that a glucometer should achieve a total error (system + user) of less than 10% for the plasma glucose concentration range 1.6–22.2 mmol/L (30–400 mg/dL). NCCLS in 1994 ascertained that for glucose concentrations less than 5.5 mmol/L (100 mg/dL), discrepancies should be no more than 0.83 mmol/L (15 mg/dL) [4].

In recent years, numerous studies have been published analyzing the accuracy of glucometers specifically in the setting of neonatal hypoglycemia. Ho, *et al*. [5] reported on the sensitivity and negative predictive value of 5 glucometers in detecting neonatal hypoglycemia. They found that not even 1 of the 5 was able to meet the ADA standards, whereas 2 of the devices were able to meet the NCCLS standards. Khan, *et al*. [6] compared 7 glucometers and reported agreement between glucometer readings in the hypoglycemic range but found wide discrepancy in the correlation between reference and POCT devices both in the hypo and hyperglycemic range to the tune of 60%. The study by

Ngerncham, *et al.* [7] appearing in this volume of the journal too has used an elegant split sample design and meticulously compared OneTouch SureStep Hospital Test Strips (photometric glucose oxidase system) with a Nova StatStrip (modified glucose oxidase based amperometric system) using Roche Modular P 800 for the reference laboratory measurement. Another recent study reported good correlation as well as recommended their use in neonatal clinical practice [8]. All these studies highlight that POC devices may be used as screening devices for neonatal hypoglycemia, but confirmation of hypoglycemia with laboratory measurement of plasma glucose is still crucial.

It needs to be realized that laboratory estimation too is fraught with preanalytical (sample collection, transport and physiological factors) errors. POCT devices are prone for both pre-analytical and analytical errors (precision of the device being used). The comparison of POCT devices with laboratory sample which has been poorly processed can lead to erroneous estimation of discrepancy where little or none may exist. Any further studies on comparison of POCT devices with reference standard should focus on comparing improved second generation POCT devices with a reference laboratory device taking utmost care to ensure precise laboratory estimation without any processing delays and fall in glucose secondary to glycolysis.

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