Paracetamol in Patent Ductus Arteriosus: "Flavour of the Month" or Here to Stay?

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The ductus arteriosus closes over the first few days of life in most newborns. In preterm infants, it may remain open even after 4-7 days of life leading to increased shunting of blood into the pulmonary circulation and potentially compromising circulation to systemic organs. This assumption is the keystone on which the decision to close the patent ductus arteriosus (PDA) in a preterm baby rests.

Though spontaneous closure of the ductus is the norm in term newborns, two-thirds of very low birth weight (VLBW) babies have spontaneous closure in the first seven days of life and only 30% of extremely low birth weight (ELBW) close their ductus during the neonatal period [1]. A PDA in a VLBW baby is associated (though not causal) with adverse outcomes like broncho-pulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC) and death [2]. However, trials have not shown any definite change in these outcomes by treating a PDA. Treatment of PDA thus remains one of the most debated topics in neonatal medicine with no consensus on whether to treat, and when and how to treat! Nick Evans aptly calls it a "conundrum" [2-4]. Be that as it may, most neonatologists would prefer to attempt ductal closure in preterm neonates with symptoms or in those on respiratory support.

Hemodynamic significance of PDA in clinical practice is determined by echocardiographic assessment of size of PDA and its association with clinical signs – mainly respiratory. Closure is attained either pharmacologically (with prostaglandin inhibitors) or surgically. In the year 1976, indomethacin was first used to treat PDA in a preterm neonate [5]. After that, ibuprofen came into use. A Cochrane meta-analysis comparing these two stated that ibuprofen was as effective as indomethacin in closing a PDA with lesser risk of NEC or transient renal insufficiency, thus being the drug of choice [6]. Hammerman, *et al.* [7] in 2009, first described the successful use of oral paracetamol for ductal closure in a case series of 5 preterm babies who either had contra-indications to or failed closure with indomethacin.

Paracetamol acts mainly by inhibiting peroxidase enzyme activity. It is a weak inhibitor of cyclo-oxygenase enzyme. Because of the ease of availability, lesser cost and wider margin of safety, paracetamol has generated interest among neonatologists as a potential first line drug for ductal closure. There have been two recent randomized controlled trails (RCTs) which have looked at efficacy of paracetamol as first line drug for closure of hemodynamically significant PDA in comparison to ibuprofen [8,9]. A meta-analysis of these trials opined that paracetamol was as effective as oral ibuprofen. A cautionary note was introduced in view of animal studies suggesting adverse effects on developing brain after use of paracetamol. Thus the author advised that long-term neurological outcomes should be looked at regarding use of paracetamol in newborn [10].

In this issue, Dash, *et al.* [11] have published a RCT comparing oral paracetamol with intravenous indomethacin with the primary outcome being closure of the PDA at 7 days. This is the first RCT that has compared oral paracetamol with indomethacin. The authors randomized 77 VLBW preterms having a PDA (diagnosis based on echocardiographic findings) within 48 hours of life to receive either paracetamol or indomethacin. PDA closure rates were 100% and 94.6% in the paracetamol and indomethacin groups, respectively. There were no differences in secondary outcomes such as need for surgical closure of PDA, gastrointestinal bleed, necrotizing enterocolitis, hepatotoxicity, hypothermia, renal dysfunction or mortality between the two groups. The authors have rightly pointed out that the study was underpowered to demonstrate the anticipated difference of efficacy between the two intervention drugs. As the study recruited neonates in the first 48 hours of life, some of these neonates might have had spontaneous closure of

PDA. Even with these limitations, this study will definitely add to the existing evidence on use of paracetamol in therapy for PDA.

Paracetamol can be used cautiously as the first line drug in the absence of indomethacin/ibuprofen or when these drugs are contraindicated. Larger studies comparing paracetamol versus indomethacin/ibuprofen in symptomatic PDA may be needed before paracetamol can be accepted as the first line drug in treatment of PDA. It would be worthwhile to also follow-up this cohort to see the neuro-developmental outcomes, and the same should be applicable to future RCTs using paracetamol for closure of PDA.

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Paracetamol for Closure of Patent Ductus Arteriosus

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Whether or not to treat all neonates with PDA remains controversial. Association of PDA with adverse outcomes suggests a need to intervene in neonates with PDA. However, pharmacological as well as surgical treatment strategies have failed to show promising long-term benefits. So, the dilemma remains!

It is well known that the incidence of symptomatic and pathologic PDA is significantly higher in preterm infants with ≥28 weeks' gestation and/or ≥1000 g birth weight [1]. This suggests the need to select candidates for treatment of PDA judiciously. Treatment options for PDA include surgical and pharmacological modalities. Conservative management includes fluid restriction, and high positive end-expiratory pressure (PEEP) and low inspiratory time (0.35s) during ventilation [2]. These approaches need more scientific evidence, including randomized controlled studies. Also, restricted fluid regimens and high PEEP are most difficult to follow in extremely low gestational ages (<28 weeks). Pharmacological therapy is thus the mainstay for treatment of PDA. Surgical therapy is often used as a last resort for treatment of PDA.

Indomethacin and ibuprofen act by blocking the conversion of arachidonic acid to prostaglandins, and have been adequately studied for ductal closure [3].