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].
However, due to their adverse effects, paracetamol came up into clinical practice as a new treatment option for PDA [1]. Paracetamol acts by directly inhibiting the activity of prostaglandin synthase. Unlike ibuprofen, it is thought to act on prostaglandin synthase at the peroxidase region of the enzyme. In 2011, Hammerman, et al. [4] first published used paracetamol in preterm infants with PDA. Thereafter, Oncel, et al. [5-7] published case series about enteral and/or intravenous paracetamol treatment in preterm infants with clinically significant PDA. These studies showed that paracetamol is effective for treatment of PDA in preterm infants.

In this issue of Indian Pediatrics, Dash, et al. [8] provide valuable new comparative data between enteral paracetamol and intravenous indomethacin for closure of PDA in preterm neonates. The investigators prospectively enrolled 171 preterm infants with birthweight ≥1500 g, within 48 hours of birth, and with one of the following echocardiographic criteria: duct size >1.5 mm, a left atrium-to-aorta ratio >1.5. Finally, 38 preterm neonates were randomized to receive enteral paracetamol and 39 were randomized to receive intravenous indomethacin. PDA closure rates with oral paracetamol and indomethacin were 100% and 95%, respectively. There were no significant differences between two groups for side effects or other co-morbidities. The PDA closure rates were quite high in both study groups (>95%) which may be related to the high mean gestational age (31.6 weeks). In contrast, PDA closure rate with paracetamol therapy in an earlier study [1] was 72.5%. The other striking result of this study is high intestinal bleeding rate in paracetamol group (26.3%). In a study [7] from our group, we did not see any intestinal side effects of paracetamol groups. Most of the paracetamol solutions have osmolalities about 4000 ±1000 mOsmol/L which need to be diluted to reduce it tenfold to 400 mOsmol/L. The excessive intestinal problems in this study may have been related to the high osmolality of paracetamol solutions used for treatment. The results of present study are similar to those of two randomized controlled studies in the past [1,9]. All these studies showed that paracetamol is a safe and successful alternative agent for pharmacological treatment of PDA. However, there is a need for further studies evaluating the effects, especially the long-term neurodevelopmental outcome in infants treated with paracetamol.

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**REFERENCES**