

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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## REFERENCES

1. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol.* 2012;36:123-9.
2. Evans N. Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist? *Semin Fetal Neonatal Med.* 2015. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1744165X15000402>. Accessed June 15, 2015.
3. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis & quest. *J Perinatol.* 2010;30:241-52.
4. Benitz WE. Patent ductus arteriosus: to treat or not to treat? *Arch Dis Child Fetal Neonatal Ed.* 2012;97:F80-2.
5. Friedman WF. A look back: the clinical initiation of pharmacologic closure of patent ductus arteriosus in the preterm infant. *NeoReviews.* 2003;4:e259-62.
6. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev.* 2015;2:CD003481.
7. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics.* 2011;128:e1618-21.
8. Dang D, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. *PLoS One.* 2013;8:e77888.
9. Oncel MY, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, *et al.* Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. *J Pediatr.* 2014;164:510-4.e1.
10. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants. *Cochrane Database Syst Rev.* Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010061.pub2/full>. Accessed June 18, 2015.
11. Dash SK, Kabra NS, Avasthi BK, Sharma SR, Padhi P, Ahmed J. Enteral paracetamol or intravenous indomethacin for closure of patent ductus arteriosus in preterm neonates: a randomized controlled trial. *Indian Pediatr.* 2015;52:573-8.

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## Paracetamol for Closure of Patent Ductus Arteriosus

SADIK YURTTUTAN

*Division of Neonatology, Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey.  
sdyurttutan@gmail.com*

**W**hether 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  $\geq 28$  weeks' gestation and/or  $\geq 1000$  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  $\geq 1500$  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 comorbidities. 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 ( $\pm 1000$ ) 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

1. Oncel MY, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, *et al.* Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. *J Pediatr.* 2014;164:510-4.
2. Dani C, Bertini G, Corsini I, Elia S, Vangi V, Pratesi S, *et al.* The fate of ductus arteriosus in infants at 23-27 weeks of gestation: from spontaneous closure to ibuprofen resistance. *Acta Paediatr.* 2008;97:1176-80.
3. Demirel G, Erdeve O, Dilmen U. Pharmacological management of PDA: oral vs intravenous medications. *Curr Clin Pharmacol.* 2012;7:263-70.
4. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics.* 2011;128:1618-21.
5. Oncel MY, Yurttutan S, Uras N, Altug N, Ozdemir R, Ekmen S, *et al.* An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2013;98:F94.
6. Oncel MY, Yurttutan S, Degirmencioglu H, Uras N, Altug N, Erdeve O, *et al.* Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birthweight infants. *Neonatology.* 2013;103:166-9.
7. Yurttutan S, Oncel MY, Arayici S, Uras N, Altug N, Erdeve O, *et al.* A different first choice drug in the medical management of patent ductus arteriosus: oral paracetamol. *J Matern Fetal Neonatal Med.* 2013;26:825-7.
8. Dash SK, Kabra NS, Avasthi BK, Sharma SR, Padhi P, Ahmed J. Enteral paracetamol or Intravenous indomethacin for closure of patent ductus arteriosus in preterm neonates: a randomized controlled trial. *Indian Pediatr.* 2015;52:573-78.
9. Dang D, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. *PLoS One.* 2013;8:e77888.