RESEARCH PAPER

Enteral paracetamol or Intravenous Indomethacin for Closure of Patent Ductus Arteriosus in Preterm Neonates: *A Randomized Controlled Trial*

Swarup Kumar Dash, Nandkishor S Kabra, Bhupendra S Avasthi, Shobha R Sharma, Phalguni Padhi and Javed Ahmed

From Department of Neonatology, Surya Children's Hospital, Mangal Ashirwad, Santacruz West, Mumbai, India.
Correspondence to: Dr Nandkishor S Kabra, Department of Neonatology, Surya Children's Hospital, Mangal Ashirwad, Junction of S V Road and Dattatraya Road, Santacruz West, Mumbai 400 054, India. nskabra@gmail.com
Received: August 06, 2014; Initial review: October 04, 2014; Accepted: April 21, 2015.

Objective: To compare the efficacy of enteral paracetamol and intravenous indomethacin for closure of patent ductus arteriosus (PDA) in preterm neonates.

Design: Randomized controlled trial.

Setting: Level III neonatal intensive care unit.

Participants: 77 preterm neonates with birth weight ≤1500 g and PDA size ≥1.5 mm, with left to right ductal flow with left atrium to aortic root ratio >1.5:1; diagnosed by 2D-Echo within first 48 hours of life.

Intervention: Paracetamol drops through the infant feeding tube (15mg/kg/dose 6 hourly for 7 days) or intravenous indomethacin (0.2 mg/kg/dose once daily for 3 days).

Outcome measures: *Primary*: PDA closure rate assessed by echocardiography. *Secondary*: need for surgical closure of PDA, renal impairment, gastrointestinal bleed, necrotising enterocolitis, hepatotoxicity, pulmonary hemorrhage, sepsis, hypothermia, retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia and mortality.

Results: PDA closure rate was 100% (36/36) in enteral paracetamol group as compared to 94.6% (35/37) in intravenous indomethacin group (*P*=0.13). The secondary outcomes were also similar between the two groups. There was no occurrence of hepatotoxicity.

Conclusions: Enteral paracetamol is safe but not superior to intravenous indomethacin in the treatment of PDA in preterm neonates.

Key words: *Echocadiography, Neonate, Patent ductus arteriorus, Treatment*.

Trial Registration: *CTRI/2012/12/003/63.*

Ductus arteriosus may close spontaneously by day 7 of life in only 70% of infants with birth weight between 1000 to 1500 g and 30%-35% of infants with birth weight <1000 g [1,2]. If the patent ductus arteriosus (PDA) is hemodynamically significant and symptomatic, therapeutic interventions may be required to facilitate its closure [3,4]. Reported efficacy rate for ductal closure using both indomethacin and ibuprofen is about 60% to 80 % [5]. However, both indomethacin and ibuprofen have been associated with potential adverse effects including peripheral vasoconstriction, gastrointestinal perforations, necrotizing enterocolitis (NEC), renal impairment, platelet aggregation dysfunction, and hyperbilirubinemia [6-11].

Paracetamol is efficacious in closure of PDA in preterm infants [12-14]. It acts mainly by inhibiting the peroxidase enzyme activity. Peroxidase is activated at lower peroxide concentration than that of cyclo-oxygenase, suggesting that paracetamol may work well at decreased peroxide concentrations like in hypoxia [12-14]. It also has a wide margin of safety, but there is paucity of controlled trials comparing paracetamol with indomethacin for closure of PDA.

This study compared the efficacy and safety of enteral paracetamol with intravenous indomethacin in closure of hemodynamically significant PDA in preterm neonates.

Accompanying Editorials: Pages 567-69.

Methods

This open-label randomized controlled trial was conducted at a level III neonatal intensive care unit (NICU) of a private hospital in Mumbai, India. The study was approved by hospital's local academic research and ethics committee. Written informed consent was obtained from the parents prior to enrolment of their infants. Inclusion criteria were: (*i*) preterm infant with birth weight ≤1500 grams and (*ii*) echocardiography performed within the first 48 hours of life demonstrating

PDA size ≥1.5 mm at the narrowest diameter, left to right shunt across the duct and ratio of the diameter of the left atrium to that of the aortic root (LA:AO) >1.5:1. Exclusion criteria were: (*i*) inability to administer the study drug within 48 hours of birth, (*ii*) structural duct-dependent congenital heart disease, renal disease (such as multicystic dysplastic kidney and polycystic disease of kidney), (*iii*) dysmorphic features or congenital anomalies likely to affect life-expectancy or neurologic development, (*iv*) maternal tocolytic therapy with indomethacin or another prostaglandin inhibitor within 72 hrs prior to delivery, (*v*) overt clinical bleeding at more than one site, (*vi*) Platelet count $<50\times10^9$/L, (*vii*) hydrops fetalis, and (*viii*) infant not considered viable.

An echocardiogram which included doppler flow studies was performed by a trained pediatric cardiologist within 48 hours of birth to look for presence of any hemodynamically significant PDA. PDA was considered hemodynamically significant if size was ≥1.5 mm at the narrowest diameter [15,16], left to right shunt was seen across the duct and the LA:AO ratio was more than 1.5:1. The study period was from March 2012 to September 2013. All the relevant data was collected using a predesigned case record form.

All eligible neonates meeting the inclusion criteria were randomized into two groups, using a 1:1 ratio. Random sequence generation was performed by using random allocation software in variable blocks of 2 or 4. This sequence was generated by a statistician who was not part of the study. Allocation concealment was done by sequentially numbered sealed opaque envelopes. When a patient meeting the inclusion criteria was ready to be enrolled in the study, the doctor on duty obtained written informed consent from the parents. The serially numbered opaque sealed envelope was opened by the doctor and the patient was enrolled into the respective intervention group.

As per randomization, patients received paracetamol drops (Calpol drops, 100 mg/mL, Glaxo SmithKline) through the infant feeding tube at a dose of 15 mg/kg/dose four times daily for 7 days (28 doses) or IV indomethacin (1mg/mL, Lygacin IV, Alliance Overseas) at a dose of 0.2 mg/kg/dose, diluted with normal saline to make 5 mL solution and infused over 20 minutes by syringe pump once daily for three days [17]. As per study protocol, two additional extra doses of indomethacin were allowed in the indomethacin group, if clinical evaluation after three doses showed persistence of PDA as demonstrated by clinical signs and symptoms such as tachycardia, wide pulse pressure and persistent murmur.

The primary outcome measure of the study was PDA closure. The first screening echocardiography was performed within 48 hours of life. Subsequent follow-up echocardiography was performed after completion of 7 days from initiation of treatment. The PDA was considered to be closed if there was no evidence of any flow in the ductus arteriosus on echocardiographic and doppler flow assessment. Serum electrolyte and serum creatinine values were measured before starting treatment with the drug, and subsequently thereafter at regular intervals as per standard unit policy. Urine output was measured daily. Renal impairment was defined as presence of either oliguria (urine output of < 0.5 mL/kg/hr) over a 6 hour period or serum creatinine levels more than twice the age appropriate norms. Gastro-intestinal (GI) bleeding was defined as the presence of blood-stained or coffee ground brown gastric aspirates. Mild gastric aspirate was defined as blood-stained or altered brownish blood in the aspirate, and major GI bleeding was defined as presence of frank blood in the gastric aspirate. Necrotising enterocolitis (NEC) was diagnosed as per modified Bell's staging [18]. Liver function tests were measured on day 7 of life; hepatotoxicity was defined, if the hepatic enzymes were elevated more than twice of the normal reference values. Pulmonary hemorrhage was diagnosed if a blood tinged tracheal aspirate was obtained. Positive early- and late-onset sepsis screen was defined as positive C-reactive protein (CRP) before and after first 72 hours of life (CRP >6 mg/L), respectively. Early-onset sepsis was defined as isolation of pathogenic organism from a blood culture collected in first 72 hours of life. Late onset sepsis was defined as isolation of pathogenic organism from a blood culture collected after first 72 hours of life. All blood cultures were collected in BacT/ALERT 3D (Biomerieux) blood culture bottles. Hypothermia was defined as occurrence of temperature ≤36º celsius during the therapy period. Retinopathy of prematurity (ROP) was classified as per the International classification of retinopathy [19]. ROP needing either laser or anti-VEGF (Avastin) therapy was labelled as severe ROP. Neurosonography was performed as per our unit protocol, at least twice; first sonography between day 5 to 7 of life and second sonography between days 21 to 28 of life. A third cranial ultrasonography was performed if an infant was still admitted to the NICU at 36 weeks corrected gestational age. Grading of intraventricular hemorrhage (IVH) was performed according to the Papile grading system [20], and features of periventricular leukomalacia (PVL) were also assessed. Requirement of supplemental oxygen at 28 days of postnatal age was assessed. Bronchopulmonary dysplasia (BPD) /chronic lung disease (CLD) was defined by the need for supplemental oxygen at 36 weeks of postmenstrual age [21]. The

success rate of indomethacin for closure of PDA was estimated to be 50 percent [22], and a sample size of 72 (36 in each group) was calculated to be adequate for a 30% difference with a two-sided alpha error of 0.05 and beta error of 0.2 (power 80%).

To compare the outcome variables on continuous and ordinal scale, two sample t tests or the Mann Whitney test were used. To compare the outcome variables on nominal type of data, Fisher exact test was used. Relative risk (RR) and 95% CI were calculated as a measure of association for the dichotomous outcomes. The analysis was performed by applying the intention to treat principle. Analysis was performed by using IBM SPSS 21 software.

RESULTS

A total of 171 premature neonates with birth weight <1500 g were admitted in NICU during the study period and were assessed within 48 hours of birth for presence of PDA. Out of these, 38 were randomized to the enteral paracetamol group and 39 were randomized to the intravenous indomethacin group (***Fig.* 1**). Two infants in each group died before the time of assessment of PDA closure by echocardiography.

In the enteral paracetamol group, six neonates (GI bleeding 3, NEC 1, deaths 2), and in the intravenous indomethacin group, one neonate (metabolic acidosis and deteriorating clinical condition) failed to complete the full intended course of the study drug. One patient in the indomethacin group received 2 extra doses as clinical examination performed after 3 doses revealed persistence of PDA. There were no significant differences in the baseline characteristics of the mothers and their infants between the two study groups (***Table* I**).

***Table* II** compares the outcomes in two study groups. There was no significant difference in the PDA closure rate between the two groups. None of the infants in either group required surgical closure of PDA.

DISCUSSION

The results of our study suggest that enteral paracetamol is safe but not superior to intravenous indomethacin in promoting closure of the hemodynamically significant PDA in premature infants when treatment commences in the first 48 hours after diagnosis by echocardiography and Doppler. Our study did not find any significant difference in the frequency of adverse events, outcomes including GI bleed, NEC, ROP, IVH/PVL, pulmonary hemorrhage and CLD/BPD.

The main limitation of our study was lack of blinding of the caregivers to the study intervention. Also, it is possible that some of our neonates might have had

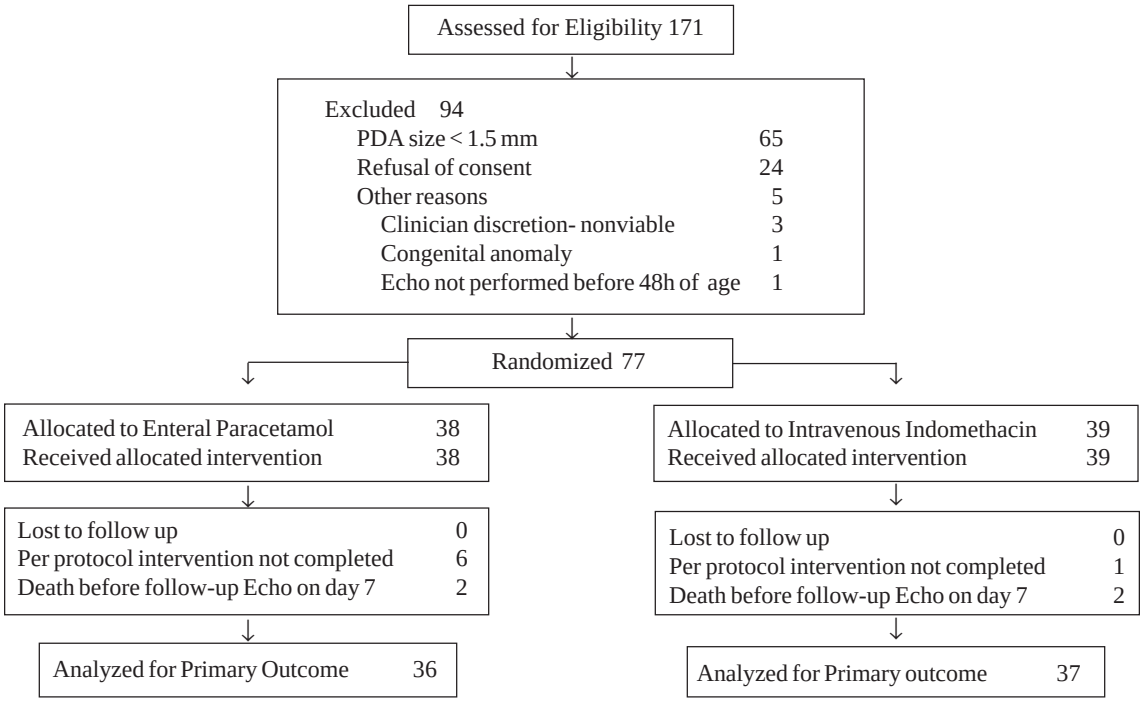

FIG.1 *Participant flow in the study.*

TABLE I BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS

Characteristics	*Paracetamol Group (n=38)*	*Indomethacin Group (n= 39)*
Mother		
*Age, y	31.6 (5.3)	31.2 (4.9)
Preeclampsia/Eclampsia	10 (26.3)	12 (30.7)
Tocolysis <7d before delivery	2 (5.2)	3 (7.6)
Antenatal glucocorticoids	33 (86.8)	31 (79.4)
Caesarean delivery	23 (60.5)	28 (71.7)
Infant		
*Gestational age, wk	28.5 (2.7)	28.9 (2.6)
Gestational age ≤27 weeks	14 (36.8)	11 (28.2)
*Birth weight, g	989 (299)	1027 (262)
AGA	26 (68.5)	33 (84.6)
SGA	12 (31.5)	6 (15.4)
Male gender	14 (36.8)	13 (33.3)
Singleton	22 (57.9)	20 (51.3)
#APGAR, 1 min	6 (5-6)	6 (5-7)
#APGAR, 5 min	7.5 (7-8)	8 (7-8)
Surfactant	33 (86.8)	33 (84.6)
*1st Echo age in h	14.7 (8.4)	15.9 (11.8)
*PDA size in mm	2.02 (0.42)	2.11 (0.53)
Mechanical ventilation	19 (50)	21 (54)
CPAP	12 (32)	14 (36)
Oxygen by hood	7 (18)	4 (10)

*Values in *mean (SD); #Median (IQR); Rest all in No.(%).*

spontaneous PDA closure during the first 7 days, as the follow up echocardiographic study was performed only after completion of full 7 days after initiation of treatment. Additional limitation of our study is that we have only evaluated short-term outcomes, in a selected group of premature infants, one-fourth of whom were SGA. This would significantly affect generalizability of this study. When we planned the study, we assumed PDA closure rate of 50% in indomethacin group and 80% in paracetamol group. On completion of our study we found that PDA closure rate was 95% in indomethacin group and 100% in paracetamol group. Our study, therefore, was underpowered to demonstrate this minor difference between two intervention drugs.

Case series describing use of paracetamol for PDA have been published [12-14,17,23]. More recently, two randomized controlled trials comparing oral paracetamol with ibuprofen have been published [24,25]. Both of these trials documented that paracetamol in dose of 15 mg/kg/dose every 6 hourly for 3 days had comparable efficacy (73-81%) to ibuprofen (78-79%), in obtaining PDA closure. In our study, paracetamol was used for 7 days, and closure rate was almost 100%.

We conclude that oral paracetamol is safe but not superior to intravenous indomethacin in closure of PDA. In developing countries, where intravenous indomethacin use is constrained by scarcity, high cost and difficulty in monitoring the side effects, oral paracetamol may be considered as an alternative. We recommend studies with

TABLE II COMPARISON OF PDA CLOSURE RATE AND ADVERSE EVENTS WITH PARACETAMOL AND INDOMETHACIN

Outcomes	*Paracetamol Group No. /Total No. (%)*	*Indomethacin Group No. /Total No. (%)*	*RR (95% CI)*	*P*
PDA Closure	36/36 (100)	35/37 (94.6)	1.05 (0.96-1.16)	0.49
Secondary Outcomes				
Renal impairment	1/38 (2.6)	0/39 (0)		0.49
GI Bleed	10/38 (26.3)	7/39 (17.9)	1.47 (0.62-3.45)	0.38
NEC (all grades)	2/38 (5.3)	4/39 (10.3)	0.51 (0.10-2.64)	0.42
Early onset sepsis - screen positive	21/38 (55.3)	17/39 (43.6)	1.26 (0.80-2.00)	0.31
Early onset sepsis -blood culture positive	1/38 (2.6)	0/39 (0)		0.49
Pulmonary hemorrhage	3/38 (7.9)	0/39 (0)		0.99
ROP (all grades)	24/29 (82.8)	26/30 (86.7)	0.95 (0.77-1.19)	0.68
Severe ROP needing treatment	8/29 (27.6)	7/30 (23.3)	1.18 (0.49-2.84)	0.71
IVH all grades and PVL	8/37 (21.6)	7/38 (15.6)	1.17 (0.47-2.09)	0.73
O_2 requirement at 28 d	13/27 (48.1)	17/31 (54.8)	0.88 (0.53-1.48)	0.61
O_2 requirement at ≥36 wk	5/27 (18.5)	6/30 (20.0)	0.93 (0.32-2.69)	0.89
Death	8/38 (21.1)	8/39 (20.5)	1.02 (0.43-2.45)	0.95

PDA: Patent ductus arteriosus; NEC: necrotizing enterocollitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage; PVL: periventricular leucomalacia; GI: gastrointestinal.

WHAT IS ALREADY KNOWN?

- Oral paracetamol is comparable to ibuprofen in terms of PDA closure rate.

WHAT THIS STUDY ADDS?

- Enteral paracetamol for preterm infants with hemodynamically significant PDA is safe but not superior to intravenous indomethacin.

an appropriate sample size, simultaneously looking at long-term neurodevelopmental outcome effects of paracetamol in treatment of PDA.

Contributors: SKD: review of literature, data collection and wrote the first draft; NSK: designing of study, drafting the article, analysis and interpretation of data. He will and will act as guarantor; BSA, SRS, PP, JA: designing of study, collection of data and drafting the manuscript. The final manuscript was approved by all the authors.

Funding : None ; *Competing interests* : None stated.

REFERENCES

1. Nemerofsky SL, Parravicini E, Bateman D, Kleinman C, Polin RA, Lorenz JM. The Ductus arteriosus rarely requires treatment in infants >1000 grams. Am J Perinatol. 2008; 25:661-6.
2. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics. 2006;117:1113-21.
3. Herrman K, Bose C, Lewis K, Laughon M. Spontaneous closure of the patent ductus arteriosus in very low birth weight infants following discharge from the neonatal unit. Arch Dis Child Fetal Neonatal Ed. 2009; 94:F48-50.
4. Jhaveri N, Moon-Grady A, Clyman RI. Early surgical ligation versus a conservative approach for management of patent ductus arteriosus that fails to close after indomethacin treatment. J Pediatr. 2010;157:381-7.
5. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, *et al.* A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med. 2000;343:674-81.
6. Sankaran K, Puckett B, Lee DS, Seshia M, Boulton J, Qiu Z, *et al*. Variations in incidence of necrotizing enterocolitis in Canadian neonatal intensive care units. J Pediatr Gastroenterol Nutr. 2004;39:366-72.
7. Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study. J Pediatr. 1983;102:895-906.
8. Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L, *et al.* Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. Eur J Pediatr. 2002;161:202-7.
9. Vieux R, Desandes R, Boubred F, Semama D, Guillemin F, Buchweiller MC, *et al.* Ibuprofen in very preterm infants impairs renal function for the first month of life. Pediatr Nephrol. 2010;25:267-74.
10. Ahlfors CE. Effect of ibuprofen on bilirubin-albumin binding. J Pediatr. 2004;144:386-8.
11. Rheinlaender C, Helfenstein D, Walch E, Berns M, Obladen M, Koehne P. Total serum bilirubin levels during cyclooxygenase inhibitor treatment for patent ductus arteriosus in preterm infants. Acta Paediatr. 2009;98:36-42.
12. 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.
13. Yurttutan S, Oncel MY, Arayicý 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.
14. 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.
15. Evans N. Diagnosis of patent ductus arteriosus in the preterm newborn. Arch Dis Child. 1993;68:58-61.
16. Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr. 1995; 127:774-9.
17. Young TE, Mangum B. Neofax ® 2010, 23rd edition, Montavale NJ, Thomson Reuters; 2010.p.180-1.
18. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al.* Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187:1-7.
19. International Committee for the Classification of Retinopathy of Prematurity. The International classification of retinopathy of prematurity revisited. Arch Ophthalmol. 2005;123:991-9.
20. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92:529-34.
21. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: Prediction from oxygen requirement in the neonatal period. Pediatrics. 1988;82:527-32.
22. Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized

trials. Semin Neonatol. 2001;6:63-73.
23. Jasani B, Kabra N, Nanavati RN. Oral paracetamol in treatment of closure of patent ductus arteriosus in preterm neonates. J Postgrad Med. 2013;59:312-4.
24. 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.
25. 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.