ORIGINAL ARTICLE

Use of Paracetamol for Treatment of Patent Ductus Arteriosus in Preterm Neonates: A 5-Year Experience From a Tertiary Hospital in India

Deepika Kainth, Satya Prakash, Vivek Kumar, R Dhinakaran, Ankit Verma, Ramesh Agarwal

Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Prof. Ramesh Agarwal, Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.
ra.aiims@gmail.com

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ABSTRACT

Objective: We evaluated ductal closure rates in preterm neonates with hemodynamically significant patent ductus arteriosus (hsPDA) who received paracetamol (PCM) as first-line therapy.

Methods: In this retrospective chart review, we included inborn preterm (< 37 weeks) neonates (January 2017-December 2021) with hsPDA (ductal diameter > 1.5 mm and left atrium-to-aortic root ratio (La/Ao > 1.4) who were treated with oral or intravenous PCM**.** Primary outcome was hsPDA closure (defined as small or no PDA) following 3-day treatment. Secondary outcomes were need for retreatment and surgical ligation, pulmonary hypertension (PH), and in-hospital morbidities.

Results: Out of 2784 preterm birth, 117 neonates were diagnosed with hsPDA. Out of 96 neonates who received PCM in the first course, 20 died before the completing the first course. The median (IQR) gestation and birth weight of neonates who received PCM were 28 (26, 29) weeks and 841 (714, 1039) g, respectively. Out of 76 neonates who completed treatment with first course of PCM (57 intravenous, 19 oral), 43 (56.6%) achieved successful closure and five (6.6%) developed PH. Out of 14 neonates who received a second course of PCM, 10 achieved closure of hsPDA while one neonate expired.

Conclusion: Paracetamol is associated with successful closure of hsPDA in 56.6% of preterm neonates after one course and 70% of premies after two courses

***Keywords*:** Cardiac, Congenital heart disease, Acetaminophen, Newborn, Prematurity

INTRODUCTION

Patent ductus arteriosus (PDA) is the most common cardiac condition in preterm neonates. Spontaneous closure of PDA varies inversely with gestational age. The incidence of PDA persisting beyond 4 days is 10-20% in 30-37 weeks' gestation and as high as 80% in those born <28 weeks' gestation [1,2]. In case of a hemodynamically significant PDA (hsPDA), a continuous left-to-right shunting of blood results in major complications either due to pulmonary overcirculation [edema, hemorrhage, and/or bronchopulmonary dysplasia (BPD)] or systemic hypoperfusion, compromising the cerebral, renal, and gastrointestinal blood flow. Despite abundance of literature on therapeutic approaches for PDA management, the need, timing, and choice of treatment remain contentious. Although 30-50% PDA close spontaneously [3], an early therapeutic closure of PDA seems prudent to prevent life-threatening complications.

In comparison to non-steroidal anti-inflammatory drugs, paracetamol (PCM) has emerged as a promising agent due to its better adverse effect profile and ready availability as intravenous (IV) or per oral (PO) preparations. In a recent network meta-analysis, oral PCM was ranked as the second best agent, next to high dose ibuprofen, in terms of successful PDA closure [4]. The overall closure rate ranged between 70-100%. An updated systematic review adjudged PCM to be safe, but with efficacy not superior to indomethacin [5]. Due to significant heterogeneity and 'low to unclear' risk of bias in these meta-analyses, the therapeutic

efficacy of PCM, particularly in extremely preterm (<28 weeks) and extremely low birth weight (ELBW) neonates, is still a matter of debate. Although PCM seems to be safe, anecdotal evidence raises concerns about its adverse hemodynamic effects on pulmonary vasculature with a potential to cause pulmonary hypertension [7].

In this study, we present our 5-year experience of using PCM as first line treatment for *hs*PDA in terms of its efficacy and adverse effects, along with its association with short-term mortality and morbidity outcomes.

METHODS

We conducted a single-center retrospective chart review of all inborn preterm neonates (<37 weeks) with hsPDA born between January 2017 to December 2021 and who received PCM as the first-line therapy. The primary objective of the study was to evaluate the efficacy of PCM for hsPDA closure, defined as no or small PDA after completion of first course and resolution of clinical signs. Secondary objectives were to assess the need for repeat pharmacotherapy, surgical ligation, and development of new-onset pulmonary hypertension after PCM treatment. In-hospital mortality and other morbidities such as pulmonary hemorrhage, retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), intraventricular hemorrhage (IVH), and BPD were also evaluated. hsPDA was defined as a ductal diameter >1.5 mm and a left atrium-to-aortic root ratio (La/Ao) >1.4 on functional echocardiography performed by a trained neonatology fellow.

The individual case records were screened by atleast two independent observers for inclusion in the study. **Web Table 1** depicts screening protocol for hsPDA in neonates at our center. If there were features suggesting pulmonary hypertension before the diagnosis, pharmacotherapy was not instituted. PCM was administered in a dose of 15 mg/kg/dose (PO or IV) q 6 hours for 12 doses over three days (first course) as early targeted or symptomatic treatment. A confirmatory echocardiography is performed after completion of the first course. A repeat treatment course of PCM or oral ibuprofen (low dose regimen: 10 mg/kg followed by 5 mg/kg q 12-24 hours for 3 doses; or high dose regimen: 20 mg/kg followed by 10 mg/kg q 12-24 hours for 3 doses) was instituted for another 72 hours if PDA is not closed. Neonates with persistence of hsPDA, along with clinical signs despite two pharmacological courses, were considered for PDA ligation.

Assuming 6 potential associated factors (gestation, birth weight, age at treatment, immediate cord clamping, ductal diameter, and route) and approximately 70% success rate [7], a total of 85 neonates receiving PCM were needed. We included all neonates during the study period. $P < 0.05$ was considered statistically significant.

Statistical analysis: The baseline characteristics and the details of treatment were analyzed using Stata14.2 (StataCorp4905 Lakeway, College Station, TX). Categorical variables were expressed as frequencies and percentages, and analyzed using Fisher exact test or Chi square test. Continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range, IQR) and analyzed using Student's t-test or Wilcoxon rank sum test, as applicable. Univariate and multivariable logistic regression (LR) were performed to identify factors associated with successful closure of hsPDA with PCM, based on literature review, biological plausibility, and clinical expertise.

RESULTS

The study flow is depicted in **Fig. 1**. Of the 2784 preterm live births during the study period, 117 (4.2%) had hsPDA. Sixteen (14%) neonates had pulmonary hypertension (PH) pattern at diagnosis, precluding medical treatment. 101 (86.3%) neonates received treatment either with only pharmacotherapy (n = 92; 88 PCM and 4 ibuprofen), or pharmacotherapy followed by ligation (n = 8) or only surgical ligation (n = 1).

A total of 96 neonates received PCM as the first-choice treatment; 75 (78%) were initiated on PCM by IV route (**Table I**). The median (IQR) age at detection of hsPDA and initiation of treatment was 4 (3, 6.5) days. Out of these, 20 died before completion of first course and 76 completed the first course of pharmacotherapy. The median (IQR) gestation and birth weight were 28 (26, 29) weeks and 841 (714, 1039) g, respectively.

Successful PDA closure using PCM was achieved in 43 of 76 neonates (56.6%; 95% CI 45%, 68%) (**Table II**). Out of 76 neonates, 19 (25%) received oral PCM therapy. Twenty-eight neonates (36.8%) required repeat pharmacotherapy; PCM in 14, low dose ibuprofen in 13, and high dose ibuprofen in one neonate. Additionally, 10 neonates (13.1%) had PDA closure after a repeat course with PCM. Thus, closure rate after one or two courses of PCM was 69.7% (53 out of 76). Five (6.6%) neonates developed PH following treatment. Surgical ligation was performed in eight (10.5%) neonates at a median (IQR) age of 31 (28, 57) days. There were 43 (44.8%) deaths.

Gestation, birth weight, postnatal age at treatment, and route of drug were not significantly associated with closure on univariate analysis, when compared to non-closure. However, on multivariable LR, each 1 mm increase in ductal diameter at diagnosis decreased the odds of closure (OR 0.45, 95% CI 0.21, 0.93) and oral route significantly increased the odds of PDA closure (OR 4.9, 95% CI 1.12, 22.02) after the first course (**Web Table II**).

DISCUSSION

The overall closure rate with PCM in our study was 56.6% after the first and an additional 13.1% after a repeat course. We observed a relatively lower closure rate as compared to other studies in literature. Several factors could have resulted in such a finding. First, the inclusion of predominantly smaller (28 weeks, 841 g) neonates in our study, in contrast to the studies included in the meta-analyses, could be a possible explanation [4,5]. Over half of all neonates were extremely preterm in our study, compared to predominantly moderate preterm neonates in the meta-analyses. In another study by Dash et al the closure rate was reported to be 100% (compared to indomethacin) in neonates born at 28 weeks and weighing 989 g [8]. Although similar to our population, the neonates were given oral PCM for 7 days and in the first 48 hours only (median age 14.7 hours), when most PDAs would likely have closed spontaneously.

We included all neonates who received PCM irrespective of their sickness. Only those sick neonates with pulmonary hypertension before the diagnosis of hsPDA were not treated with PCM, and did not constitute our study cohort. Almost 50% were ventilated on day 1 and around one-third were growth-restricted. On the contrary, in a randomized trial design framework, sick neonates with comorbid conditions like sepsis, asphyxia, bleeding and renal injury get excluded due to the control limb receiving either

indomethacin or ibuprofen. The findings from our study could possibly reflect the true efficacy of PCM in sick and small neonates.

Dissimilar findings could also have resulted from the use of a different definition for hemodynamic significance of PDA and its closure [5]. The definition of closure of PDA is inconsistently reported, with some studies using only echocardiographic parameters, whilst others considering only resolution of clinical signs [9,10]. Our definition may be considered liberal thereby limiting generalizability. Differences in institutional protocols pertaining to titration of ventilator pressures and degree of fluid restriction could significantly affect closure rates. These parameters are, however, not reported appropriately in the literature.

There is a dearth of literature on identification of significant factors associated with PDA closure. Identification of such factors can assist in screening of those neonates who are at high-risk of treatment failure with PCM. Although underpowered to truly identify 'predictors', our study found that a smaller duct size and oral route of PCM treatment were most significantly associated with successful closure of PDA. These results should be interpreted with caution as they may only reflect a relatively lesser sickness severity in a preterm neonate, thereby resulting in successful PDA closure.

A noteworthy finding observed in our study was the development of PH following PCM treatment in five neonates. Although the effects of PCM on pulmonary vasculature have not been well-described, there are anecdotal reports of a pulmonary vasoconstrictive effect. A plausible underlying mechanism is the dysregulation of arachidonic acid metabolism, thereby altering vasomotor tone in pulmonary vessels and leading to elevated pulmonary pressures [7]. This effect may be more pronounced in neonates born below 29 weeks, as seen in our study. Perhaps, a decrease in left-to-right shunt could also explain an improvement in clinical signs, rather than a decrease in size of PDA following PCM treatment (defined as closure in our study).

Our study has several limitations. Due to its retrospective design, a comparison of PCM with any other intervention or conservative management could not be assessed. The association of PH and PCM use cannot be reliably stated from our study and will need further exploration. Due to high mortality in our study population, the burden of comorbidities may have been underestimated. Further, since deaths were excluded from analysis, the efficacy of PCM in this group is possibly inappropriately inflated. There is a need of a well-designed, preferably multicentric randomized trial, that evaluates the efficacy of paracetamol in extremely preterm and sick neonates, when compared to agents like ibuprofen, indomethacin and indeed, conservative management. Further research should also focus on detailed evaluation of ventilation and fluid strategies in closure of PDA, in addition to medical therapy. Paracetamol is associated with successful closure of hsPDA in 56.6% cases after one course and 70% cases after two courses.

Ethics clearance: Institute Ethics Committee No. IECPG-04 dated Jan 31, 2023.

Contributors: DK, VK: Conceptualised the study; DR, SP: Data collection; DK, SP: Drafted the manuscript; RA: Supervised the conduct of the study, data analysis and finalised the manuscript. AV, RA: Provided critical inputs for analysis and data interpretation. All authors approved the final version.

Funding: None. *Competing interest:* None stated.

WHAT THIS STUDY ADDS?

- A single course of paracetamol results in closure of hemodynamically significant patent ductus arteriosus in 56.6% preterm neonates.
- Association between pulmonary hypertension and paracetamol use needs further exploration.

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Table I Baseline Characteristics of the Neonates with Hemodynamically Significant Patent Ductus Arteriosus who Received Paracetamol Treatment (*n* = 96)

Characteristic	*n = 96*
Gestational age (completed wk)[a]	28 (26, 29)
Gestational age 24 to 25 wk [b]	23 (23.9)
Gestational age 26 to 27 wk [b]	19 (19.8)
Gestational age 28 to 31 wk [b]	46 (47.9)
Gestational age 32 to 36 wk [b]	8 (8.3)
Birth weight (g) [a]	841 (714, 1039)
Birth wight < 750 g [b]	33 (34.4)
Birth wight 750 to 999 g [b]	36 (37.5)
Birth wight 1000 to 1499 g [b]	22 (23.9)
Birth wight ≥ 1500 g [b]	5 (5.2)
Small for gestational age [b]	31 (32.3)
Caesarean delivery [b]	62 (64.5)
Male gender [b]	48 (50.0)
Singleton births [b]	64 (66.7)
Apgar at 5 min [a]	7 (6, 8)
Complete course of antenatal steroids [b]	47 (48.9)
Delayed cord clamping [b]	22 (22.9)
Need for surfactant [b]	60 (62.5)
Invasive ventilation on day 1[b]	46 (47.9)
Culture positive sepsis (onset before *hs*PDA diagnosis) [b]	13 (13.5)

Values expressed as [a]median (IQR) or [b]n (%)
hsPDA Hemodynamically significant persistent ductus arteriosus

Table II Outcomes of Neonates who Received Paracetamol for Hemodynamically Significant Patent Ductus Arteriosus

Primary outcome	
Successful PDA closure after first course [c,d]	43/76 (56.6)
Route	
Successful closure with IV PCM [a,c,d]	32/57 (56.1)
Successful closure with oral PCM [a,c,d]	11/19 (57.9)
Secondary outcomes	
Need for repeat pharmacotherapy [c,d]	28/76 (36.8)
Need for PDA ligation [c,d]	8/76 (10.5)
Overall deaths [c]	43/96 (44.7)
Cause of death after completion of first course[c]	
PDA	1/23 (4.3)
Sepsis with multiorgan dysfunction	13/23 (56.5)
Bronchopulmonary dysplasia	4/23 (17.4)
Necrotizing enterocolitis	3/23 (13.0)
Pulmonary hypertension	2/23 (8.7)
Postnatal age at death (days) [b]	8 (4, 23)
Duration of hospital stay among survivors (days) [b]	67 (50, 85)
Pulmonary hemorrhage [c]	4/96 (4.2)
Postnatal age at pulmonary hemorrhage (days) [b]	3 (2, 4)
Pulmonary hypertension after treatment [c]	5/96 (5.2)
Bronchopulmonary dysplasia (any grade) [c]	31/96 (32.3)
Severe ROP requiring laser [c]	10/96 (10.4)
Necrotizing enterocolitis (any stage) [c]	5/96 (5.2)
Intraventricular hemorrhage (any grade) [c]	28/96 (29.2)
Periventricular leukomalacia (any grade) [c]	24/96 (25.0)
Persistent PDA at discharge [c]	6/96 (6.2)

[a] The route at the initiation of treatment was considered for analysis.
Values expressed as [b]median (IQR) or [c]n/N (%)
[d]Proportions expressed using denominator as those who survived till discharge
IV Intravenous, PDA Patent ductus arteriosus, ROP Retinopathy of prematurity, IQR Interquartile range

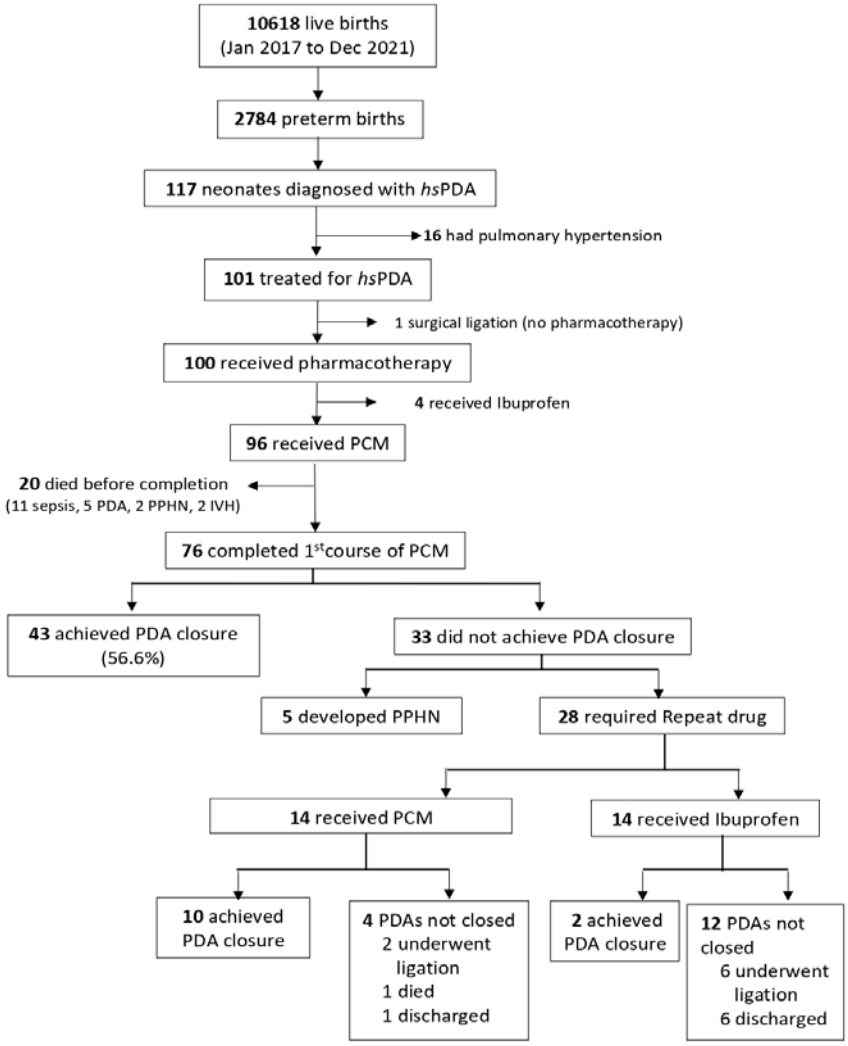

Fig. 1 Flow of enrolled neonates in the study

IVH Intraventricular hemorrhage, PCM Paracetamol, PPHN Persistent pulmonary hypertension

Web Table I Standardized Protocol for Screening in Preterm Neonates for Hemodynamically Significant Persistent Ductus Arteriosus

Gestation	*Timing of screening*	*Treatment*
≤28 wk	36 ± 6 h, 72 ± 6 h, and d 7	Early targeted (Asymptomatic)
29-30 wk	36 ± 6 h and 72 ± 6 h	Early targeted (Asymptomatic)
<37 wk	At the onset of symptoms	Symptomatic

Web Table II Predictors of Successful Closure after First Course of Paracetamol Using Univariate and Multiple Logistic Regression

Characteristics	*PDA closure (n = 43)*	*Non closure (n = 33)*	*Odds ratio or mean difference [d] (95% CI)*	*P Value**	*Adjusted odds ratio (95% CI) [e]*	*P Value*
Gestation (weeks) [a]	28 (2.8)	28.6 (2.3)	0.58 (-0.61, 1.76)	0.33	1.13 (0.66, 1.93)	0.65
Birth weight (g) [a c]	921 (408)	949 (240)	27.8 (-131.6, 187.3)	0.72		
Immediate cord clamping [b]	35 (81.4)	21 (63.6)	2.5 (0.89, 6.97)	0.08	1.46 (0.47, 4.50)	0.50
Age at treatment (days) [a]	5.3 (3.8)	8 (8.3)	2.7 (-0.09, 5.57)	0.34	0.89 (0.79, 1.01)	0.07
Ductal diameter (mm) [a]	2.2 (0.8)	2.45 (0.7)	0.29 (-0.06, 0.64)	0.06	0.45 (0.21, 0.93)	0.03
Oral route [b]	11 (25.6)	8 (24.2)	1.07 (0.38, 2.99)	0.89	4.9 (1.12, 22.02)	0.03

** For continuous variables, P value calculated using t-test and Wilcoxon rank sum test for normally and non-normally distributed variables, respectively. Chi-square test used for categorical variables*
Values expressed as [a] mean (SD) or [b] n (%) for univariate analysis
[c] Significantly correlated with gestation, not included in multiple logistic regression
[d] Univariate analysis depicting odds ratio calculated for categorical variables and mean difference for continuous variables
[e] Odds ratio depicted for selected variables using multiple logistic regression