Original Article

Comparison of efficacy of paracetamol and ibuprofen for treatment of hemodynamically significant patent ductus arteriosus in preterm infants

R Swathi[1], Maulik Shah[2], Agnes Puthussery[1]

From [1]Junior Resident, [2]Associate Professor, Department of Pediatrics, Shri M P Shah Government Medical College, Jamnagar, Gujarat, India

ABSTRACT

Background: Indomethacin and ibuprofen (IBU) have been approved for the pharmacological closure of hemodynamically significant patent ductus arteriosus (hsPDA) in preterm infants. Recent works have demonstrated that paracetamol (PCM) can also be used but more research is required regarding efficacy and safety. **Objectives:** The objective is to compare the efficacy and safety of PCM and IBU for the treatment of hsPDA in preterm infants. **Methodology:** An observational study was designed with ethical clearance and parental consent. Patients were evaluated for hsPDA by clinical and 2 D echo findings. After inclusion and exclusion criteria, consecutive 100 patients were assigned between PCM and IBU and were given a 3-day course. After echocardiographic and clinical evaluation, if required, a second course with same drug was given. The outcome measures were the rate of ductal closure, the safety of drugs, and adverse events. **Results:** The PCM group had a closure rate of 76.25% and the IBU group had 75%. IBU had a significantly higher rate of closure in the first course (45% vs. 16.25%). The mean closure time observed was 4.54 days and 4 days for PCM and IBU, respectively. PCM gave a higher closure rate in the low-birth-weight group and where platelet counts were below normal. Regarding the safety aspect also no significant difference between groups was observed. **Conclusion:** PCM can be advised as a first-line treatment for hsPDA cases in preterm infants and is a better choice in cases of comorbidities and patients with low platelet count.

Key words: Hemodynamically significant patent ductus arteriosus, Ibuprofen, Paracetamol, Platelet count, Preterm infants

Incidence of patent ductus arteriosus (PDA) is very high in preterm infants ranging from 20% to 60% [1]. The increase in incidence is attributed to lack of normal closure mechanism because of immaturity. Moreover, gestational age and birthweight are closely linked to PDA closure. PDA is present in 80% of babies weighing <1200 g at birth. In babies with <2000 g, the rate becomes 40% [2]. Another report shows that symptomatic PDA is present in 48% of infants with birthweight <1000 g [3]. Moreover, 80% of infants having respiratory distress syndrome (RDS) have PDA [4].

Significant morbidity and mortality are attributable to hemodynamically significant PDA (hsPDA). It includes intra ventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD).

Ductus arteriosus (DA) comprises smooth muscle fibers which are arranged in longitudinal and spiral layers and surrounded by concentric layers of elastic tissue. After birth the medial smooth muscle fiber contract due to exposure to oxygen-rich air. This leads to constriction of lumen and shortening of DA length which begins at the pulmonary end until there is functional closure between 24 and 48 h [5]. The second stage of closure starts with proliferation of medial and intimal connective tissue and smooth muscle atrophy. This in turn leads to a lamentation and non-contractile structure over the next 3 weeks.

The exact mechanism of DA closure is still not clear, but the involvement of prostaglandins synthesized by cyclooxygenase enzymes cox1 (ptgs1) and cox2 (ptgs2) are critical mediators of DA patency and closure. The cox product prostacyclin PGI2 and PGE2 have been well established as vasodilators of DA. It is observed that with advancing gestation and afterbirth the COX-2 expression is increased suggesting that COX-2 expression in the DA of premature offspring prevented its post-natal constriction [6]. Prostaglandins exert their efforts through a family of G Protein receptors. The E P family of receptors is of importance. EP4 subtype appears to play an essential role [7]. Unlike closely related NSAIDs paracetamol interferes with peroxidase activity of COX isoenzymes, predominantly COX2, particularly when the cellular environment is low in arachidonic acid and peroxides. This explains PCMs apparent central effect

Access this article online

Received- 22 March 2023
Initial Review- 25 March 2023
Accepted- 01 April 2023

DOI: 10.32677/ijch.v10i5.3942

Quick Response code

Correspondence to: R Swathi, Department of Pediatrics, Shri M P Shah Government Medical College, Jamnagar, Gujarat, India. E-mail: 9442700321@gmail.com

as COX2 is constitutively expressed in neural tissue and why it appears ineffective in inflamed tissue [8].

For the management of PDA in preterm neonates, a lot of research work and published papers have appeared since the first use of indomethacin in 1976. Currently, FDA has approved indomethacin and ibuprofen (IBU) for the pharmacological closure of PDA. Because of its adverse effects, indomethacin use has been reduced over the years and has largely been replaced by IBU Even then it continues to be a topic of discussion and controversy. Recently, PCM is being tried for PDA, but till now FDA has not approved its use for it. Further studies are required comparing PCM with IBU for treatment of hsPDA in terms of percentage of closure, drug safety, and long-term outcome. It is in this context that the present study is envisaged. The objectives are to compare the efficacy and safety of PCM and IBU for the treatment of hsPDA in preterm infants. The study also focuses on the various prenatal and postnatal factors that may affect pharmacological closure and also various comorbidities associated with PDA.

METHODOLOGY

The study was designed as an observational study. Ethical clearance and parental consent were obtained. Premature infants with PDA admitted to NICU from July 2021 to June 2022 were studied. Patients were evaluated for hsPDA by clinical and echocardiographic findings. If a decision was taken for pharmacological closure, the participants were screened for inclusion and exclusion criteria, assigned between oral or intravenous PCM and oral IBU. Consecutive 100 cases assigned between two groups were studied. Operational definitions of hsPDA were made based on the clinical history and 2 D echocardiographic findings. Outcome measures were also defined.

Infants receive oral/iv PCM at the dose of 15 mg/kg every 6 h for 3 days or oral IBU at the initial dose of 10 mg/kg, followed by 5 mg/kg after 24 and 48 h. Option of whether to treat with PCM or IBU depended on individual patient characteristics such as serum bilirubin level, creatinine, platelets, and presenting comorbidities. Whether a subject received a second course of treatment depends on echocardiography evaluation after the first course. If only minor ductal shunting was present after two courses without the need of respiratory support, no further treatment was given. In treatment failure cases, the patients were evaluated and if it was fit for rescue treatment, the alternate drug was tried as a third course. The patient was evaluated again and if clinical management was not possible it was referred for surgical or catheter ligation. Drug safety factors were assessed daily during the treatment, including 24-h urine output, tendency to bleed, IVH grade, and serum creatinine and bilirubin levels. Furthermore, eye examination conducted 4 weeks after birth. The occurrence of any of the following conditions prompted the stopping of treatment: renal failure, NEC, IVH grade 3–4, and gastrointestinal bleeding. Main outcome measures were the rates of ductal closure after treatment and whether patient improved hemodynamically, i.e., weaning from ventilator support, oxygen requirement decreased investigations vise CBC, RFT, LFT came to normal range. Every infant was monitored by echocardiography daily during the treatment. Secondary outcomes like the safety of both drugs, including early adverse events (e.g., oliguria, emerging IVH, tendency to bleed, NEC, hyperbilirubinemia, death) and late adverse events, for example BPD, periventricular leukomalacia (PVL), NEC, ROP, sepsis, death will be studied in both groups. The early adverse events were defined as those occurring during and up to 1 week after administration of the treatment.

Inclusion Criteria Included

Gestational age ≤34 weeks, postnatal age ≤14 days, and echocardiographic diagnosis of hsPDA.

Exclusion Criteria Included

Congenital heart disease which required PDA to maintain blood flow, Infants older than 34 weeks GA, Major congenital malformations.

All relevant data were collected, tabulated and statistical analysis was performed with MS Excel. Categorical variables were compared using Chi-square test, continuous variables with t test and proportions with z test. Logistic regression analysis was performed with software online. A $p \leq 0.05$ was considered statistically significant.

RESULTS

Patients qualified as per inclusion and exclusion criteria were clinically evaluated for PCM and IBU treatment. Patients with oliguria, hyperbilirubinemia, platelet count below 95000, GI bleeding or sepsis were given PCM treatment. Out of 100 patients 80 were assigned to PCM and 20 to IBU.

Overall closure rate achieved in the study was 76%. PCM group had a closure rate of 76.25% and IBU group had a closure rate of 75%. The results are given in Table 1. There was no significant difference between groups ($p=1.0931$). Overall outcome of treatment with respect to PDA closure after the first and second course of treatment are given in Table 2. Results showed that IBU had a significantly higher rate of closure in the first course (45% vs. 16.25%).

The results show that PCM requires a longer period of treatment to achieve a better closure rate.

Treatment outcomes based on gestational age and birth weight were analyzed. Comparisons between PCM and IBU in different GA groups and BW were also studied. It was seen that closure rate increased with gestational age as expected. However, similar trend was not observed concerning body weight, where maximum closure was observed in birth weight group more than 2.5 kg, These parameters were again compared between PCM and IBU groups, results given in Fig. 1.

Table 1: Treatment outcome

Medication	Closed	Closed (%)	Referred	Referred (%)	Death	Death (%)	Total
Paracetamol	61	76.25	1	1.25	18	22.5	80
Ibuprofen	15	75	1	6.67	4	26.67	20
Total	76	76	2	2	22	22	100

Table 2: Closure rate in the first and second course

Medication	Closed in first course (%)	Closed in second course (%)
Paracetamol	16.25	71.6
Ibuprofen	45	54.5

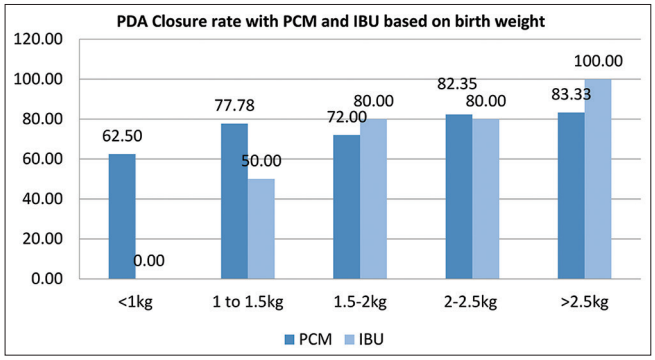

Figure 1: PDA Closure rate with PCM and IBU based on birth weight

Effects of various parameters on PDA closure were statistically analyzed. The parameters were: Use of antenatal steroid (p=0.78), Mechanical ventilation support (p=0.87), age of start of medication <7 days versus >7 days (p=0.61), RDS (p=0.87), gestational age <30 weeks versus >30 (p=0.47), PDA size ≤3 mm versus >3 mm (p=0.97), La/Ao ratio ≤3 versus >3 (p=0.98), and platelet count. All parameters except platelet count showed any statistical significance between groups. Regarding platelet count, between pre-treatment values below 150,000 and above 150,000 were compared for outcome. There was found to be significant difference between the groups (p=0.0004). Platelet count <150,000 (pre-treatment) showed a better closure rate. On further analysis, with PCM, on logistic regression, it was seen that a positive correlation existed on platelet count up to 150,000 (p=0.06). Beyond 150,000 no correlation was observed (p=0.4).

Out of 80 patients in the PCM group, 14 had a history of early-onset sepsis (EOS), 11 had neonatal jaundice (NJ) and 22 had creatinine values above 1 mg/dL, closure percentage achieved in the study were 85.7%, 81.82%, and 68.18%, respectively. Corresponding percentage of closure in the IBU group were 71.43%, 66%, and 80%, respectively.

The pretreatment and posttreatment values of platelet were compared between PCM and IBU and no statistically significant difference were observed.

Mean time required for closure observed in the study was 4.43 days. Slight difference in this period was observed between groups. PCM had 4.54 days and IBU had 4 days.

The mean time of the start of medication in the study was 3.62 days of age. The mean diameter of PDA was 2.68 mm. The mean LA/AO ratio observed in this study was 2.19.

Regarding safety parameters of the two drugs, pre-treatment and post-treatment values of platelets, creatinine, urea, and bilirubin were collected and compared statistically. None of the parameters showed significant differences in pre-treatment and post-treatment values. In the PCM group increase in bilirubin values were observed in pre- and post-treatment mean values, 7.812 versus 10.986, but it was not statistically significant (p=0.0885). IBU group did not show this difference. Results are given in Table 3.

The result showed that both PCM and IBU are safe for the treatment of hsPDA and between these two there was no difference in safety outcomes. Patients were examined for development of NEC, EOS, LOS, hypocalcemia, hyponatremia, BPD, IVH, gastrointestinal bleeding, etc. It was observed that the infants with hsPDA often have more than one of the comorbidities. No case of IVH, BPD, and gastrointestinal bleeding were observed in both groups.

Operational Definitions hsPDA: Anti-natal and perinatal history, Clinical findings, bounding pulse/hyper active precordium and with continued need for respiratory support, hypotension needing vasopressor support. Echocardiographic findings PDA size >1.5 mm, LA/ Ao ratio > 1.5,Absent or retrograde No PDA or small PDA : <1.5 mm diameter, along with clinical resolution [9].

DISCUSSION

It is well established that pharmacological treatment of hsPDA in pre-term infants is beneficial when compared with no intervention [10,11]. The effectiveness of PCM in PDA treatment and its comparison with IBU were reviewed by Yingqi *et al*., and Ohlsson *et al*. 2020 [12,13]. They showed that no significant differences were noted between PCM and IBU. It was also reported shorter mean days needed for closure, lower risk of gastrointestinal bleeding, and hyperbilirubinemia in PCM group. The same result is seen in other studies also (Ahranjani, 2020), Dang *et al*. (2012) and Oncel *et al*. 2014 [14-16].

In a previous study, it was found that first-course of treatment with PCM achieved 26% closure and 36% showing reduction in PDA size. With IBU the figures were 48.5% and 30%, respectively. (Ahranjini, *et al*.,) [14]. Yet another study reported a primary closure rate 56.3% with PCM and 78% with IBU (Dang *et al*.,) [15]. The lower percentage of closure with PCM in the first course in our study might be due to the criteria used for choice of drug. However, the overall rate of closure in the study was in agreement with earlier studies.

In a study by Meena *et al*. (2020) comparing indomethacin, IBU and PCM, no significant difference between groups for closure of PDA was observed after the completion of two courses of treatment of 3 days each [17]. The rate of closure after first course was 22.8% with indomethacin, 37.14% with IBU and

Table 3: Comparison of pre-treatment and post-treatment values of various parameters (t-test)

Parameter	PCM			IBU		
	Mean value before treatment	Mean value after treatment	p-value	Mean value before treatment	Mean value after treatment	p-value
Platelet	151286	141190	0.508	220500	190500	0.4004
Creatinine	0.55	0.595	0.7861	0.984	0.894	0.3287
Urea	29.15	28.55	0.6871	53.6	45.56	0.5317
Bilirubin	7.812	10.986	0.0885	10.33	8.77	0.5482

PCM: Paracetamol, IBU: Ibuprofen

42.46% in PCM group. The cumulative rate of PDA closure was 68% in the indomethacin group, 77.14% in the IBU group and 71.4% in PCM group (p=0.716).

Regarding the influence of birth weight, result, as shown in Fig 1, showed that PCM gave a higher closure rate in low birth weight group.

In one study, it was reported that high level of platelet (181×10^9/L) independently increased the probability of successful closure of hsPDA after IBU treatment (OR: 2.556, 95% CI: 1.101–5.932, p=0.029). The cutoff value was modestly higher than 150×10^9/L, which is the diagnosis criteria of thrombocytopenia [18].

El-Mashad *et al*., in a study, showed a significant difference in the platelet level after treatment in both IBU and indomethacin groups, whereas no thrombocytopenia occurred after PCM treatment [19]. In our study, we have analyzed the effect of pre-treatment values of platelet in closure rate for PCM. There was a positive correlation up to a level of 150×10^9/L. It was reported earlier that higher platelet counts are necessary for natural PDA closure [20]. Our result may give a predictive value of choice of drug before start of treatment, and PCM may be a better drug to select in case of low platelet count.

Regarding comorbidities, EOS and NJ patients had a better percentage of closure with PCM treatment. It may be noted that IBU was not used in patients with low values of platelet (<95000)

Regarding safety aspects, our study was in agreement with previous studies. One study regarding bilirubin in VLBW infants with PDA, IBU treatment was associated with higher bilirubin levels than indomethacin [20]. In one study (Dang), there were no significant differences between the two groups in adverse events, including BPD, PVL, NEC, sepsis, ROP, and death from 1 week after treatment onward during the hospitalization period [15].

In a study by Meena *et al*., it was observed that there is a significant increase in NEC and GI bleeding with indomethacin and IBU, which was not observed in PCM group [17]. In our study, no cases of NEC, BPD, ROP, or GI bleeding were reported both in IBU and PCM group.

A lot of controversy still exists regarding the choice and route of administration of drugs used for hsPDA treatment. Oral route have the advantage of prolonged serum levels, but it is not always practical. In the present study, PCM was given mostly parenterally and IBU given orally. Some have advocated a combination drug therapy but found to be not advantageous. Chances of reopening the DA has also been reported and require extended course of treatment.

For comparing PCM and IBU, a randomized control trial would have been ideal. However, this study could elucidate data in various aspects which were very much relevant. It is a fact that a significant percentage of patients were still not responding to treatment, and the underlying factors must be studied in detail. Hence also, long-term outcome studies are required regarding PCM treatment in neonates considering the experimental neurodevelopmental studies in animal models.

CONCLUSION

The present study found that PCM was as effective as IBU in efficacy and safety aspects for the treatment of hsPDA cases in pre-term infants. PCM gave higher closure rate in low-birth-weight group. The study also highlighted the benefit of PCM in cases with comorbidities and also in cases where platelet counts were below normal. The findings were in agreement with other published works regarding efficacy and safety of PCM comparing with IBU. Hence, it was concluded that PCM can be advised as a first-line treatment for hsPDA cases in preterm infants.

REFERENCES

1. Dice JE, Bhatia J. Patent ductus arteriosus: An overview. J Pediatr Pharmacol Ther 2007;12:138-46.
2. Hammerman C. Patent ductus arteriosus. Clinical relevance of prostaglandins and prostaglandin inhibitors in PDA pathophysiology and treatment. Clin Perinatol 1995;22:457-79.
3. Ellison RC, Peckham GJ, Lang P, Talner NS, Lerer TJ, Lin L, *et al*. Evaluation of the preterm infant for patent ductus arteriosus. Pediatrics 1983;71:364-72.
4. Smith GC. The pharmacology of the ductus arteriosus. Pharmacol Rev 1998;50:35-58.
5. Parkerson S, Philip R, Talati A, Sathanandam S. Management of patent ductus arteriosus in premature infants in 2020. Front Pediatr 2021;11:590578.
6. Reese J. Towards a greater understanding of the ductus arteriosus. Semin Perinatol 2018;42:199-202.
7. Nguyen M, Camenisch T, Snouwaert JN, Hicks E, Coffman TM, Anderson PA, *et al*. The prostaglandin receptor EP4 triggers remodelling of the cardiovascular system at birth. Nature 1997;390:78-81.
8. McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol - a review. Br J Clin Pharmacol 2018;84:2218-30.
9. Arlettaz R. Echocardiographic evaluation of patent ductus arteriosus in preterm infants. Front Pediatr 2017;5:147.
10. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev 2010;2010:CD000174.
11. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2011;7:CD004213.
12. Xiao Y, Liu H, Hu R, You Q, Zeng M, Jiang X. Efficacy and safety of paracetamol for patent ductus arteriosus closure in preterm infants: An updated systematic review and meta-analysis. Front Pediatr 2020;7:568.
13. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus

arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev 2020;1:CD010061.
14. Ahranjani BM, Dalil H, Nashtifani ZH, Shariat M, Khorgami M. The comparison between intravenous acetaminophen versus oral ibuprofen in preterm newborns with patent ductus arteriosus: A clinical trial. Acta Med Iran 2020;58:631-6.
15. 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:e7788.
16. 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.
17. Meena V, Meena DS, Rathore PS, Chaudhary S, Soni JP. Comparison of the efficacy and safety of indomethacin, ibuprofen, and paracetamol in the closure of patent ductus arteriosus in preterm neonates-a randomized controlled trial. Ann Pediatr Cardiol 2020;13:130-5.
18. Kulkarni VV, Dutta S, Sundaram V, Saini SS. Preterm thrombocytopenia and delay of ductus arteriosus closure. Pediatrics 2016;138:e20161627.
19. El-Mashad AE, El-Mahdy H, El Amrousy DE, Elgendy M. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. Eur J Pediatr 2017;176:233-40.
20. 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.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Swathi R, Shah M, Puthussery A. Comparison of efficacy of paracetamol and ibuprofen for treatment of hemodynamically significant patent ductus arteriosus in preterm infants. Indian J Child Health. 2023; 10(5):65-69.