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Original Research Article

Comparative Efficacy of Intravenous Ibuprofen and Intravenous Paracetamol for Pharmacological Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Neonates

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Conflict of interest: Nil

Abstract

Background: Hemodynamically significant patent ductus arteriosus (HsPDA) is a common cardiovascular condition in preterm neonates and is associated with considerable neonatal morbidity. Pharmacological closure using intravenous (IV) ibuprofen or IV paracetamol is widely practiced, although evidence regarding their comparative efficacy continues to evolve.

Objective: To compare the efficacy of intravenous ibuprofen and intravenous paracetamol for pharmacological closure of hemodynamically significant patent ductus arteriosus in preterm neonates.

Materials and Methods: This combined retrospective and prospective comparative study was conducted in a Level III NICU of a tertiary care hospital in Nashik over a period of 24 months. A total of 44 preterm neonates with birth weight below 1500 g and echocardiographically confirmed HsPDA requiring pharmacological treatment were included. Twenty-four neonates received IV paracetamol, while twenty received IV ibuprofen. Baseline characteristics, treatment parameters, duration of management, therapeutic response, and clinical outcomes were compared between the two groups using appropriate statistical tests.

Results: Baseline neonatal and maternal characteristics were comparable between the groups. Infants treated with IV ibuprofen required significantly fewer treatment doses (4.3±1.3 vs. 25.2±11.4; $p<0.001$), shorter treatment duration (4.3±1.3 vs. 6.3±2.8 days; $p=0.006$), and fewer total days of PDA management (4.3±1.3 vs. 6.7±3.3 days; $p=0.005$). No statistically significant differences were observed in mortality, duration of hospital stay, oxygen requirement, or major neonatal morbidities between the treatment groups.

Conclusion: Intravenous ibuprofen and intravenous paracetamol demonstrated comparable efficacy for the pharmacological management of hemodynamically significant patent ductus arteriosus in preterm neonates. Although intravenous ibuprofen achieved treatment with fewer doses and a shorter duration of therapy, short-term neonatal outcomes were similar between the two groups.

Keywords: Hemodynamically significant patent ductus arteriosus, Intravenous ibuprofen, Intravenous paracetamol, Preterm neonates, Pharmacological closure, Neonatal outcomes.

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Introduction

Hemodynamically significant patent ductus arteriosus (HsPDA) is one of the most frequently encountered cardiovascular disorders in preterm neonates, particularly among those with very low birth weight and lower gestational age.

Failure of physiological ductal closure after birth results in persistent left-to-right shunting, leading to pulmonary over circulation and reduced systemic perfusion. This abnormal circulation has been associated with several serious neonatal complications, including bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), prolonged ventilatory support, and increased neonatal mortality. Although spontaneous closure may occur in some infants, preterm neonates with clinically significant ductal shunting often require pharmacological

intervention to reduce morbidity and improve clinical outcomes [1,2].

Cyclooxygenase inhibitors such as indomethacin and ibuprofen have traditionally been the standard pharmacological agents for ductal closure because they inhibit prostaglandin synthesis, thereby promoting constriction of the ductus arteriosus. Among these agents, intravenous ibuprofen has gained wider acceptance due to its efficacy and comparatively favorable safety profile. Nevertheless, ibuprofen may still be associated with adverse effects including renal impairment, gastrointestinal complications, oliguria, and alterations in mesenteric and cerebral blood flow, which may limit its use in extremely premature infants with multiple comorbidities [3,4].

Paracetamol has recently emerged as an alternative therapeutic option for PDA closure. Unlike non-steroidal anti-inflammatory drugs, paracetamol inhibits the peroxidase component of prostaglandin H_2 synthase, thereby reducing prostaglandin production through a different mechanism. Several recent randomized controlled trials and systematic reviews have demonstrated that paracetamol achieves ductal closure rates comparable to ibuprofen while potentially causing fewer renal and gastrointestinal adverse effects. However, concerns remain regarding the duration of therapy, optimal dosing regimen, and long-term efficacy, particularly in extremely preterm neonates [5,6]. Considering the evolving evidence and the continued need for an effective yet safe pharmacological strategy, the present study was undertaken to compare the efficacy of intravenous ibuprofen and intravenous paracetamol for the pharmacological closure of hemodynamically significant patent ductus arteriosus in preterm neonates. The study also evaluated treatment duration, therapeutic response, and short-term clinical outcomes associated with both treatment modalities.

Materials and Methods

This combined retrospective and prospective comparative study was conducted in a Level III NICU of a tertiary care hospital in Nashik over a period of 24 months from July 2023 to June 2025. The study included preterm neonates with a birth weight of less than 1500 g who had clinically and echocardiographically confirmed hemodynamically significant patent ductus arteriosus (HsPDA) requiring pharmacological treatment. Neonates treated with intravenous paracetamol before July 2024 constituted the retrospective cohort, whereas those receiving intravenous ibuprofen from July 2024 onwards formed the prospective cohort. A total of 44 eligible preterm neonates were included in the study.

Inclusion Criteria

- Preterm neonates with gestational age <34 weeks.
- Birth weight <1500 g.
- Clinically symptomatic and echocardiographically confirmed hemodynamically significant PDA.
- Neonates requiring pharmacological treatment for HsPDA.

Exclusion Criteria

- Term neonates with PDA.
- Birth weight >1500 g.
- Major congenital anomalies.
- Asymptomatic PDA.
- Neonates managed conservatively or those who did not receive pharmacological treatment for HsPDA.

Statistical Analysis: Statistical analysis was performed using IBM SPSS Statistics version 26. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Comparisons between the intravenous ibuprofen and intravenous paracetamol groups were performed using the independent t-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 44 preterm neonates with hemodynamically significant patent ductus arteriosus (HsPDA) were included in the study. Of these, 24 neonates received intravenous paracetamol, while 20 received intravenous ibuprofen for pharmacological PDA closure.

The baseline demographic characteristics, treatment-related variables, and clinical outcomes of both groups were analyzed and are presented in the following tables and figures.

A total of 44 preterm neonates were included in the study, comprising 24 infants in the intravenous paracetamol group and 20 infants in the intravenous ibuprofen group.

The distribution of sex, gestational age, birth weight, 5-minute Apgar score, multiple pregnancy, and small-for-gestational-age status was comparable between the two treatment groups.

No statistically significant differences were observed for any baseline infant characteristics (all $p>0.05$), indicating that both groups were well matched at baseline.

Table 1: Baseline Infant Characteristics of the Study Population According to Treatment Group

Infant characteristics		Paracetamol (n=24)	Ibuprofen (n=20)	P-value
Gender	Female	11 (45.8%)	10 (50%)	0.783
	Male	13 (54.2%)	10 (50%)	
Gestational age (weeks)	<28	4 (16.7%)	7 (35%)	0.162
	28to37	20 (83.3%)	13 (65%)	
Birth Weight (grams)	<1000	7 (29.2%)	8 (40%)	0.450
	1000to1500	17 (70.8%)	12 (60%)	
Apgar Score at 5minutes	<5	3 (12.5%)	4 (20%)	0.498
	>5	21 (87.5%)	16 (80%)	
Multiple pregnancy	Yes	12 (50%)	8 (40%)	0.507
	No	12 (50%)	12 (60%)	
SGA	Yes	11 (45.8%)	12 (60%)	0.349
	No	13 (54.2%)	8 (40%)	

Table 2: Diagnosis of Hemodynamically Significant Patent Ductus Arteriosus According to Treatment Group

Diagnosis	Paracetamol (n=24)	Ibuprofen (n=20)	P-value
Day of life PDA was diagnosed (Mean+ SD)	3.4 ± 2.8	4.0 ± 4.5	0.428
PDA size (mm) (Mean+ SD)	2.4 ± 0.9	2.7 ± 0.7	0.105

The mean postnatal age at diagnosis of hemodynamically significant patent ductus arteriosus and the mean ductal diameter were similar in both treatment groups. No statistically significant differences were found in either parameter ($p>0.05$), suggesting comparable disease severity before initiation of therapy.

Table 3: Comparison of Treatment Characteristics between the Intravenous Paracetamol and Intravenous Ibuprofen Groups

Treatment	Paracetamol (n=24)	Ibuprofen (n=20)	P-value
No of doses received (Mean+ SD)	25.2 ± 11.4	4.3 ± 1.3	0.0001
No of days of treatment (Mean+ SD)	6.3 ± 2.8	4.3 ± 1.3	0.006

Infants treated with intravenous ibuprofen required significantly fewer drug doses and a shorter duration of treatment than those receiving intravenous paracetamol. Both treatment parameters showed statistically significant differences ($p<0.05$), indicating that ibuprofen achieved pharmacological management with a shorter treatment course.

Table 4: Duration of Clinical Management Following Pharmacological Treatment

Duration of Management	Paracetamol (n=24)	Ibuprofen (n=20)	P-value
Total days of management	6.7 ± 3.3	4.3 ± 1.3	0.005
Duration of hospital stay (mean+ SD)	41.04 ± 25.1	44.3 ± 26.2	0.408
Duration of oxygen requirement (mean+ SD)	19.5 ± 17.8	22.9 ± 21.5	0.139

The total duration of PDA management was significantly shorter in the intravenous ibuprofen group compared with the intravenous paracetamol group ($p=0.005$). However, no significant differences were observed in the duration of hospital stay or oxygen requirement between the two groups, demonstrating comparable short-term clinical recovery despite differences in treatment duration.

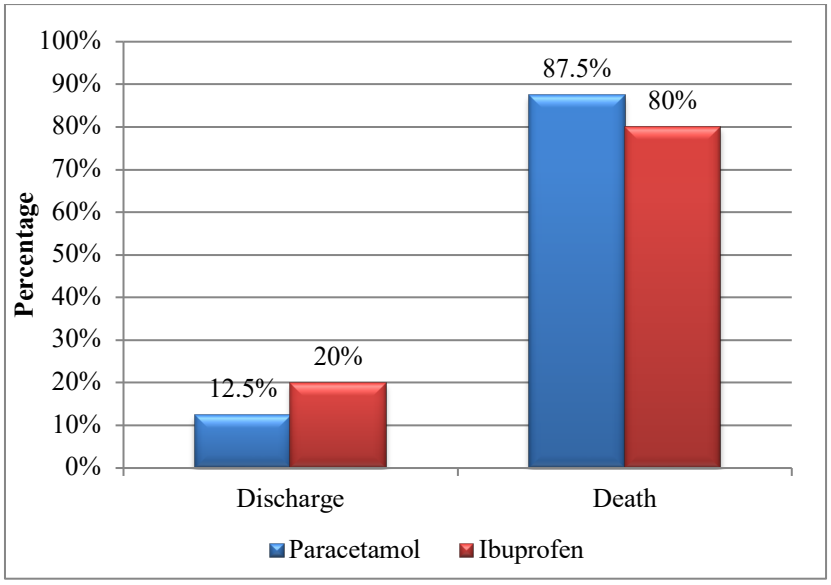

Figure 1: Primary Clinical Outcomes in the Intravenous Paracetamol and Intravenous Ibuprofen Groups

The proportions of discharge and mortality were comparable between the intravenous paracetamol and intravenous ibuprofen groups. No statistically significant difference was observed in the primary clinical outcomes ($p>0.05$), indicating similar short-term survival outcomes with both treatment strategies.

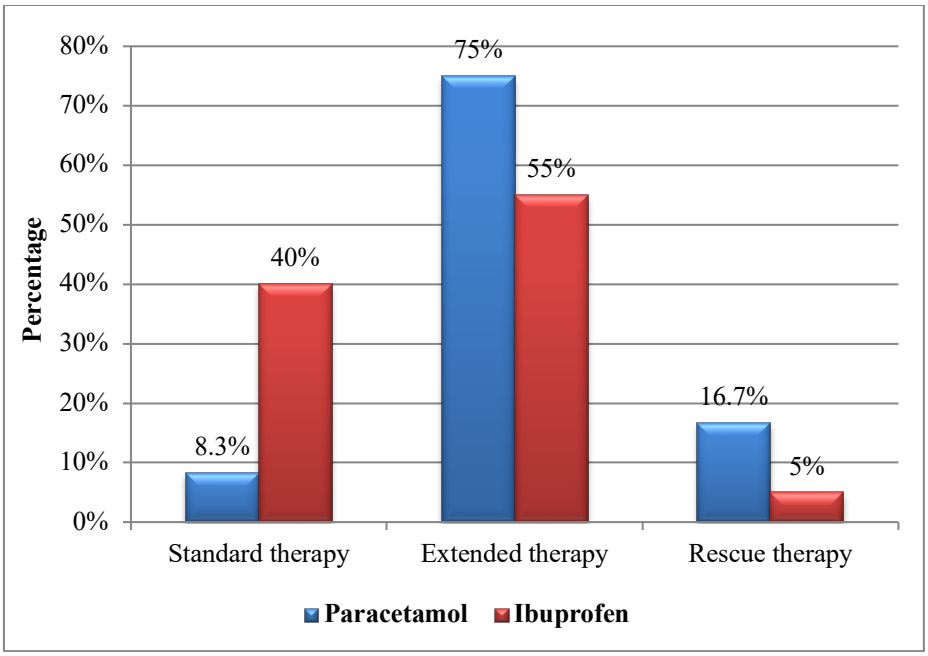

Figure 2: Distribution of Standard, Extended, and Rescue Therapy in the Two Treatment Groups

Standard therapy was administered significantly more frequently in the intravenous ibuprofen group than in the intravenous paracetamol group (40.0% vs. 8.3%; $p=0.027$).

Although extended and rescue therapy were more commonly required in the paracetamol group, these differences were not statistically significant, suggesting that ibuprofen more often achieved treatment success with the standard therapeutic regimen.

Discussion

Hemodynamically significant patent ductus arteriosus (HsPDA) is a common cardiovascular disorder in preterm neonates and is associated with increased risks of pulmonary overcirculation, systemic hypoperfusion, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and prolonged respiratory support. Pharmacological closure remains the preferred initial treatment, with intravenous ibuprofen being widely used, while intravenous paracetamol has recently emerged as a promising alternative because of its favorable safety profile [7,8]. In the present study, baseline neonatal characteristics, including gestational age, birth weight, sex, Apgar

score, multiple pregnancy, and small-for-gestational-age status, were comparable between the intravenous paracetamol and intravenous ibuprofen groups. Similarly, no significant differences were observed in the timing of PDA diagnosis or ductal size, indicating that both groups had comparable disease severity before initiation of treatment.

The major finding of this study was that infants treated with intravenous ibuprofen required significantly fewer doses and a shorter duration of treatment compared with those receiving intravenous paracetamol. In addition, the overall duration of PDA management was significantly shorter in the ibuprofen group. These findings suggest that intravenous ibuprofen achieves pharmacological closure more rapidly, which is consistent with its mechanism of cyclooxygenase inhibition leading to faster suppression of prostaglandin synthesis [9,10].

Despite the shorter treatment course with ibuprofen, important neonatal outcomes, including duration of hospital stay, oxygen requirement, mortality, bronchopulmonary dysplasia, severe intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and late-onset sepsis, were comparable between both treatment groups. These findings indicate that both intravenous ibuprofen and intravenous paracetamol provide similar short-term clinical effectiveness in the management of HsPDA.

Our findings are consistent with the randomized controlled trial by Balachander et al., which demonstrated comparable efficacy of paracetamol and ibuprofen for PDA closure in preterm neonates. Likewise, the Cochrane systematic review by Jasani et al. reported no significant difference in PDA closure rates between acetaminophen and ibuprofen, supporting paracetamol as an effective alternative, particularly when ibuprofen is contraindicated [11,12]. Another important observation in the present study was that standard therapy was used significantly more often in the ibuprofen group, whereas extended or rescue therapy was more frequently required in the paracetamol group, suggesting that paracetamol may require a longer treatment course to achieve similar therapeutic success.

Overall, the findings of the present study suggest that both intravenous ibuprofen and intravenous paracetamol are effective options for pharmacological management of HsPDA in preterm neonates. While intravenous ibuprofen offers the advantage of a shorter treatment duration, intravenous paracetamol achieves comparable short-term clinical outcomes and remains a suitable alternative, especially in infants at risk of NSAID-related adverse effects.

Conclusion

Both intravenous ibuprofen and intravenous paracetamol were effective for the pharmacological management of hemodynamically significant patent ductus arteriosus in preterm neonates. Intravenous ibuprofen required significantly fewer doses, a shorter duration of therapy, and reduced overall treatment duration compared with intravenous paracetamol. However, short-term clinical outcomes, including mortality, duration of hospital stay, oxygen requirement, and major neonatal morbidities, were comparable between the two groups. These findings suggest that intravenous ibuprofen provides a faster therapeutic response, while intravenous paracetamol remains an effective and appropriate alternative, particularly in preterm neonates with contraindications to ibuprofen.

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