

## Research Article



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## ASSESSMENT OF THE SAFETY AND EFFICACY OF PARACETAMOL IN THE MANAGEMENT OF HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN PRETERM NEWBORNS

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### ABSTRACT

**Background:** In preterm babies, hemodynamically significant patent ductus arteriosus (hsPDA) causes significant mortality and morbidity affecting 20% very of birth weight infants where medical management is the main modality. Conventionally used cyclooxygenase inhibitors have many serious adverse effects warranting alternative drugs such as paracetamol to be used in NICU in preterm neonates with hsPDA.

**Aim:** The present study aimed to assess the safety and efficacy of paracetamol in preterm neonates having hemodynamically significant patent ductus arteriosus (hsPDA).

**Methods:** The present study assessed 28 preterm neonates who were diagnosed with hemodynamically significant patent ductus arteriosus on echocardiographic and clinical assessment in NICU (neonatal intensive care unit) on days 3-14 of life for 13 months. Birth weight of 1000 grams and 1650 grams and gestational age of 28-33 weeks were assessed in the study. Paracetamol in the dose of 15mg/kg/dose every 6 hours was given to all the neonates for 3 days and neonates were echocardiographically reevaluated after 3 days of the treatment.

**Results:** The study results reported that in 86% (n=24) subjects from 28 subjects assessed, patent ductus arteriosus was closed, whereas, in 14% (n=4) study subjects, hemodynamic closure was non-significant residual flow was achieved. Paracetamol showed efficacy in all 100% of study subjects. In the present study, no adverse event was noted during the treatment.

**Conclusions:** The present study concluded that paracetamol in low doses is a highly efficacious and safe drug in managing subjects with hemodynamically significant patent ductus arteriosus in premature infants.

**Keywords:** hemodynamically significant patent ductus arteriosus, hsPDA, paracetamol, preterm infants, NICU

### INTRODUCTION

In conditions where a preterm infant recovers from RDS (respiratory distress syndrome), a hs PDA (hemodynamically significant patent ductus arteriosus) has significant clinical implications. PGHS (prostaglandin H2 synthetase) produces PGs (prostaglandins) and these inflammatory mediators help in the regulation of ductal patency. However, these COX

(cyclooxygenase) inhibitors) have a high success rate of nearly 70%, and complications such as bleeding, kidney failure, and necrotizing enterocolitis pose limitations on their use in preterm infants that are critically sick.<sup>1</sup>

Paracetamol poses inhibition on prostaglandin production by blocking the peroxidase component in the PGHS enzyme that leads to the closure of the ductus. Paracetamol has been used widely in Pediatric subjects and is being considered as an agent for pharmacological closure of hemodynamically significant patent ductus arteriosus.<sup>2</sup>

Various studies in the literature have depicted the efficacy and safety of paracetamol. However, existing literature data is scarce concerning the use of paracetamol in neonates with patent ductus arteriosus.<sup>3</sup> Hence, the present study aimed to assess the efficacy of paracetamol in the closure of hemodynamically significant patent ductus arteriosus in preterm neonates from India.

## **MATERIALS AND METHODS**

The present study aimed to assess the efficacy of paracetamol in the closure of hemodynamically significant patent ductus arteriosus in preterm neonates from India. The study subjects were from the Outpatient Department of Pharmacology of the Institute. Verbal and written informed consent were taken from all the subjects before participation.

The study included all the preterm neonates aged <33 weeks of gestation and that had hemodynamically significant patent ductus arteriosus that presented to the institute within the defined study period. The exclusion criteria for the study were subjects that needed exchange transfusion due to jaundice, thrombocytopenia with <60,000/mm<sup>3</sup>, serum creatinine >1.5mg/dl, intraventricular hemorrhage, life-threatening infection with organ failure, major structural malformation, and major congenital heart anomaly.

In all the included neonates, detailed history was recorded followed by comprehensive general and systemic examination. The neonates were selected based on echocardiographic and clinical criteria where clinical criteria were hemodynamically significant patent ductus arteriosus presenting as increased continued need of mechanical ventilation of CPAP (continuous positive airway pressure), bounding peripheral pulses, active precordium, tachycardia, and tachypnea as evidence of pulmonary over circulation.<sup>4</sup>

For echocardiographic criteria of hsPDA, the presence of one/more following observations was considered necessary as absent and reverse diastolic flow in the descending aorta, pulsatile and unrestrictive flow in the duct, left-atrium to-aortic-root ratio >1.6, and internal ductal diameter  $\geq$ 1.5 mm.<sup>5</sup> Relevant assessments as a stool for occult blood, active thromboplastin time, prothrombin time, liver function test, bilirubin, and serum creatinine were assessed before intervention and 72 hours following intervention along with routine investigations. ECG (echocardiography) was also done before intervention and 72 hours following intervention.

Depending on echocardiographic and clinical assessment, 28 subjects were included finally in the study that were treated with either intravenous or oral paracetamol. In all the subjects, demographic data, echocardiographic findings, and clinical features were assessed. In all the included neonates, the oral suspension form of paracetamol was given as 60mg/kg/day in four doses divided for 3 days via an OG tube and intravenous paracetamol in the same dose given to two infants owing to continued ongoing supportive treatment and feed intolerance.

Statistical analysis of gathered data was using SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk, NY, USA) for assessment of descriptive measures, Student t-test, ANOVA (analysis of variance), Fisher's exact test, Mann-Whitney U test, and Chi-square test. The results were expressed as mean and standard deviation and frequency and percentages. The p-value of <0.05 was considered.

## **RESULTS**

The present study aimed to assess the efficacy of paracetamol in closure of hemodynamically significant patent ductus arteriosus in preterm neonates from India. The present study assessed 28 preterm neonates who were diagnosed with hemodynamically significant patent ductus arteriosus on echocardiographic and clinical assessment in NICU (neonatal intensive care unit) on days 3-14 of life for 13 months.

The gestational age of study subjects was 28-33 weeks with birth weight of 1000-1650 grams. There were 57.14% (n=16) males and 42.85% (n=12) females in the present study. The age of study participants at enrolment was 3-14 days. Resuscitation at birth, RDS, surfactant, bounding peripheral pulses, CCF, CPAP, and mechanical ventilation was done in

64.29% (n=18), 57.14% (n=16), 42.84% (n=12), 92.86% (n=26), 64.29% (n=18), 57.14% (n=16), and 64.29% (n=18) study subjects respectively (Table 1).

The study results showed that for preintervention echocardiographic findings in study subjects, reversal of flow in descending aorta was reported in 71.43% (n=20), left atrium to aortic root ratio >1.6 was seen in 92.86% (n=26) subjects, and diameter of the ductus as  $\geq 1.5$ mm was seen in all 100% (n=28) study subjects respectively (Table 2).

It was seen that for post-intervention echocardiographic findings in study subjects, reversal of flow in descending aorta was reported in no study subject, left atrium to aortic root ratio >1.6 was seen in 100% (n=28) study subject, ductal diameter closed was seen in 86% (n=24) study subjects. Ductal diameter of 1-1.5 and <1 was seen in 7.1% (n=2) of study subjects each (Table 3).

On assessing the laboratory parameters before and after intervention in study subjects, aPTT decreased non-significantly from baseline to after paracetamol intake with  $p=0.1090$ . A similar non-significant decrease was seen for prothrombin time from baseline to after paracetamol with  $p=0.09$ . A non-significant decrease was seen in AST and ALT from baseline to after paracetamol intake with  $p=0.72$  and  $0.46$  respectively. Serum bilirubin and serum creatinine levels also decreased non-significantly from baseline to after paracetamol intake with  $p=0.07$  and  $0.33$  respectively (Table 4).

## DISCUSSION

The present study assessed 28 preterm neonates who were diagnosed with hemodynamically significant patent ductus arteriosus on echocardiographic and clinical assessment in NICU (neonatal intensive care unit) on days 3-14 of life for 13 months. The gestational age of study subjects was 28-33 weeks with birth weight of 1000-1650 grams. There were 57.14% (n=16) males and 42.85% (n=12) females in the present study.

The age of study participants at enrolment was 3-14 days. Resuscitation at birth, RDS, surfactant, bounding peripheral pulses, CCF, CPAP, and mechanical ventilation was done in 64.29% (n=18), 57.14% (n=16), 42.84% (n=12), 92.86% (n=26), 64.29% (n=18), 57.14% (n=16), and 64.29% (n=18) study subjects respectively. These data were comparable to the studies of DeMauro SB et al<sup>6</sup> in 2014 and Oncel MY et al<sup>7</sup> in 2014 where authors assessed neonates with hsPDA and demographics comparable to the present study in their respective studies.

It was seen that for preintervention echocardiographic findings in study subjects, reversal of flow in descending aorta was reported in 71.43% (n=20), left atrium to aortic root ratio >1.6 was seen in 92.86% (n=26) subjects, and diameter of the ductus as  $\geq 1.5$ mm was seen in all 100% (n=28) study subjects respectively. These results were consistent with the findings of Dang D et al<sup>8</sup> in 2013 and Dash SK et al<sup>9</sup> in 2015 where preintervention echocardiographic findings before paracetamol in hsPDA reported by the authors in their studies were comparable to the results of the present study.

The study results showed that for post-intervention echocardiographic findings in study subjects, reversal of flow in descending aorta was reported in no study subject, left atrium to aortic root ratio >1.6 was seen in 100% (n=28) study subject, ductal diameter closed was seen in 86% (n=24) study subjects. Ductal diameter of 1-1.5 and <1 was seen in 7.1% (n=2) of study subjects each. These results were in agreement with the findings of Hammerman C et al<sup>10</sup> in 2011 and Noori S et al<sup>11</sup> in 2009 where post-intervention echocardiographic findings comparable to the present study were also reported by the authors in their respective studies.

Concerning the assessment of the laboratory parameters before and after intervention in study subjects, aPTT decreased non-significantly from baseline to after paracetamol intake with  $p=0.1090$ . A similar non-significant decrease was seen for prothrombin time from baseline to after paracetamol with  $p=0.09$ . A non-significant decrease was seen in AST and ALT from baseline to after paracetamol intake with  $p=0.72$  and  $0.46$  respectively. Serum bilirubin and serum creatinine levels also decreased non-significantly from baseline to after paracetamol intake with  $p=0.07$  and  $0.33$  respectively. These findings were in line with the results of Jaleel MA et al<sup>12</sup> in 2013 and Agarwal R et al<sup>13</sup> in 2008 where laboratory parameters before and after paracetamol intervention reported by the authors in their studies were comparable to the results of the present study.

## CONCLUSIONS

The present study, within its limitations, concludes that paracetamol in low doses is a highly efficacious and safe drug in managing subjects with hemodynamically significant patent ductus arteriosus in premature infants. However, further longitudinal studies in the future are warranted with a larger sample size and longer monitoring to reach a definitive conclusion.

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Characteristics	Number (n)	Percentage (%)
Total number of neonates	28	100
Gestational age (weeks)	28-33	
Birth weight (grams)	1000-1650	
Gender		
Males	16	57.14
Females	12	42.85
Age at enrolment (days)	3-14	
Resuscitation at birth	18	64.29
RDS	16	57.14
Surfactant	12	42.84
Bounding peripheral pulses	26	92.86
CCF	18	64.29
CPAP	16	57.14
Mechanical ventilation	18	64.29

**Table 1: Demographic and disease characteristics of the study subjects**

Echocardiographic findings	Number (n)	Percentage (%)
Reversal of flow in descending aorta	20	71.43

Left atrium to aortic root ratio >1.6	26	92.86
The diameter of the ductus $\geq$ 1.5mm	28	100

**Table 2: Preintervention echocardiographic findings in study subjects**

Echocardiographic findings	Number (n)	Percentage (%)
Reversal of flow in descending aorta	-	-
Left atrium to aortic root ratio <1.6	28	100
Ductal diameter closed (mm)	24	86
1-1.5	2	7.1
<1	2	7.1

**Table 3: Post-intervention echocardiographic findings in study subjects**

Lab parameters	Baseline	After paracetamol	p-value
aPTT	31.77 $\pm$ 3.71	29.29 $\pm$ 4.15	0.1090
Prothrombin time	15.63 $\pm$ 1.83	14.44 $\pm$ 1.75	0.09
Stool for occult blood	-	-	-
AST	25.87 $\pm$ 9.97	24.22 $\pm$ 12.30	0.72
ALT	25.6 $\pm$ 10.29	22.85 $\pm$ 11.46	0.46
Serum bilirubin	8.05 $\pm$ 2.09	6.61 $\pm$ 1.87	0.07
Serum creatinine	0.49 $\pm$ 0.12	0.44 $\pm$ 0.14	0.33

**Table 4: Laboratory parameters before and after intervention in study subjects**