COMPARISON OF INTRAVENOUS PARACETAMOL VERSUS ORAL IBUPROFEN FOR THE CLOSURE OF HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN PRETERM AND TERM NEONATES: AN OPEN-LABEL RANDOMIZED STUDY

Parthiban G[1*], Preethi N[2], Divakar R[3], Anand V[3], Senthilkumaran G[4]

[1*]Assistant Professor, Department of Cardiology, Mahatma Gandhi Medical College and Research Institute, Pondicherry.

[2]Senior Resident, Department of Paediatrics, Government Thoothukudi Medical College, Thoothukudi.

[3]Assistant Professor, Department of Paediatrics, Government Thoothukudi Medical College, Thoothukudi.

[4]Associate Professor, Department of Paediatrics, Government Thoothukudi Medical College, Thoothukudi.

Corresponding Author: Parthiban G

Assistant Professor, Department of Cardiology, Mahatma Gandhi Medical College and Research Institute, Pondicherry.

Abstract

Background: Patent ductus arteriosus is a common congenital heart defect among preterm neonates. Preterm newborns with prolonged ductal patency have been linked to considerable short- and long-term morbidities, as well as higher mortality; however, systematic treatment of everyone during the neonatal period has resulted in a detectable improvement in long-term results. COX inhibitors like Indomethacin and Ibuprofen are approved for PDA closure in preterm neonates. This study compares the efficacy and safety of IV Paracetamol and oral Ibuprofen in preterm and term neonates with HsPDA.

Material and Methods: This is an open-label randomized study that was conducted on preterm and term neonates with HsPDA at the NICU of the Government Thoothukudi Medical College among 104 neonates. In total 104 neonates were examined, 52 of whom received 15mg/kg/q6hr of intravenous paracetamol for 3 days, and 52 neonates received 10mg/kg oral ibuprofen on the first day, 5 mg/kg for the next 2 days. The clinical and echocardiography findings were compared. Non-constricted neonates after the first course were subjected to the same drugs for the second course. The closure and constriction rates were studied using echocardiography.

Results: Out of 52 neonates in both groups, 38 neonates(73.07%) had closure of PDA in the paracetamol group vs 42 neonates(80.7%) had closure of PDA in the ibuprofen group. There is no significant difference in closure rate between intravenous paracetamol vs oral ibuprofen after 2 courses of treatment.

Conclusion: Intravenous paracetamol had a similar efficacy compared to oral ibuprofen for PDA closure in preterm and term neonates. Intravenous Paracetamol is a safe and effective alternative for PDA closure when compared with Ibuprofen.

Key Words: Patent ductus arteriosus, congenital heart defect, NICU, echocardiography.

INTRODUCTION

Patent ductus arteriosus (PDA) is a common congenital heart defect among preterm neonates of less than 28 weeks. About 60-70 % of preterm neonates require pharmacological, device, or surgical closure of PDA. In term neonates, PDA accounts for 5-10 % of all congenital heart diseases. The incidence of PDA is inversely proportional to gestational age and birth weight. PDA is a functional defect in term neonates, whereas it is due to prematurity in preterm neonates. Ductus arteriosus [DA] is essential for maintaining fetal circulation because it helps to provide partially oxygenated blood to the systemic circulation, connecting the pulmonary artery to the descending aorta. After birth, DA closes resulting in separate systemic and pulmonary circulation.[1]

Persistence of DA after birth, when hemodynamically significant [HsPDA] leads to cardiovascular dysfunction, respiratory distress, pulmonary hemorrhage, intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, acute kidney injury, prolonged ventilatory support, increased mortality. Hence, it's important to actively close HsPDA.[2]

The HsPDA can be closed by pharmacological, interventional, and surgical methods. Cyclooxygenase inhibitors are the first-line pharmacological agent for the closure of HsPDA. The commonly used cyclooxygenase inhibitor for HsPDA closure is indomethacin and ibuprofen. Interventional/surgical closure is indicated when there is a contraindication to cyclooxygenase (COX) inhibitors or when pharmacological closure fails.[3]

The adverse effect profile of these drugs is high involving the gut, kidneys, and pulmonary vasculature.[4,5] Hence surgical ligation was the only option when COX inhibitors are contraindicated. As an alternative option to the treatment of closure of HsPDA, the role of paracetamol has gained attention because of its superior safety profile[6,7]. However, the evidence regarding the indication, the route of administration, the dosage, and the effectiveness of the long-term effects of paracetamol are yet to be studied.

Hence in this study, we attempt to analyze the efficacy of intravenous paracetamol versus oral ibuprofen in the closure of hemodynamically significant PDA in both preterm and term neonates.

AIM OF THE STUDY

To study the efficacy of intravenous paracetamol versus oral ibuprofen for the closure of hemodynamically significant patent ductus arteriosus (HsPDA) in preterm and term neonates

OBJECTIVES

PRIMARY OBJECTIVE:

- To compare the efficacy of intravenous paracetamol versus oral ibuprofen in the closure of HsPDA among preterm and term neonates.

SECONDARY OBJECTIVES:

- To compare the constriction of HsPDA after primary treatment with intravenous paracetamol in comparison withoral ibuprofen.

- The closure of HsPDA and the constriction rate in neonates who need the second course of treatment with the same medicine as their primary treatment.
- To determine in subgroup analyses the effectiveness and safety of intravenous paracetamol and oral Ibuprofen for closure of a PDA in relation to gestational age (< 28 weeks, 28 to 32 weeks+6 days, 33 to 36 weeks+6 days, 37 weeks to 40 weeks); b. birth weight (< 1000 g,1000 to 1500 g, 1501 to 2500 g, >2500g)

MATERIALS AND METHODS

STUDY DESIGN: Prospective open-label randomized study

STUDY DURATION: December 2020 to May 2022 (18 months)

NUMBER OF SUBJECTS: 104 neonates admitted in NICU with HsPDA (calculated with alpha/type 1 error=0.05, beta /type 2 errorpower is set at 0.80)

Subject selection

INCLUSION CRITERIA:

*Neonates (Gestational age of 28 weeks to 40 weeks) between 24 and 72 hours of life and within the first 28 postnatal days of life with hemodynamicallysignificant PDA (hs-PDA), diagnosed clinically and confirmed by echocardiography.

*Parental consent.

EXCLUSION CRITERIA:

* Neonates with major congenital anomalies, with PDA-dependent systemic /pulmonary circulation.

*All congenital heart diseases, and life-threatening infections. Recent (within previous 24 h) IVH (Grade 3 and 4), blood urea >60 mg/dl, serum creatinine >1.8 mg/dl, Platelet count < 60000, active necrotizing enterocolitis (NEC), evidence of Severe birth asphyxia.

METHODS:

All the preterm and term neonates, who were mentioned in the inclusion criteria admitted to the NICU of Government Thoothukudi Medical College, who had a heart murmur, cardiovascular, respiratory, and hemodynamic disturbance, and long-term respiratory support were examined for HsPDA.

HsPDA is defined if any one of the below-mentioned clinical/biochemical signs is present:

Signs of significant left to right shunt: Hyperdynamic pulsatile precordium, bounding peripheral pulses, and wide pulse pressure(>25mmHg)

Signs of systemic under perfusion: Poor peripheral pulse Volume, prolonged CRT, decreased urine output, derangedrenal function test, metabolic acidosis, and hypotension.

signs of pulmonary over perfusion: Abnormal weight gain, increase in liver size, new onset or increase in ventilator requirement that primarily involve positive end-expiratory pressure(PEEP) Peak inspiratory pressure(PIP), and a fraction of inspired oxygen (fio2), respiratory acidosis, pulmonary crepitation, and hemorrhagic pulmonary edema.

Neonates with these clinical signs will be screened by a cardiologist with Echocardiography. Echocardiographic features indicative of HsPDA are a transductal diameter of ≥1.5mm plus one of the following: Evidence of left atrial enlargement (Lt atrium: aortic root diameter ratio≥1.3), Ductal velocity<2m/s, Absent or reversed diastolic blood flow pattern in descending thoracic aorta.

Eligible neonates after parents' consent will be randomly divided into 2 groups in a ratio of 1:1. Patient in group 1 will receive 15mg/ kg/6h IV Paracetamol for 3 days and the patient in group 2 will receive oral ibuprofen initial dose of 10mg/kg followed by 5 mg/kg after 24hrs and 48hrs. Neonates in both groups who failed the closure and had a persistent HsPDA after the first course of treatment receive a second course of respective medications as in their first course. Neonates who had failed closure of HsPDA after the second course will be been sent for surgical/device closure.

The allocation sequences consist of computer-generated random numbers. Since the frequency of the PDA is inversely related to thegestational age, the inclusion of patients was balanced in each treatment group according to the following gestational ages: <28 weeks, 28+0– 32weeks+6 days,33 to 36weeks+6 days, 37 weeks to 40 weeks.

Neonates will the assessed hemodynamically daily and Echocardiography was repeated every 24 hr during the first treatment course, and 24 hours after the last dose of the treatment who were blinded to the study and treatment groups. Blood investigation will be repeated at required intervals, and an echocardiogram will be performed by expert personnel, specifically a cardiologist.

INVESTIGATIONS: Laboratory tests were performed at patients' screening, at the end of the first and second courses of treatment, Clinical laboratory tests included a count of red blood cells, white blood cells, and platelets, serum value measurement of hematocrit, c- reactive protein, creatinine, urea nitrogen, total bilirubin, total proteins, liver enzymes, sodium, potassium, and calcium; USG cranium; Echocardiography.

STATISTICAL DATA ANALYSIS: Data will be recorded on predesigned proforma and managed on an Excel spreadsheet. Group comparison will be done by applying the T-test and Chi-square test where applicable. A p-value of less than 0.05 was taken as the significant statistical analysis was done using SSPS statistical software.

Sources of funding and financial requirements for the proposal: nil

Ethical issues involved: approved.

RESULTS

After obtaining informed consent and approval from the ethical committee for the study, 104 neonates with evidence of HsPDA both clinically and echocardiographically were randomized to study the efficacy of intravenous paracetamol versus oral ibuprofen for the closure of hemodynamically significant patent ductus arteriosus (HsPDA). In our study the neonates with HsPDA are being evaluated for gender, birth weight, gestational age, mode of delivery, maternal complication, antenatal steroid intake, birth asphyxia, Apgar at 5 mins, surfactant use, sepsis, the character of left to right shunt, the efficacy of IV para and oral ibuprofen after the first course and second closure, constriction rate of HsPDA after the first course and second closure, initial echo and post-intervention ECHO of transductal size and LA/AO, adverse effect, mode of ventilation, number of days of oxygen requirement.

Data collected are compared internally, tabulated, analyzed, and interpreted using descriptive and

inferential statistics based on the primary and secondary objectives of the study. Descriptive statistics were done for all data and reported in terms of mean value and percentage. Statistical tests of comparison were done. Group comparison will be done by applying the T-test and Chi-square test where applicable. A p-value of less than 0.05 was taken as significant statistically. The data were analyzed using Microsoft Excel 2019 and IBM SPSS version 29.0.0.0.

DISTRIBUTION OF GENDER

Table 1: Distribution of Gender of the neonates based on the type of intervention

Gender	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
Male	24 (46.2%)	26 (50%)	0.24	0.69
Female	28 (53.8%)	26 (50%)		

Female neonates are slightly higher in the paracetamol group. There is no significant difference in the gender distribution between the two intervention groups.

DISTRIBUTION OF GESTATIONAL AGE

Table 2: Distribution of Gestational age of the neonates based on the type of intervention

Gestational age	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
< 28 weeks	15 (28.8%)	14 (26.9%)	0.58	0.99
28-32 weeks	21 (40.4%)	22 (42.3%)		
33-36 weeks	12 (23.1%)	12 (23.1%)		
Term	4 (7.7%)	4 (7.7%)		

Most of the neonates in both groups had gestational ages ranging between 28-32 weeks(40.4% in the paracetamol group vs 42.3% in the ibuprofen group). There are only 4(7.7%) neonates belonging to term pregnancy in both groups. There is no significant difference in the gestational age distribution between the two groups. (p = 0.99)

DISTRIBUTION OF BIRTH WEIGHT

Table 4: Distribution of Birth weight of the neonates based on the type of intervention

Birth Weight	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
< 1 Kg	16 (30.8%)	18 (34.6%)	0.47	0.98
1-1.5 Kg	18 (34.6%)	19 (36.5%)		
1.5-2 Kg	12 (23.1%)	10 (19.2%)		
2- 2.5 Kg	2 (3.8%)	2 (3.8%)		
>2.5 Kg	4 (7.7%)	3 (5.8%)		

The majority of neonates (65.4% in the paracetamol group vs 71.1% in the ibuprofen group)belong to the very low birth weight category (< 1.5 kg). There is no significant differencein the birth weight distribution between the two groups (p=0.98).

DISTRIBUTION OF MODE OF DELIVERY

Table 5: Distribution of Mode of delivery based on the type of intervention

Mode of delivery	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
NVD	24 (46.1%)	22 (42.3%)	0.382	0.83
LSCS	23 (44.2%)	26 (50%)		
AVD	5 (9.6%)	4 (7.7 %)		

The majority (46.1%) of them had normal vaginal delivery in the paracetamol group, whereas LSCS (50%) was the major mode of delivery seen in the ibuprofen group. There is no significant difference in the mode of delivery between the two groups (p=0.83).

DISTRIBUTION OF MATERNAL COMPLICATION

Table 6: Distribution of Maternal complication based on the type of intervention

Maternal complication	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
GDM	8 (15.4%)	9 (17.3%)	1.284	0.97
HT	13 (25%)	11 (21.2%)		
Abruptio placenta	9 (17.3%)	7 (13.5%)		
Placenta previa	7 (13.5%)	8 (15.4%)		
Hypothyroid	4 (7.7%)	6 (11.5%)		
PROM	6 (11.5%)	7 (13.5%)		
Nil	5 (9.6%)	4 (7.7%)		

The most common maternal complication in both groups was hypertension (25% vs 21.2%), followed by abruption placenta (17.3%) in the paracetamol group. GDM was the second most common maternal complication in the ibuprofen group (17.3%) and the third most common complication (15.4%) in the paracetamol group. There is no significant difference in the distribution of maternal complications between the two groups (p=0.97).

DISTRIBUTION OF ANTENATAL STEROID INTAKE

Table 7: Distribution of Antenatal steroid intake based on the type of intervention

Antenatal steroid intake	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
Yes	31 (59.6%)	30 (57.7%)	0.40	1.00
No	21 (40.4%)	22 (42.3%)		

There is no statistical difference between antenatal steroid intake in the two groups(p=1.00).

DISTRIBUTION OF BIRTH ASPHYXIA

Table 8: Distribution of Birth asphyxia status based on the type of intervention

Birth asphyxia	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
Yes	9 (17.3%)	7 (13.5%)	1.839	0.26
No	43 (82.7%)	45 (86.5%)		

9 neonates had birth asphyxia in the paracetamol group, whereas 7 neonates had birth asphyxia in the ibuprofen group, but there is no statistically significant difference betweenthe occurrence of birth asphyxia in both the groups (p=0.26)

DISTRIBUTION OF APGAR SCORE

Table 9: Distribution of Apgar score@5 min based on the type of intervention

Apgar score@5 min	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
5	3 (5.7%)	2 (3.8%)	1.002	0.80
6	13 (25%)	11 (21.2%)		

7	25 (48.1%)	24 (46.2%)		
8	11 (21.2%)	15 (28.8%)		

The majority of the neonates in both groups had an Apgar score of 7 (48.1% in the paracetamol group vs 46.2% in the ibuprofen group) at 5 min. There is no difference in the Apgar scores between the two groups (p=0.80).

DISTRIBUTION OF SURFACTANT

Table 10: Distribution of surfactant use based on the type of intervention

Surfactant use	**Intervention Group**		**Chi-square value**	**P value**
	Paracetamol (N=52)	**Ibuprofen (N=52)**		
Yes	34 (65.4%)	31 (59.6%)	0.369	0.69
No	18 (34.6%)	21 (40.4%)		

There is no statistically significant difference in the surfactant use between both groups (p=0.69)

DISTRIBUTION OF SEPSIS STATUS

Table 11: Distribution of sepsis status in neonates based on the type of intervention

Sepsis	**Intervention Group**		**Chi-square value**	**P value**
	Paracetamol (N=52)	**Ibuprofen (N=52)**		
Yes	5 (9.6%)	7 (13.5%)	0.377	0.76
No	47 (90.4%)	45 (86.5%)		

5 neonates developed sepsis in the paracetamol group, whereas 7 neonates in the ibuprofengroup had sepsis, but the difference was not statistically significant (p=0.76)

DISTRIBUTION OF CLINICAL FEATURES

Table 12: Distribution of Clinical features across both intervention groups

Clinical Features		**Intervention Group**		**Chi-square value**	**P value**
		Paracetamol (N=52)	**Ibuprofen (N=52)**		
Tachycardia	Yes	49 (94.2%)	51 (98.1%)	1.04	0.62
	No	3 (5.8%)	1 (1.9%)		

Hyper pulsatile precordium	Yes	37 (71.2%)	31 (59.6%)	1.53	0.30
	No	15 (28.8%)	21 (40.4%)		
Bounding pulse	Yes	32 (61.5%)	30 (57.7%)	0.160	0.84
	No	20 (38.5%)	22 (42.3%)		
Wide PP	Yes	14 (26.9%)	12 (23.1%)	0.205	0.821
	No	38 (73.1%)	40 (76.9%)		

Tachycardia was present in 94.2% of participants in the paracetamol group and 98% in the ibuprofen group (p=0.62). Hyper pulsatile precordium was seen in 71.2% of neonates in the paracetamol group but only in 59.6%of neonates in the ibuprofen group (p=0.30). The occurrence of bounding pulse and wide PP was more or less equal in both groups (p=0.80). There is no statistical difference between both groups.

COMPARING THE EFFICACY OF IV PARACETAMOL AND ORALIBUPROFEN AFTER THE FIRST COURSE OF TREATMENT

Table 13: Comparison of efficacy of intravenous paracetamol and oralibuprofen in the outcome of HsPDA after the first course of treatment

Outcome	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
Closed	30 (57.7%)	32 (61.5%)	0.159	0.69
Constricted	13 (25%)	13(25%)	0	>0.99
Neither closed nor constricted	9 (17.3%)	7 (13.5%)	0.295	0.59

After the first course, IV paracetamol had a closure rate of 57.7% and oral ibuprofen had a slightly better closure rate of 61.5% which was statistically not significant (p = 0.69), and the success rate in constricting the DA was similar (25% vs. 25%; P >0.99).

COMPARISION OF EFFICACY OF IV PARACETAMOL AND ORAL IBUPROFEN CONSTRICTION RATE OF HsPDA AFTER FIRSTCLOSURE

Table 14: Comparison of efficacy of intravenous paracetamol and oralibuprofen in constriction rate of hsPDA after the first course of treatment

Constriction Rate	Intervention Group	P value Based on

	Paracetamol (N=13)	**Ibuprofen (N=13)**	**student T test**
Mean ± SD	37.59 ± 5.49	41.25 ± 3.28	0.09
Median (IQR)	37.90 (7.45)	41.90 (5.75)	
Min-Max Value	26.6%-46.4%	36.0%-46.4%	

The mean constriction rate of PDA was higher in the ibuprofen group when compared to the paracetamol group but it was not statistically significant (p value=0.09)

COMPARISON OF TRANSDUCTAL SIZE AND LA/AO RATIO BEFOREAND AFTER INTERVENTION

Table 15: Comparison of Initial ECHO and Post-intervention ECHO of transductal size and LA/AO in paracetamol and ibuprofen group

Intervention group	**ECHO findings**							
	Transductal size				**LA/AO ratio**			
	Pre-ECHO	Post ECHO After 24 hrs	Post ECHO After closure	P value	Pre- ECHO	Post ECHO After 24 hrs	Post ECHO After closure	P Value
Paracetamol	2.24 +	2.02 +	1.22 +	<0.00	1.65 +	1.59 +	1.33 +	<0.001
etamol	0.49	0.58	0.88	1	0.15	0.58	0.28	
I								
Ibupr	2.40 +	2.04 +	1.23 +	<0.00	1.76 +	1.65 +	1.33 +	<0.001
ofen	0.47	0.56	0.88	1	0.16	0.19	0.31	
p	0.76	0.80	>0.99		0.65	<0.00	0.47	

value						1		

There is a statistically significant reduction in the transductal size and LA/AO ratio in pre and post-ECHO in both paracetamol and ibuprofen groups (p-value <0.001). There is a statistically significant difference in LA/AO ratio in post-ECHO after 24 hrs between the paracetamol and ibuprofen group (p-value <0.001)

COMPARISON OF EFFICACY OF IV PARACETAMOL AND ORAL IBUPROFEN AFTER THE SECOND COURSE OF TREATMENT

Table 16: Comparison of efficacy of intravenous paracetamol and oralibuprofen in the outcome of hsPDA after the second course of treatment

Outcome	Intervention Group		Chi-square value	P value
	Paracetamol (N=22)	Ibuprofen (N=20)		
Closed	8 (36.3%)	10 (50%)	0.63	0.42
Constricted	6 (27.2%)	4(20%)	0.34	0.52
Neither closed nor constricted	8 (36.3%)	6 (30%)	2.02	0.60

Oral ibuprofen had a better closure rate than IV paracetamol (50% vs. 36.3%; P = 0.42) during the second course of treatment and it is not statistically significant. The success rate in constricting the DA is not statistically different between the paracetamol group and the ibuprofen group (27.2% vs. 20%; P=0.52).

COMPARING THE CONSTRICTION RATE OF IV PARACETAMOL AND ORAL IBUPROFEN OF HsPDA AFTER THE SECOND COURSE OF TREATMENT

Table 17: Comparison of efficacy of intravenous paracetamol and oral ibuprofen in constriction rate of hsPDA after the second course of treatment

Constriction Rate	Intervention Group		P value Based on student T Test
	Paracetamol (N=2)	Ibuprofen (N=3)	
Mean $\pm$ SD	37.7 $\pm$ 3.52	35.03 $\pm$ 1.75	0.42

Median (Range)	36.0 (8.1)	35 (3.5)	
Min-Max Value	34.7%-42.8%	33.3%-36.8%	

The mean constriction rate of PDA was slightly higher in the paracetamol group when compared to the ibuprofen group but it was not statistically significant (p value=0.42)

DISTRIBUTION OF ADVERSE EVENTS BETWEEN 2 GROUPS Table 18: Adverse events distribution in paracetamol and ibuprofen group

Adverse Events	**Intervention Group**		**Chi-square Value**	**P value**
	Paracetamol (N=52)	**Ibuprofen (N=52)**		
NEC	8 (15.4%)	9 (17.3%)	1.105	0.75
AKI	4 (7.7%)	8 (15.4%)	1.507	0.35
Hemorrhagic pulmonary edema	3 (5.8%)	5 (9.6%)	0.501	0.72
Bleeding	4 (7.7%)	6 (11.5%)	0.443	0.74
Sepsis	10 (19.2%)	13 (25%)	0.502	0.64
CCF	10 (19.2%)	13 (25%)	0.502	0.64
IVH	7 (13.5%)	8 (15.4%)	0.570	1.00
Thrombocytopenia	5 (9.6%)	8 (15.4%)	0.790	0.56
LFT	4 (7.7%)	7 (13.5%)	0.915	0.53

Among 52 infants in the paracetamol group 8 (15.4%) developed NEC, whereas, in the ibuprofen group out of 52, 9 (17.3%) developed NEC. AKI was higher (15.4%) in the ibuprofen group vs (7.7%) in the paracetamol group. Hemorrhagic pulmonary edema was seen in 5.8% and 9.6% of infants in the paracetamol and ibuprofen groups respectively. There is no significantdifference in the adverse event occurrence between both groups.

DISTRIBUTION OF MODE OF VENTILATION BETWEEN BOTH GROUPS

Table 19: Distribution of Mode of ventilation across both intervention groups

Ventilation mode	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
CPAP	36 (69.2%)	38 (73.1%)	1.054	0.79
Ventilator	12 (23.1%)	12 (23.1%)		
O2	3 (5.8%)	1 (1.9%)		
Nil	1 (1.9%)	1 (1.9%)		

The most common mode of ventilation in both groups is CPAP (69.2% in the paracetamol group vs 73.1% in the ibuprofen group) followed by ventilator. There is no difference between the mode of ventilation in both groups (p=0.79).

DISTRIBUTION OF NO OF OXYGEN REQUIREMENTS

Table 20: Distribution of No. of days of oxygen requirement in both groups

No. of days requiringoxygen support	Intervention Group		Chi-square value	P value
	Paracetamol (N=52)	Ibuprofen (N=52)		
0	1 (1.9%)	1(1.9%)	8.170	0.612
1	2 (3.8%)	1(1.9%)		
2	16 (30.8%)	18 (34.6%)		
3	11 (21.2%)	15 (28.8%)		
4	6 (11.5%)	3 (5.8%)		
5	7 (13.5%)	4(7.7%)		
6	2 (3.8%)	5 (9.6%)		

7	4 (7.7%)	2 (3.8%)		
8	2 (3.8%)	1(1.9%)		
9	0(0%)	2 (3.8%)		
10	1(1.9%)	0 (0%)		

Most neonates required 2 to 5 days of oxygen therapy in both groups. There is no statistically significant difference in the number of days infants required oxygen support inboth groups (p=0.612)

DISTRIBUTION OF INOTROPE BETWEEN GROUPS

Table 21: Distribution of inotrope support across both groups:

Inotrope support	**Intervention Group**		**Chi-square value**	**P value**
	Paracetamol (N=52)	**Ibuprofen (N=52)**		
Yes	19 (36.5%)	16 (30.8%)	0.388	0.68
No	33 (63.5%)	36 (69.2%)		

There is no statistically significant difference in the inotrope support between the two groups

DISTRIBUTION OF PDA CLOSURE AFTER THE FIRST COURSE IN RELATION TO GESTATIONAL AGE

Table 22: Distribution of PDA closure in intravenous paracetamol and oral Ibuprofen after the first course treatment for closure of a PDA in relation to gestationalage

Gestational age	**Closure of PDA after first course of treatment**		**P value based on chi-square test**
	Paracetamol (N=30)	**Ibuprofen (N=32)**	
< 28 weeks	9 (30%)	8 (25%)	0.99
28-32 weeks	11 (36.7%)	11 (34.4%)	

33-36 weeks	10 (33.3%)	11 (34.4%)	
Term	0 (0%)	2 (6.3%)	

Out of 48 preterm neonates in both groups, 30 neonates (62.5%) in the paracetamol group 30 neonates in the ibuprofen group (62.5%) had closure of PDA after the first course, and out of 4 term neonates in each group, 2 neonates (50%) had closure of PDA in the ibuprofen group whereas no neonates had closure in the paracetamol group. Distribution based on gestational week does not show any significant difference in the closure rate in the paracetamol and ibuprofen group after the first course of treatment (p=0.99)

DISTRIBUTION OF PDA CLOSURE IN IV PARACETAMOL AND ORAL IBUPROFEN AFTER THE FIRST COURSE IN RELATION TO BIRTH WEIGHT

Table 23: Distribution of PDA closure in intravenous paracetamol and oral Ibuprofen after the first course treatment for closure of a PDA in relation to Birth weight

Birth Weight	**Closure of PDA after first course of treatment**		**P value based on chi-square test**
	Paracetamol (N=30)	**Ibuprofen (N=32)**	
< 1 Kg	9 (30%)	9 (28.1%)	0.87
1-1.5 Kg	9 (30%)	11 (34.4%)	
1.5-2 Kg	11 (36.6%)	9 (28.1%)	
2- 2.5 Kg	1 (3.4%)	2 (6.3%)	
>2.5 Kg	0 (%)	1 (3.1%)	

In the extreme low birth weight category, after the first course of treatment, 9 out of 16 (56.2%) neonates had closure of PDA in the paracetamol group vs 9 out of 18 (50%) neonates had closure of PDA in the ibuprofen group. In the very low birth weight category, 9 out of 18 (50%) neonates had closure of PDA in the paracetamol group vs 11 out of 19 (57.8%) neonates had closure of PDA in the ibuprofen group. In the low birth weight category, 12 out of 14 (85.7%) neonates had closure of PDA in the paracetamol group vs 11 out of 12 (91.6%) neonates had closure of PDA in the ibuprofen group. In the normal birth weight category, none of the neonates had closure in the paracetamol group whereas 1 out of

3 (33.3%) neonates in the ibuprofen group had closure of PDA. Distribution based on birth weight does not show any significant difference in the closure rate in the paracetamol and ibuprofen group after the first course of treatment (P=0.87).

DISTRIBUTION OF PDA CLOSURE IN IV PARACETAMOL AND ORAL IBUPROFEN AFTER THE SECOND COURSE

Table 24: Distribution of PDA closure in intravenous paracetamol and oral Ibuprofen after the second course treatment for closure of a PDA in relation to gestational age

Gestational age	Closure of PDA after the second course of treatment		P value based on chi-square test
	Paracetamol (N=8)	Ibuprofen (N=10)	
< 28 weeks	1 (12.5%)	2 (20%)	0.27
28-32 weeks	4 (50%)	6 (60%)	
33-36 weeks	2 (25%)	1 (10%)	
Term	1 (12.5%)	1 (10%)	

Out of 48 preterm neonates in both groups, 39 neonates (81.2%) in the paracetamol group 40 neonates in the ibuprofen group (83.3%) had closure of PDA after the second course, and out of 4 term neonates in each group, 3 neonates (75%) had closure of PDA in the ibuprofen group and 1 neonate had closure in the paracetamol (25%) group. Distribution based on gestational week does not show any significant difference in the closure rate in the paracetamol and ibuprofen group after the second course of treatment (p=0.27).

DISTRIBUTION OF PDA CLOSURE IN IV PARACETAMOL AND ORAL IBUPROFEN AFTER THE SECOND COURSE IN RELATION TO BIRTH WEIGHT

Table 25: Distribution of PDA closure in intravenous paracetamol and oral Ibuprofen after second course treatment for closure of a PDA in relation to Birth weight

Birth Weight	Closure of PDA after the second course of treatment		P value based on chi-square test
	Paracetamol (N=8)	Ibuprofen (N=10)	
< 1 Kg	2 (25%)	3 (30%)	0.53
1-1.5 Kg	4 (50%)	5 (50%)	
1.5-2 Kg	0 (0%)	1 (10%)	
2- 2.5 Kg	1 (12.5%)	0 (0%)	
>2.5 Kg	1 (12.5%)	1 (10%)	

In the extreme low birth weight category, after the second course of treatment, 11 out of 16 (68.7%) neonates had closure of PDA in the paracetamol group vs 12 out of 18 (66.6%) had closure of PDA in the ibuprofen group. In the very low birth weight category, 13 out of 18 (72.2%) neonates had closure of PDA in the paracetamol group vs 16 out of 19 (84.2%) neonates had closure of PDA in the ibuprofen group. In the low birth weight category, 13 out of 14 (92.8%) neonates had closure of PDA in the paracetamol group vs 12 out of 12 (100%) neonates had closure of PDA in the ibuprofen group. In the normal birth weight category, 1 out of 4 (25%) neonates in the paracetamol group vs 2 out of 3 (66.6%) neonates in the ibuprofen group had closure of PDA Distribution based on birth weight does not show any significant difference in the closure rate in paracetamol and ibuprofen group after the second course of treatment (p=0.53). Out of 52 neonates in both groups, 38 neonates (73.07%) had closure of PDA in the paracetamol group, vs 42 neonates (80.7%) had closure of PDA in the ibuprofen group. There is no significant difference in closure rates between intravenous paracetamol vs oral ibuprofen after 2 courses of treatment (p=0.35)

DISCUSSION

This study was a hospital-based randomized controlled study aimed at comparing the efficacy of IV paracetamol vs oral ibuprofen among the preterm and term neonates with HsPDA admitted in the NICU of government Thoothukudi Medical College.

GESTATIONAL AGE:

Out of 104 neonates, 96 were preterm (92.3%) and 8 term (7.7%). Among the preterm, 29 neonates belong to the extreme low birth weight group(27.8%), and 67 neonates belong to the low birth weight group(64.4%). The distribution between groups was statistically not significant.

El Hajjar M et al[8] reported that the incidence of PDA in preterm neonates is much greater ranging from 20-60%. Schneider et al[9] have found the incidence of PDA in term neonates is 5-10% of congenital heart disease.

BIRTH WEIGHT: Out of 104 neonates, 34 neonates belong to extreme low birth weight categories (32.7%), 37 neonates belong to very low birth weight categories(35.5%),26 neonates belong to low birth weight category(25%) and 7(6.7%) neonates belong to normal birth weight categories. The distribution among the group was statistically insignificant.

COMPLICATIONS: Our study demonstrated a similar safety profile between IV paracetamol and oral ibuprofen. However, the incidence of AKI was higher in the ibuprofen group when compared with the IV paracetamol group but the difference is statistically insignificant with a p-value of 0.35. The incidence of NEC, pulmonary hemorrhage, bleeding, IVH, thrombocytopenia, and deranged LFT was nearly similar in both groups and was statistically insignificant. Studies have shown that treatment of PDA with paracetamol was associated with reduced risk of renal failure and GI bleeding. In our study, we did not find a significant difference in renal failure and GI bleeding. Similar results were found in multiple studies where statistically significant differences in morbidities (NEC, IVH) were not established.

COMPARISON OF EFFICACY BETWEEN PARACETAMOL AND IBUPROFEN

There are several studies have been conducted for the treatment of HsPDA in preterm neonates and few studies on term neonates. Our study was conducted among 104 preterm and term neonates, with hemodynamically significant PDA, they were randomly divided into 2 groups and were given paracetamol and ibuprofen in a ratio of 1:1. Out of 52 neonates in both groups, 38 neonates accounting for 73.07% had closure of PDA in the paracetamol group, vs 42 neonates accounting for 80.7% had closure of PDA in the ibuprofen group.

However, the closure rate of the ductus was similar. This closure rate is similar to the study conducted by Rathia et al[10], done at All India Institute of Medical Science in Chhattisgarh, Raipur, India where 21 neonates were given iv paracetamol with a closure rate accounting for 85.7%, and 9 cases were allocated with oral ibuprofen with a closure rate of 77.87%.

In a similar RCT study conducted by Dani et al[11], 52 neonates with HsPDA received iv paracetamol the closure rate was 52 % and that of 49 neonates of ibuprofen group the closure rate was 78%. Paracetamol has less effectiveness in the closure of HsPDA than ibuprofen, However, the constriction rate of the ductus was similar which was confirmed by logistic regression analysis.

In the study conducted by Sunil et al, at Kembagowda Institute of Medical Science,

Bangalore 36 neonates were studied for closure of HsPDA with IV paracetamol of which 27 neonates had PDA closed with closure rate accounting for 74 %, with no significant side effect.

In a study done by Sinha et al, Punjab 10 neonates with HsPDA were given IV paracetamol closure rate accounting to 100%.

In the study conducted by Dang et al[12], which was conducted among 160 neonates of gestational age <34 weeks with paracetamol and ibuprofen group was found to have an 81.2 % closure rate for the paracetamol group and 78.8% closure rate with neonates of ibuprofen group and with lower indicine of side effects like hyperbilirubinemia and gastrointestinal bleeding.

In the case series study conducted by Memisoglu et al[7], the ductal closure with the paracetamol group was found to have 90.0% with no side effects.

In a study conducted by Cakir et al[13], which was done in 101 neonates with IV paracetamol and 169 with IV ibuprofen during Jan 2017 and December 2017 in preterm neonates of GA <32 weeks and birth weight <1500gm showed a closure rate of 74.3 % in the iv paracetamol group and 72.8% in the IV ibuprofen group.

In a study conducted by Valerio et al[14], the PDA closure rate of iv paracetamol accounted for 77.8%.

In a study conducted by Al-Lawama et al[15], where a total of 120 premature infants were given oral paracetamol or oral ibuprofen. The primary closure rate was 69 % in the paracetamol group versus 78% in the ibuprofen group.

In a study conducted by Sancak et al for the treatment of HsPDA in VLBW preterm infants with oral versus intravenous paracetamol has a closure rate of 88% in the oral paracetamol group and 70% in the IV paracetamol group. However, it was not statistically significant.

In a study conducted by El Rahman et al, the closure rate of paracetamol therapy was 80 % and 77% in the ibuprofen group.

CONSTRICTION RATE – DUCTAL DIAMETER

In our study, On comparison of the initial echocardiogram and post-intervention echocardiogram of PDA measurements like Transductal size and LA/AO in the paracetamol and ibuprofen group showed a statistically significant reduction with a p-value of <0.001. There is a statistical difference in LA/AO in post echo after 24 hrs between the paracetamol and ibuprofen group with p-value <0.001. In a study conducted by Risky et al, it was noted that there was a significant reduction in ductal diameter following the course of iv paracetamol for HsPDA with a p-value <0.0001

In a study conducted by Harkin et al, the ductal caliber was found to be significantly reduced with a p-value <0.016.in a study conducted by Terrin et al[16], a significant reduction in median

ductal diameter was noted

COURSE OF TREATMENT

In our study on comparison of the efficacy of closure of IV paracetamol and oral ibuprofen after the first course of treatment, the closure rate for paracetamol was 57.7% and oral ibuprofen was 61.5% with a better closure rate, was not statistically significant (P=0.69). However, the success rate in constricting the DA was 25% vs 25%,(P>0.99). On comparing the efficacy after the second course of treatment, oral ibuprofen had a better closure rate than IV paracetamol of 50% vs 36.3% with a p-value of 0.42 which is not statistically significant. The success rate in constricting the DA after the second course is not statistically different between the paracetamol group and the ibuprofen group(27.7% vs 20%: P = 0.52). Thus out of 52 neonates in both groups, the PDA was closed in (73.07%) of 38 neonates among the iv paracetamol group and (80.7 %) of 42 neonates in the ibuprofen group. With no significant difference in closure rate between IV paracetamol vs oral ibuprofen after the second course of treatment(P=0.35).

In a study conducted by Dani et al[11], the closure rate of paracetamol was 52% and that of ibuprofen was 78%, with p=0.026. However, the constriction rate of the ductus was similar with p=0.202 (81 vs 90%) among the paracetamol vs ibuprofen group respectively.

In the study conducted by Jennifer et al, the closure rate of acetaminophen was 72.5% to 81.2%. In a study conducted by Ahranjani et al[17], on comparison of IV paracetamol versus oral ibuprofen on PDA closure in preterm neonates showed the closure rate of paracetamol is 72% and ibuprofen is 84%,with no statistical significance.

In a study conducted by Ghaderian et al[18], Isfahan University of Medical Science stated that the closure rate of IV acetaminophen was 80% and that of oral ibuprofen was 85%. Both had equal effectiveness in the closure of PDA.

In a study conducted by Meena et al conducted at AIIMS, Jodhpur, Rajasthan, the closure rate of IV paracetamol was 71.43%, and ibuprofen was 77.14%. And showed that IV paracetamol is as effective as ibuprofen in the closure of HsPDA among preterm infants.

In a study conducted by Potsiurko et al, which was conducted in neonates of gestational age less than 32 weeks with birth weight less than 1500gm the incidence of PDA closure rate after the first and/or second course of treatment was 71% in the ibuprofen group and 79% iv paracetamol group with P >0.05.

CLOSURE RATE IN RELATION TO GESTATIONAL AGE:

Out of 48 preterm neonates in both groups, 39 neonates (81.2%) in the paracetamol group and 40 neonates in the ibuprofen group (83.3%) had closure of PDA after the second course. In a study by Al Lawama et al[15], who used oral paracetamol had a primary closure of 69% in the paracetamol group and 78% in the ibuprofen group, and also they did not find a significant difference in short-term neonatal outcomes. Meta-analysis of 5 studies concluded a similar outcome with no significant outcome between the paracetamol and ibuprofen group. (Al Lawama M et al, Oncel my et al, Dang et al, El Mashad et al, and Yang et al, n=559

neonates)[12,15,19,20,21].

CLOSURE RATE IN RELATION TO BIRTH WEIGHT

In the extreme low birth weight category, after the second course of treatment, 11 out of 16 (68.75%) neonates had closure of PDA in the paracetamol group vs 12 out of 18 (66.6%) had closure of PDA in the ibuprofen group. Oncel et al[20] concluded extreme low birth weight neonates had 100% closure with paracetamol whereas in studies done by Terrin et al[16] had 75% and Nadir et al[22] had 71.4% closure with paracetamol in extreme low birth weight neonates. Eun Mi Yang et al concluded that oral ibuprofen had a closure of 81.8% in neonates treated with ibuprofen[21].

LIMITATIONS

- Spontaneous closure confounding the results couldn't be assessed.
- Follow-up of long-term effects including neurodevelopmental outcome was not done.

CONCLUSION

Our study showed that IV paracetamol when compared with oral ibuprofen among term and preterm neonates had similar efficacy, with oral ibuprofen having a slightly higher closure rate but the difference was statistically insignificant. Hence IV Paracetamol can be used as a safe and effective alternative for PDA managed pharmacologically when compared to Ibuprofen.

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