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**EFFICACY OF IBUPROFEN AND PARACETAMOL IN THE MANAGEMENT OF HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN PRETERM BABIES.**

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**ABSTRACT**

**Background:** Preterm babies are at high risk for many complications and multiple morbidities. A patent ductus arteriosus (PDA) is one of the major problem which causes significant alteration in hemodynamics. There are various modalities of closing hemodynamically significant PDA such as surgical ligation and closure by various pharmacological agents like Indomethacin, Ibuprofen and Paracetamol. The present study was performed to explore the use of oral Indomethacin, Ibuprofen and Paracetamol in preterm babies in a rural based tertiary care center which has its own limitations. **Aims & Objectives:** To compare the efficacy, side-effects and outcome of Ibuprofen and Paracetamol in the management of hemodynamically significant Patent Ductus Arteriosus in preterm babies. **Material and Methods:** All neonates admitted at Pravara Rural Hospital during December 2020 to April 2022 with birth weight < 1800 grams were included in our study. All babies fulfilling the inclusion criteria were given either oral ibuprofen or paracetamol and result to each of these along with side effects was monitored for. **Results:** PDA closure rate was maximal with oral paracetamol though the difference in closure rate of these drugs was statistically not significant. Preterm with gestational age lesser than 32 weeks showed better results with oral ibuprofen. Preterm with gestational age more than 32 weeks showed better closure rates with oral paracetamol. **Conclusion:** This study demonstrates that Patent Ductus Arteriosus closure in preterm babies can be attempted with oral use of any of these drugs i.e Ibuprofen and Paracetamol. In our study maximal success was obtained with use of oral paracetamol though the difference in closure rate of both drugs was statistically not significant

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**INTRODUCTION:**

Patent Ductus Arteriosus plays an important role during fetal life as well as have great consequences in neonatal period. During fetal period Ductus arteriosus is necessary for fetal circulation. It shunts blood from the pulmonary artery to aorta. During fetal life low systemic arterial oxygen tension and elevated circulating prostaglandins (PG) from the mother cause vasodilatation and thus keep duct patent. Within a few hours after birth, PaO<sub>2</sub> increases and circulating PG decrease leads to constriction of ductus. [1] Ductus arteriosus develops ischemic hypoxia which transforms the ductus into a non-contractile ligament and thus it no longer remains patent. It usually closes within 72 hours of birth but at times may take several days to completely close.[2]

In preterm infants, the ductus may fail to close within first 72 hours following birth as it fails to develop profound hypoxic ischemia needed to cause remodeling of the artery. There is also increased nitric oxide production from the ductus arteriosus which causes vasodilation. The incidence rates of PDA accounts for 6 - 11% of all congenital heart defects. In babies born at < 28 weeks gestation PDA may be found in upto 60 % of babies. In babies with birth weight < 1000 grams 65% may have PDA at 72 hours after birth and 85% of these require treatment for the same. [3]

A patent ductus arteriosus (PDA) is one of the major problem which causes significant alteration in hemodynamics. The severity of effects a PDA can have depends upon various factors as gestational age, weight of baby, size of duct and other comorbidities.

There are various modalities of closing PDA as surgical ligation and various pharmacological agents like Indomethacin, Ibuprofen and Paracetamol. These pharmacological agents have been used both orally and parenterally at various doses by several workers. There is still no consensus on what is best. There are various constraints due

to cost and availability of a particular pharmacological preparation. [4]

The present study was performed to explore the use of oral Ibuprofen and Paracetamol in preterm babies in a Rural based tertiary care center which has its own limitations.

**AIMS & OBJECTIVES:**

1. To compare the efficacy of Indomethacin, Ibuprofen and Paracetamol in the management of hemodynamically significant Patent Ductus Arteriosus in preterm babies
2. To evaluate the immediate outcomes (upto 72 hrs) and delayed effects of above drugs (upto 2 weeks)
3. To evaluate side effects and safety profile of above drugs

**MATERIALS AND METHOD:**

It was a prospective, randomized, longitudinal observational study conducted during December 2020 to April 2022 in preterm babies with weight <1800 grams at level II NICU, Pravara rural hospital.

**Inclusion criteria:**

- Preterm babies with birth weight less than 1800 grams
- Post natal age of more than 72 hrs
- Duct should be hemodynamically significant (based on defined criteria)
- One of the following ECHO criterias must be present
  - o Duct size > 1.5mm
  - o Left atrium to Aorta ratio >1.5
  - o End diastolic reversal of blood flow in aorta
  - o Poor cardiac function
- Written consent was obtained from parents for inclusion of their baby in study.

**Exclusion criteria:**

- Presence of other congenital anomalies
- Right to left ductal shunting
- Persistent pulmonary hypertension.
- Platelet count <50000/mm<sup>3</sup>

ECHOCARDIOGRAPHY - was done to confirm the presence of PDA. PDA was evaluated by Pediatric Cardiologist and was confirmed to be hemodynamically significant

as per the criteria. Once included in study baby was treated for PDA closure by one of the following drug regimen -

- Ibuprofen (10mg/kg/dose once on day 1 followed by 5mg/kg/dose once each on day 2 and day 3)
- Paracetamol (15mg/kg/dose 8 hourly for 3 days)

These patients were continued on other supportive management also as per the requirement. Response to treatment was assessed at 24 hours, 48 hours and 72 hours

when the babies were monitored in NICU. We repeated Blood investigations as mentioned above at 24 and 72 hours after administration of drugs. Echocardiography was also performed at every 24 hours' interval till closure of ductus. Echocardiography was also performed on 7<sup>th</sup> day, 14<sup>th</sup> day and 28<sup>th</sup> day.

Patients whose duct was found patent after 72 hours were treated with a full course of a different drug.

**RESULTS:**

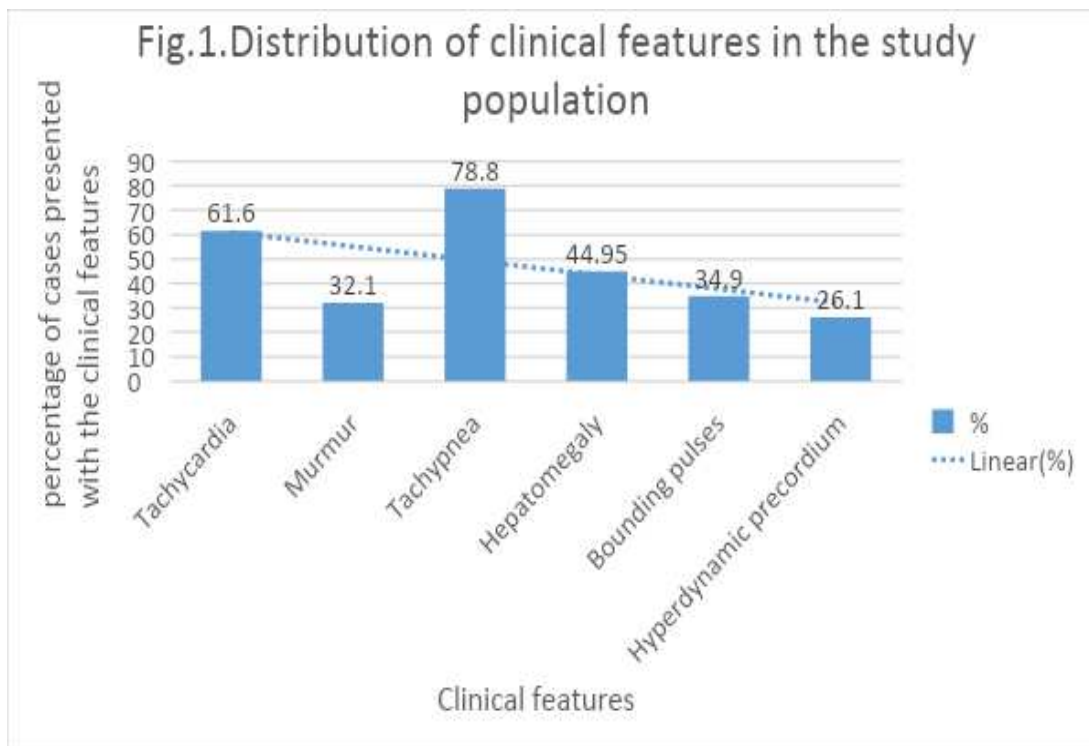
Our study was conducted on total 1450 babies with birth weight < 1800 grams which constituted 1200 inborn babies and 250 outborn babies.

<b>Table no.1. BASELINE CHARACTERISTICS OF STUDIED PATIENTS</b>			
	All babies (n=146)	Group I Ibuprofen	Group II Paracetamol
Gestation age mean (wk)	32.83 (29 - 34)	32.17 (29-34)	34 (30-34)
Birth weight Mean (grams)	1385 (800-1800)	1306 (800-1750)	1411 (810-1800)
Male Gender (n % )	56.16%	50.9%	75.5%
LSCS delivery (n%)	19.8	13.7	20.4
Platelets (mean mm <sup>3</sup> )	1,28000	1,53000	81000

Ibuprofen was given to patients with higher platelet count while Paracetamol was given to babies with low platelet count. Ibuprofen showed drop in platelet count while no such effect was seen with Paracetamol.

Babies in our study ranged from 800 to 1800 grams with mean weight of 1385 gm.

Hemodynamically significant PDA was mostly seen in ELBW (Extremely Low Birth Weight) and VLBW (Very Low Birth Weight) babies. Babies in our study ranged from 28 weeks to 34 weeks of gestation. Incidence of PDA was more common in Early Preterms than Late Preterms.

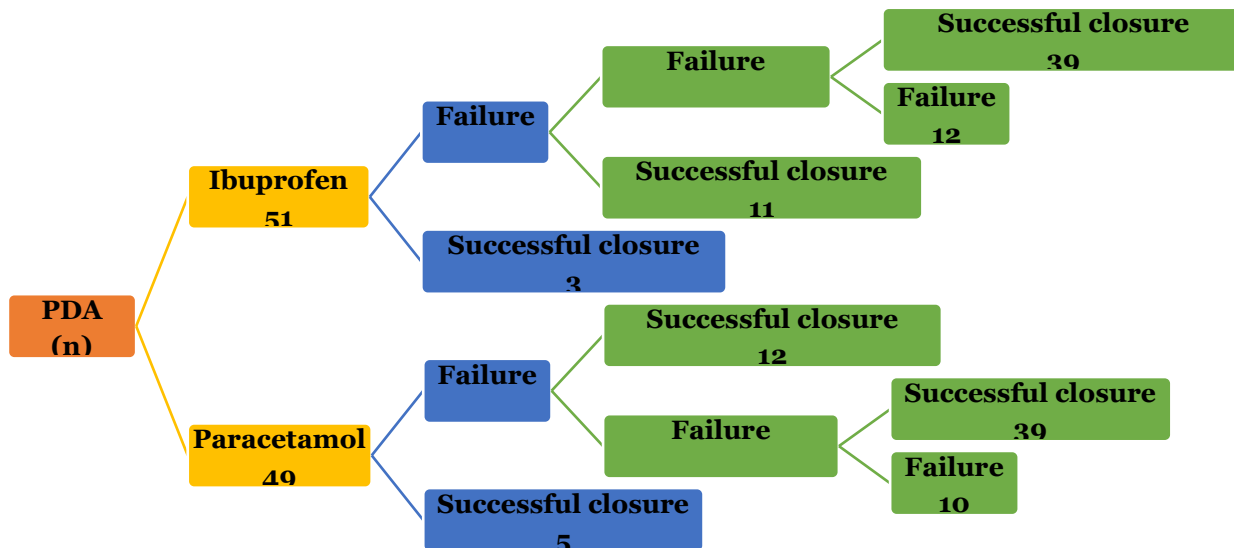


Tachycardia and Tachypnea were the most common signs observed in patients with PDA. Other important clinical findings were audible murmur, hepatomegaly and bounding pulses.

ECHO findings	Ibuprofen group (n=51 )	Paracetamol Group (n = 49 )
LA/ Aorta ratio	1.77	1.67
PDA size ( mm)	2.6	1.9
Impaired LV function ( % )	18	16
End diastolic flow reversal (%)	76	70
Postnatal age (hours)	81.5	80.5

The PDA size ranged between 1.5mm and 3.2mm causing Left Atrial Enlargement resulting in Left Atrium to Aorta ratio of more than 1.5 in all of our babies. Impaired LV Function was observed in 34% of all our babies. End diastolic reversal of blood flow

was seen in more than half of the babies with hsPDA. Babies with hsPDA after 72 hours of birth were included in our study, as PDA may undergo spontaneous closure within first three days.



**Figure no. 2** Describes the success and failure rate of ibuprofen and paracetamol at 24 hours, 48 hours and 72 hours of treatment.

The overall success rate of PDA closure with Ibuprofen and paracetamol in this study was 76.4% and 79.6% respectively. The success rate post 24 hours of medication was more in

the group who received paracetamol and similar trend was seen after 48 hours and 72 hours after medication.

**Table no.3.** Outcome of Study Infants ( n = 146 )

Outcome	Group I (n=51) Ibuprofen	Group II (n=49) Paracetamol
NEC ( % )	17.6	4
IVH (%)	5.8	4.1
ROP (%)	17.64	14.28
Pulmonary Hemorrhage(%)	9.80	6.12
Duration of Ventilation (days)	2.3	2.1
Duration of CPAP(days)	4.1	5.2
Hospital stay total(in days)	16	16
Mortality (%)	1.96	2.04

Neurotizing Enterocolitis (NEC) as a complication was seen more commonly in babies administered oral Ibuprofen and less commonly with groups given Paracetamol. Intraventricular hemorrhage (IVH), Retinopathy of Prematurity (ROP) and pulmonary hemorrhage as a complication showed no major difference in any of the

study groups. No significant difference was seen in duration of ventilation, CPAP or hospital stay between the study groups. There was no obvious immediate mortality in both the groups. All mortality was seen at least 10 days after administration of drugs thus showing no immediate effect on mortality due to any of these drugs.

Gestation age	Less than 32 weeks			More than 32 weeks		
Drugs	Ibuprofen	Paracetamol	Total	Ibuprofen	Paracetamol	Total
No. of cases	34	9	43	17	40	57
PDA closed	27	6	33	12	33	45
Success rate(%)	79.4%	66.6%	76.7%	70.6%	82.5%	78.9%

In preterm babies with gestation age less than 32 weeks, Ibuprofen has better success rate of PDA closure than paracetamol whereas paracetamol has better closure rate than ibuprofen in babies with gestation age more than 32 weeks.

#### **DISCUSSION:**

56% were males while 44% were females. With this sex ratio there appears no specific sex predilection in incidence of PDA in preterm babies. Weight of these babies ranged between 850 and 1800 gm with a mean of 1385 gm. Extremely low birth weight babies i.e babies weighing less than 1000gm constituted around 7 % of our study population. Our youngest patient was of 28 weeks gestation and had weight of 800 grams.

Assessment of PDA was done on the basis of clinical features and echocardiography. Tachycardia and tachypnea were the most common clinical features observed in babies with hemodynamically significant PDA. Bounding pulse and murmur though recognized in several cases were not very helpful in isolating patients with significant PDA. Size of PDA ranged between 1.5mm and 3.2mm with a mean of 2.3mm. The left atrium to aorta ratio was more than 1.5 in all our PDA patients. Left Ventricular function was

affected in 17% of cases while diastolic flow reversal was observed in about 69% of cases.

The dose schedule for Ibuprofen we followed was of 10mg/kg on day 1, followed by 5mg/kg on day 2 and day 3 orally. Similar doses were used in studies by Domelles LV et al [5]. Though ibuprofen has also been used in intravenous schedule, there have been studies showing comparable results with oral and iv route [6]. Paracetamol is being used for PDA closure since 2011. Though this drug has a different mode of action, some studies have shown better results with paracetamol [7] as compared to NSAIDs. Paracetamol was mainly introduced due to its least effect on platelet count as thrombocytopenia/bleeding were important side effects of NSAIDs. Preterm babies are as such at increases risk of bleeding due to these factors and associated co morbidities i.e sepsis and electrolyte imbalances.

We found closure rate of 76.5% with ibuprofen and 79.6 % with paracetamol. Though closure rate was more with paracetamol statistically, the difference was not significant. On further analysis we found that babies with smaller gestational age responded better to ibuprofen whereas babies with higher gestational ages responded better to paracetamol.

<b>Table no. 5.</b> Analysis of effectiveness of these drugs for PDA closure in various studies.										
Studies	Effectiveness in PDA closure									
	Balachand ar et. Al <sup>8</sup>	Jinmia o MS et al <sup>9</sup>	El- Masha d et. Al <sup>10</sup>	Dan i et. Al <sup>11</sup>	Dan g et. Al <sup>12</sup>	Onc el et. Al <sup>13</sup>	Baghe ri et. Al <sup>14</sup>	Yan g et. Al <sup>15</sup>	Kuma r et. Al <sup>16</sup>	Our stud y
Paracetamol	74.5%	37.9%	88%	52 %	81. 2%	96.6 %	91%	70. 5%	78%	79.6 %
Ibuprofen	76.4%	63.8%	83%	78 %	78. 8%	93.6 %	90.3%	76. 7%	81%	76.4 %

On comparison with similar studies, it can be concluded that paracetamol therapy for PDA closure is effective and the efficacy can be correlated with that of Ibuprofen. Many studies suggest that Paracetamol has better efficacy in closing PDA than ibuprofen which can be due to the study population which included term gestation as seen in our study where paracetamol has better closure in term gestation in comparison with pre-term group. The preterm groups had better closure rate with ibuprofen than paracetamol as seen in studies conducted by Jinmiao MS et. Al, Dani et. al, Yang et. Al and Kumar et. Al.

The limitation of our study was number of cases in each group. As our study population consisted of preterm babies with weight less than 1800 grams, total number of patients in each group was less. No statistical inference could be obtained due to lesser number of subjects. Though we had over 17000 new boms in total, finding babies with weight less than 1800 grams and significant PDA a comparative study with statistically significant inference was not possible. Large multicentric studies can only reflect advantages or disadvantage of particular drug regimen.

#### **CONCLUSION:**

This study demonstrates that closure of hemodynamically significant Patent Ductus Arteriosus in preterm babies could be attempted by any of the two drugs Ibuprofen and Paracetamol given orally. PDA closure rate observed was maximal with oral paracetamol though the difference in closure

rate of both the drugs was statistically not significant. PDA, which is the cause of increased morbidity and mortality in premature babies thus should be attempted to close by any of these drugs. Due to lack of resources and poor socio economic status in rural area, paracetamol syrup having low cost, less side-effects and being easily available may be the preferred choice.

**Conflict of interest:** Nil

**Acknowledgement:** None

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