ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 08 | August - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

OUTCOME OF PATENT DUCTUS ARTERIOSUS (PDA) IN PRETERM LOW BIRTH WEIGHT INFANTS

Pediatrics

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ABSTRACT

Introduction: Patent DA after birth results in various adverse outcomes due to left to right shunting of blood leading to pulmonary overcirculation and systemic hypoperfusion. The management of PDA is controversial, and there are diverse approaches to treatment, ranging from very conservative management through to early and aggressive securing of ductus closure, either pharmacologically or surgically. The reason for this variation is that current evidence does not mandate one treatment over other and there is relatively high incidence of spontaneous closure.
Objective: To study the outcome of patent ductus arteriosus in preterm low birth weight infants and to compare the effectiveness of ibuprofen / paracetamol / no treatment in closure of PDA.
Methods: A total of 60 neonates with GA <32 weeks and <1.5kg birth weight were included in study and randomized in three groups "Ibuprofen", "Paracetamol" and "No intervention" with 20 patients in each group. Echocardiography was performed >72 hrs of life and repeated after 10th day of life to look for closure of HsPDA after managing with Ibuprofen, Paracetamol and Conservatively according to intervention group.
Results: Out of 60 neonates, PDA closure rate was 73.33%(n=44/60). Spontaneous closure rate was 55% (n=11/20). In pharmacological intervention group, oral paracetamol was more effective (85%) as compared to oral ibuprofen (80%).
Conclusion: In newborns with birth weight >1 kg and >28 weeks GA, PDA should be managed conservatively. Oral paracetamol is as effective over oral ibuprofen and has a better safety profile.

KEYWORDS

HsPDA, Echocardiography

INTRODUCTION

A premature infant is at high risk for many complications and morbidities. Patent Ductus Arteriosus (PDA) is one of them that often presents with prematurity and can be a major cardiac defect creating variations of altered cardiac function and systemic circulation.

Preterm neonates with PDA are at greater risk for several morbidities, including higher rates for bronchopulmonary dysplasia (BPD), decreased perfusion of vital organs and mortality. A ductal left to right shunt will cause increased pulmonary blood flow resulting in pulmonary edema and decreased lung compliance. This, in turn, will lead to higher ventilator settings and prolonged ventilation.[1]

As a result, management of preterm infants with hemodynamically significant PDAs has been focused on PDA closure and prevention.

In last few years, the controversy with regard to treatment of PDA has increased. The main reason for this is relatively high incidence of spontaneous closure. There are vastly differing practices when it comes to manage Patent Ductus Arteriosus. [2]

More current data indicate that the Ductus Arteriosus (DA) is very likely to close without any intervention in babies born at > 28weeks gestation, who weigh >1kg at birth or who do not have RDS. Because of the lack of conclusive evidence that early PDA closure improves short or long term outcomes, there has been a shift in recent years from an aggressive PDA closure approach to a more expectant attitude, allowing for spontaneous closure in many infants, thus avoiding the need for therapeutic interventions. [3]

PATENT DUCTUS ARTERIOSUS (PDA)

The ductus arteriosus is derived from the distal dorsal sixth aortic arch and is completely formed by the eighth week of gestation. Its role is to shunt the blood from the nonfunctional fetal lung through its connection between the main pulmonary artery and the proximal descending aorta. Normally, the DA closes within 24-72hrs of birth, A PDA, defined as failure of the ductus arteriosus to close within 72 hours after birth. [4]

The expression "Patent DA" describes the situation of a physiological or pathological open DA. If the DA remains open, it results in a progressive increase in pulmonary over circulation and left sided cardiac volume overload. PDA is an old problem with present clinical dilemma. It has been described by Galen in the first century with the description of postnatal circular adaptation. [5]

In healthy full term newborns DA undergoes functional closure between hours followed by anatomical closure in a few weeks. For several reasons, in preterm newborns, spontaneous DA closure often fails or is delayed and has been associated with various short and long term complications.

The reported incidence of PDA in term neonates is only 1 in 2,000 births, accounting for 5%–10% of all congenital heart disease[7]. The incidence of PDA in preterm neonates is far greater, with reports ranging from 20%–60% (depending on population and diagnostic criteria)[10]. The increased incidence of PDA in the preterm infant is attributable to the lack of normal closure mechanisms due to immaturity. Gestational age and weight are intimately linked to PDA in preterm neonates. Specifically, PDA is present in 80% of infants weighing less than 1,200 g at birth, compared to 40% of infants weighing less than 2,000 g at birth[11]. Furthermore, symptomatic PDA is present in 48% of infants with a birth weight of <1,000 gms[12].

RISK FACTORS

Prematurity; Low birth weight; A family history of heart defects and other genetic conditions, such as Down syndrome, increase the risk of having a patent ductus arteriosus; Infants whose mothers had German measles (rubella) during pregnancy; Being born at a high altitude; Newborns having RDS or those who did not receive antenatal corticosteroids.

PATHOPHYSIOLOGY

The ductus arteriosus is an essential component of fetal circulation allowing for communication between the pulmonary artery and the aorta. After birth, it usually closes within 48 h. A persistently patent ductus arteriosus (PDA) is diagnosed when the ductus arteriosus fails to close after 72 hr. Patent ductus arteriosus increases pulmonary blood flow and left atrial and ventricular volumes, and produces a redistribution of systemic blood flow.

Clinical complications are dependent on the degree of left to right shunting through the ductus. Hemodynamic symptoms from a PDA are present in 55–70% of infants delivered below 1000 g or prior to 28weeks of gestation and may require either medical or surgical intervention.[1]

Foetal patency is regulated by Low Oxygen Tension and prostanoids, predominantly prostaglandin E2 (PGE2) and prostacyclin (PGI2). PGE2and PGI2 levels are high in the fetus because of both placental production and diminished clearance by the fetal lungs. [7]

The intimal layer of the DA is irregular and thick with neointimal 'cushions' composed of smooth muscle and endothelial cells. The DA smooth muscle cell (DASMC) is the site of oxygen sensing, whereas the releases vasoactive substances that are important in modulating DA tone.

After birth at term, a postnatal increase in PaO2 and a decrease in circulatory vasodilators i.e. PGE2 and PGI2 induce constriction of DASMCs and consequently, functional closure of the ductus in the newborns. [8]

The successful contraction results locally in a "HYPOXIC ZONE" and triggers cell death which result in vascular re-modelling and anatomic DA closure. Failure to generate the hypoxic zone in preterm infants by insufficient constriction prevents true anatomic closure. [7]

Factors affecting the constriction of DA after birth in preterms[9].
1. Immature smooth muscle isoforms and decreased intrinsic tone.
2. Decreased calcium entry through calcium L-channels.
3. Increased potassium Kca channels which are not regulated by oxygen.
4. Decreased endothelin production.
5. Decreased pulmonary clearance of circulating PGE2.

CONSEQUENCES OF PDA

Blood flow through a PDA in preterm infants results in a left-to-right shunting of blood from the aorta into the pulmonary arteries leading to increased flow through the pulmonary circulation and potential hypoperfusion of the systemic circulation[4].

Clinically meaningful findings are due to a hemodynamically significant PDA and include the following:
- Pulmonary edema
- Pulmonary hemorrhage
- Bronchopulmonary dysplasia (BPD)
- Intraventricular hemorrhage (IVH)
- Necrotizing enterocolitis (NEC)
- Heart failure
- Prolonged ventilator and/or oxygen support.

DIAGNOSIS OF PDA

1. Clinical Examination- Diagnosis of PDA in preterm neonates is typically made according to a high index of suspicion and the presence of characteristic signs and symptoms i.e. Tachycardia; Dyspnoea; Continuous machine like murmur; Left subclavicular thrill; Bounding pulse, widened pulse pressure; Prolonged ventilatory assistance; Low B. P, Differential cyanosis.

2. Chest X-RAY- Cardiomegaly.

3. Echocardiography- Most accurate and diagnostic.

MANAGEMENT OF PDA[13]

The management of PDA in preterm infants includes the following strategies:
- Conservative management with general supportivemeasures alone.
- Pharmacologic closure using cyclooxygenase (COX) inhibitors (e.g., indomethacin, ibuprofen) or acetaminophen (paracetamol).
- Prophylactic COX inhibitor therapy to prevent PDA.
- Surgical ligation.

It remains unclear which approach is most advantageous for preterm infants.

The uncertainties have led to variation in the management of PDA in preterm infants. In many neonatal intensive care units (NICUs), the management of PDA in preterm infants begins with conservative management with subsequent therapeutic interventions focused on PDA closure for symptomatic infants with persistent hemodynamically significant PDAs.

Whereas, in other NICUs, early targeted therapy is given to infants with large hemodynamic shunts.

AIMS AND OBJECTIVES

• To study the outcome of patent ductus arteriosus in preterm low birth weight infants.
• To see the effectiveness of ibuprofen / paracetamol / no treatment in closure of PDA.

MATERIAL & METHODS

This is a hospital based prospective randomized control trial. Preterm neonates born with gestational age <32 weeks and birth weight <1.5 kgs admitted in NICU of Balchikitsalaya, MBGH, Udaipur during the period of one year.

Neonates born with gestational age <32 weeks and birth weight <1.5 kgs were included in the study. Gestational age assessment was done by new ballard chart score and mother's last menstrual period if it was reliable. An informed written consent was taken, by the principal investigator, from either parent on admission.

Neonates having sign and symptoms of PDA clinically were confirmed by echocardiography done after 72 hours of life.

Neonates with hemodynamically significant PDA confirmed by echocardiography were randomly assigned into three groups. Each group had equal number of patients.

On the age of 1st diagnosis of HsPDA, pharmacotherapy was given to neonates in intervention group and conservative management given in no intervention group.

In 'Ibuprofen group' Ibuprofen was given orally as 10mg/kg for the first dose followed by two doses of 5mg/kg given every 24 hours. In 'Paracetamol group' Paracetamol was given orally as 15mg/kg every 6 hours for 7 days. In 'No intervention group' only conservative treatment was given for management of PDA.

2nd echocardiography was done after day 10 of life to look for closure of PDA.

In neonates, where PDA was still open on 2nd Echocardiography, 2nd course of pharmacotherapy was given and assessed clinically for closure of PDA at the end of 2nd course. None of the neonate included in the study underwent surgical ligation for PDA.

RESULTS

Table – 1 Baseline Characteristics Of Trial Population

	NO INTERVENTION		IBUPROFEN		PARACETAMOL	
CHARACTERISTIC	Mean	SD	Mean	SD	Mean	SD
Birth Weight (Kgs)	1.25	0.14	1.16	0.20	1.13	0.12
NI BP (SBP)	49.60	3.20	47.60	5.32	46.85	4.83
(DBP)	32.25	4.20	31.00	4.65	28.95	4.89
No. of LSCS	9.00	52.94%	8.00	47.06%	0	0.00%
Antenatal Steroids	5.00	35.71%	4.00	28.57%	5.00	35.71%
Male: Female	11	9	14	6	13	7
Gestational Age	28.95	1.54	28.20	2.31	27.95	1.61

Table – 2 Characteristics Of HsPDA In Trial Population

	NO INTERVENTION		IBUPROFEN		PARACETAMOL	
	Mean	SD	Mean	SD	Mean	SD
Age at 1st Diagnosis	6.25	1.94	7.20	1.74	6.65	1.84
PDA size at Diagnosis	2.23	0.64	2.69	0.38	2.50	0.43
Age at 2nd Echo.	15.20	3.16	13.70	2.58	15.90	2.67

No. of Closed PDA	11	55%	16	80%	17	85%
No closure of PDA	9	45%	4	20%	3	15%

The mean age at 2nd Echocardiography in 'No intervention' group was 15.20 days, in 'Ibuprofen' group was 13.70 days and in 'Paracetamol' group was 15.90 days. Overall mean age at 2nd echocardiography was 14.93 days.

Table – 3 Closure Of PDA According To Birth Weight

Birth Weight	CLOSED		NOT CLOSED		Total
	No.	%	No.	%	
<1	6	85.71%	1	14.29%	7
1-1.2	13	65.00%	7	35.00%	20
1.2-1.5	25	75.76%	8	24.24%	33
Total	44	73.33%	16	26.67%	60

P=0.50 (NS)

Table – 4 Closure Of PDA According To Gestational Age

Gestational Age(weeks)	CLOSED		NOT CLOSED		Total
	No.	%	No.	%	
24-26	1	100.00%	0	0.00%	1
26-28	16	64.00%	9	36.00%	25
28-30	14	77.78%	4	22.22%	18
30-32	13	81.25%	3	18.75%	16

P=0.53 (NS)

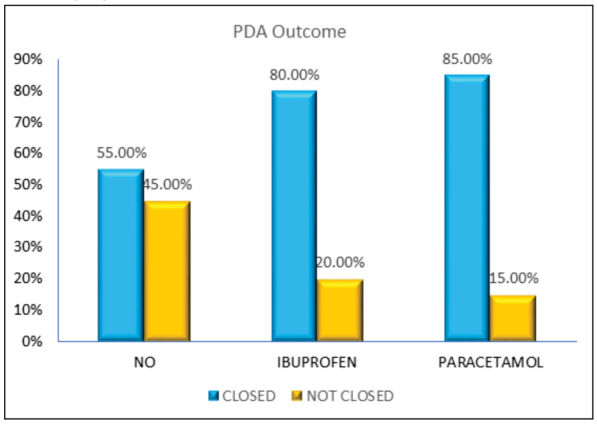

Fig. – 1 Closure Of PDA According To Intervention

P=0.04 (S)

Table – 4 Spontaneous Closure According to Birthweight

	PDA Closed without Intervention	
Birth Weight	No.	%
<1 (n=1)	0	0%
1-1.2 (n=3)	2	66.67%
1.2-1.5 (n=16)	9	56.25%
Total	11	100%

Table – 5 Spontaneous Closure According To Gestational Age

	PDA Closed without Intervention	
Gestational Age	No.	%
24-26(n=1)	0	0.00%
26-28(n=7)	2	28.57%
28-30(n=8)	5	62.50%
30-32(n=4)	4	100%
Total (n=20)	11	55%

DISCUSSION

Patent ductus arteriosus (PDA) is an old problem with present clinical dilemma. The ductus arteriosus (DA) is a vessel that bridge the pulmonary and systemic circulation during fetal life, when oxygenation of fetal blood occurs in the placenta. Its patency is required for fetal survival but is incompatible with postnatal life.[14] Failure of DA closure, called patent DA is the third most common congenital heart defect.[15]Persistence of patent DA after birth results in various adverse outcomes due to left to right shunting of blood leading to pulmonary over circulation and systemic hypoperfusion.

The management of PDA is controversial, and there are diverse approaches to treatment, ranging from very conservative management through to early and aggressive securing of ductus closure, either pharmacologically or surgically. The reason for this variation is that current evidence does not mandate one treatment over other. The main argument in favour of treating PDA is effect on various organ systems due to altered hemodynamics resulting in significant morbidity and mortality. The main argument against active intervention in PDA is significant adverse effects related to both medical and surgical treatment and that PDA is a physiological event in preterm infants and no benefit is derived from its closure.[13]

In our study, 60 neonates fulfilling the inclusion criteria were included and echocardiography was performed after 72 hours of life on clinical suspicion and HsPDA was confirmed based on certain echocardiographic criteria of ductal significance. Thereafter neonates were randomly allocated in three different groups of intervention "Ibuprofen", "Paracetamol" and "No intervention" groups with 20 neonates in each group. A repeat echocardiography was done after day 10th of life to look for closure of ductus in all three intervention groups.

Out of 20 patients in the "No intervention" group, 55%(n=11) were males and 45%(n=9) were females. In the "Ibuprofen" group 70%(n=14) were males and 30%(n=6) were females. In the "Paracetamol" group, 65%(n=13) were males and 35%(n=7) were females. The difference in the sex distribution was statistically not significant(p=0.65).

Out of 60 neonates, 66.67%(n=40) were admitted to the hospital within 24 hours of birth. 18.33%(n=11) neonates admitted on 2nd day of life while 15%(n=9) neonates were admitted after day 3 of life but <7days. The mean age on admission was 1.73 days. 11.67%(n=7) neonates were in the <1kg birth weight group, 33.33%(n=20) neonates were in the 1-1.2kg birth weight group, 55%(n=33) neonates were in the 1.2-1.5kg birth weight group. The majority of the neonates were in the 1.2-1.5 kg BW group. The mean birth weight was 1.18kg. 41.67%(n=25) neonates were born with gestational age between 26-28 weeks, 30%(n=18) neonates were born with gestational age between 28-30 weeks, 26.67%(n=16) neonates were born with gestational age between 30-32 weeks and 1.67%(n=1) neonate was born with gestational age between 24-26 weeks (Table-1).

Table-2 shows variable characteristics in all three study groups. The mean birth weight in the 'No intervention' group was 1.25 kg, in 'Ibuprofen' group mean birth weight was 1.16kg and in 'Paracetamol' group mean birth weight was 1.13 kg. The difference in mean BW according to intervention was statistically not significant.

The mean GA in 'No intervention' group was 28.95 weeks, in 'Ibuprofen' group was 28.20 weeks and in 'Paracetamol' group was 27.95 weeks. The mean NIBP in 'No intervention' group was 49.60/32.25mmHg, in 'Ibuprofen' group was 47.60/31mmHg and in 'Paracetamol' group was 46.85/28.95mmHg.

The male: female ratio in 'No intervention' group was 1.22:1, in 'Ibuprofen' group was 2.33:1 and in 'Paracetamol' group was 1.85:1. The mean GA in 'No intervention' group was 28.95 weeks, in 'Ibuprofen' group was 28.20 weeks and in 'Paracetamol' group was 27.95 weeks. All the baseline characteristics in the study groups were comparable with no statistically significant difference noted.

Characteristics of HsPDA in the studied population. Mean age at 1st diagnosis of PDA was 6.25 days in the 'No intervention' group, 7.20 days in the 'Ibuprofen' group, and 6.65 days in the 'Paracetamol' group. The mean age at 2nd echocardiography in 'No intervention' group was 15.20 days. In 'Ibuprofen' group was 13.70 days and in 'Paracetamol' group was 15.90 days. Overall mean age at 2nd echocardiography was 14.93 days.

Out of 60 neonates in the study, the cumulative rate of PDA closure was 73.33% (n=44). The closure of PDA was differed by different Birth weight strata: Out of 33 neonates in the 1.2-1.5kg birth weight group, PDA was closed significantly in 25(75.76%) of them. Out of 20 neonates in the 1-1.2kg birth weight group, PDA was closed in 13(65%) of them. Out of 7 neonates in the <1kg birth weight group,

PDA was closed significantly in 6(85.71%) of them (Table 3).

In our study closure of PDA was also differed by gestational age of neonates. Out of 25 neonates in the 26-28 weeks gestational age group, PDA was closed in 16(64%) of them. Out of 18 neonates in the 28-30 weeks of gestational age group, PDA was closed in 14(77.78%) of them. Out of 16 neonates in the 30-32 weeks gestational age group, PDA was closed in 13(81.25%) of them. 1 neonate was in 24-26 weeks gestational age in which PDA was closed after intervention (Fig. 1). Results of this randomized control trial shows that out of 20 neonates in 'No intervention' group, PDA was closed spontaneously in 11(55%) of them. Out of 20 neonates in the 'Ibuprofen' group, PDA was closed in 16(80%) of them. Out of 20 neonates in 'Paracetamol' group PDA was closed in 17(85%) of them. The difference in this distribution was statistically significant (p=0.04).

M. Vasudha[16] et al in their study reported the closure rate in 'Ibuprofen' group as 77.14% and in 'Paracetamol' group as 71.43%. Swaroop D et al concluded in their study the closure rate of paracetamol to be 100%. In a study by Souvik Mitra,[17] the highest closure rate was in oral ibuprofen group. Se In Sung et al reported the closure rate with ibuprofen as 89% while with no intervention, the closure rate as 82%.

Results of our study shows that spontaneous closure rate of PDA was 55%(n=11/20). PDA closure differed according to different birth weight and gestational age group. Previous studies have demonstrated that GA and birth weight are correlated with the likelihood of spontaneous ductal closure, the smaller and more immature the infant, the less likely the DA will close spontaneously.

In our study, spontaneous closure rate was highest in the 1.2-1.5kg birth weight group (81.82%). In 1-1.2kg birth weight group, spontaneous closure rate was 18.18% (Table 4). Our observation were in congruence with Sheri L et al who reported significantly higher rate of spontaneous DA closure (67%) in BW>1kg. In <1kg birth weight group, no spontaneous closure occurred till day 15 of life. This observation disagrees with Koch J[18] who concluded that DA closed spontaneously by day of life 10 with BW <1kg. Spontaneous closure of DA in 30-32weeks in GA group was 100%, in 28-30 weeks GA group was 62.5%, in 26-28 weeks GA group was 28.57%. No spontaneous DA closure occurred in 24-26 weeks (Table 5).

In our study, the highest proportion of closed DA was in 'paracetamol' group (85%). Rania A El-Farrash et al[19] conducted a randomized case control study with 60 preterm infants with GA <34 weeks and concluded that oral paracetamol group (93.3%) has higher rate of DA closure as compared to oral ibuprofen group (80%). Similar results were observed by Souvik Mitra et al[17] and Dan Dang et al[20] who stated that DA was closed in 81.2% in paracetamol group compared with 78.8% in ibuprofen group, with no significant differences in clinical side effects or complications.

CONCLUSION

It is evident that spontaneous closure of HsPDA is delayed as compared with pharmacological intervention. Among neonates with BW <1 kg and <28 weeks gestation, HsPDA is less likely to close spontaneously.

In those preterm neonates who require prolonged respiratory support or on mechanical ventilation, PDA should be closed to avoid further complications. In newborns with birth weight >1 kg and GA >28 weeks, PDA should be managed conservatively unless symptomatic and causing cardiovascular decompensation. HsPDA increases the mortality and complications of prematurity especially in those who are <28 weeks gestation. So early targeted treatment should be reserved in such extremely premature neonates.

Oral paracetamol is as effective as oral ibuprofen in terms of closure of HsPDA and has a better safety profile. Thus, paracetamol can be used as first line drug treatment for pharmacological management of HsPDA.

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