A DISSERTATION ON

AN OBSERVATIONAL STUDY ON ORAL PARACETAMOL IN CLOSURE OF HEMODYNAMICALLY SIGNIFICANT PDA IN PRETERM NEONATES LESS THAN 34 WEEKS

Submitted to

THE TAMILNADU DR. M. G. R. MEDICAL

UNIVERSITY, CHENNAI

In partial fulfillment of the regulations for the award of

M. D. DEGREE IN PAEDIATRICS
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Government Theni MedicalCollege Hospital

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INTRODUCTION

Patent Ductus Arteriosus is a major morbidity seen in preterm neonates with incidence being inversely related to gestational age and birth weight. Studies report incidence of 15-40% in Very Low Birth Weight <1500 gram whereas in preterm Extremely Low Birth Weight neonates <28 weeks,<1000 gram the incidence as high as 50-65%.[1,2] The closure of ductus arteriosus (DA) following birth is an important component of transitional circulation, thereby directing the entire right ventricular output to the lungs to facilitate its oxygenation.Contrary to this the ductus arteriosus acts as conduit for diverting the partially oxygenated blood to support systemic circulation in fetus.

The presence of PDA has significant effects on myocardial functions as well as systemic and pulmonaryblood flow. shunting from systemic to pulmonary circulation called *ductal steal may lead to systemic hypoperfusion and pulmonary overperfusion.* Hence hemodynamically significant PDA has negative effect on circulation of vital organs. Hemodynamically significant PDA is associated with a prolonged ventilation need and carries an increased risk of serious morbidities such as intraventricular haemarrhage, acute pulmonary haemarrhage, necrotising entercolitis, chronic lung disease, bronchopulmonary dysplasia and increased mortality.

Until recently, active PDA closure was considered beneficial.[3,4,5] Cyclooxygenase inhibitors, ibuprofen or indomethacin, are used as first line of treatment to promote ductal closure.[6,7]Surgical closure may be indicated if pharmacological therapy fails, or when contraindications to cyclooxygenase inhibitors are present[8,.9] The theoretical rationale for PDA treatment is unquestionable, but trials showing long-term benefits from PDA treatment are scarce.[3]Moreover, surgical closure

has been associated with adverse outcome though it has been debated that these studies have had problems with confounding by indication.[10-14]On the other hand, spontaneous PDA closure has recently been shown to be high, even among the most immature infants.[15-18] Early treatment of PDA might thus expose infants, in whom ductus ultimately would close spontaneously, to unnecessary treatment with potent and potentially toxic drugs.

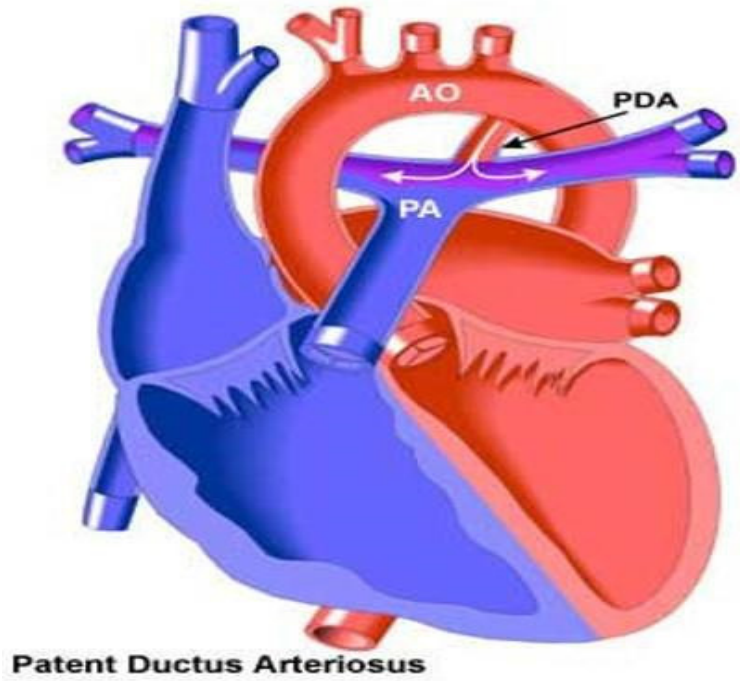
Ibuprofen and indomethacin are the current standard drugs for closure of a haemodynamically significant patent ductus arteriosus (PDA) apart from surgical ligation. These drugs have many adverse effects involving the gut, kidneys and the pulmonary vasculature. Previously in case of ibuprofen and indomethacin contraindication surgical ligation is the only option.

The role of paracetamol as an alternative treatment for closure of hsPDA has gained attention in recent years because of its superior safety profile in comparison to cyclooxygenase inhibitors Several recent observational studies and randomised controlled trial (RCT) studies also show that paracetamol may be as effective as ibuprofen and indomethacin for closing PDA of preterm infants, but with fewer side effects. However evidence regarding the indications, dosage, effectiveness, and safety including the long-term effects of paracetamol are still incomplete or lacking. In this study we attempted to study the efficacy of paracetamol in hemodynamically significant PDA in preterm neonates where ibuprofen is contraindicated.

REVIEW OF LITERATURE

Ductus arteriosus is the vascular communication connecting trunk of the pulmonary artery to the proximal descending aorta and represents the fundamental shunts of prenatal life circulation. [19]This duct usually closes automatically soon after birth.Ductus arteriosus remains persistent in upto 60% of preterm infants and its incidence is inversely related to birth weight and gestational age.

Functionally, the DA provides a bypass of the pulmonary blood flow to the descending Ao. i.e. the blood streaming from the placenta to the right atrium through the foramen ovale, to the left atrium and further to the left ventricle and out to the Ao. From the right ventricle the blood flows to the PA and as the resistance is high there, it flows through the open duct to the descending Aorta. [20]



Patent Ductus Arteriosus

A four chamber view of the heart with the right and left atriums and right and left ventricles communicating with the great vessels, the pulmonary artery (PA) and aorta (Ao). The ductus arteriosus (DA) is a vessel connecting the PA and the Ao.

In healthy full-term newborns DA generally undergoes functional closure between 24 and 72 hours of life. The closure of the duct begins from the pulmonary end. In anatomical closure of DA is generally complete by second to third week after birth through the evolution into the structure called ligamentum arteriosum.

A patent ductus arteriosus is when the DA closure is delayed . Ductal closure may be delayed in infants born with duct dependent congential heart diseases or persistent pulmonary hypertension for example due to meconium aspiration, congenital sepsis or asphyxia.[20] Furthermore, a reason for a PDA can be congenital, i.e. an anatomical PDA.[21] When the PDA has hemodynamic consequences it is defined as hemodynamically significant PDA (hsPDA).[21,22]

It has become evident that genetics are a contributing factor in ductal patency in term and probably in preterm infants also.[19,23] In term infants an incidence of approximately 0.5% has been described and it is more common in females than males.[24]

- Ductus arteriosus (DA): It is normal to be born with an open DA and during normal transition it closes spontaneously within the the first few days.
- Patent ductus arteriosus (PDA): The delayed process of closure results in a PDA.
- Hemodynamic significant ductus arteriosus (hsPDA): A PDA with hemodynamic consequences on the heart and circulation is defined as a hsPDA

MECHANISM OF DUCTAL CLOSURE IN TERM AND PRETERM INFANTS

Fetal life

During later stages of pregnancy, the vasodilating prostaglandins (PG), especially prostaglandin E2 (PGE2)maintain the ductus arteriosus (DA) open.[20]

At birth in full term infants

Ductal closure is described as occurring in two phases: functional and anatomical, with the former taking place during the first hours of life and the latter in the first week(s) of life.[20] The mechanisms conducting the closure are initiated and balanced by many factors.

Functional closure occurs when the smooth muscle cells in the vessel wall constrict and the lumen narrows determined by the following factors such as

- oxygen tension
- levels of vasoconstrictors (such as endothelin and catecholamines)
- levels of vasodilators (such as PGs and nitric oxide (NO))
- Intraluminal pressure in the DA [19,25,26]

After birth there is a decrease in circulating PGE2 due to increased removal by the lungs together with the cease in supply from the placenta once the umbilical cord is clamped.[20]Also, the PGE2 sensitivity in the ductal wall decreases. Furthermore, in the initial functional closure, platelets are believed to have a role in "sealing" the DA, which further promotes closure.[19,27] Anatomical closure is the remodeling of the lumen and vessel wall tissue, which follows the initial functional constriction of the duct.[28,29]

The mechanisms involved are:

- Connective tissue proliferation
- Lumen obstruction – intimal proliferation as well as the disruption and proliferation of subintimal layers cause the sealing of edema
- Edema – subendothelial edema
- Muscular coil spasm due to local vasoactive amine
- Emboli blocking the ductus
- Infolding and ingrowth of endothelium
- Migration of undifferentiated smooth muscle cells.

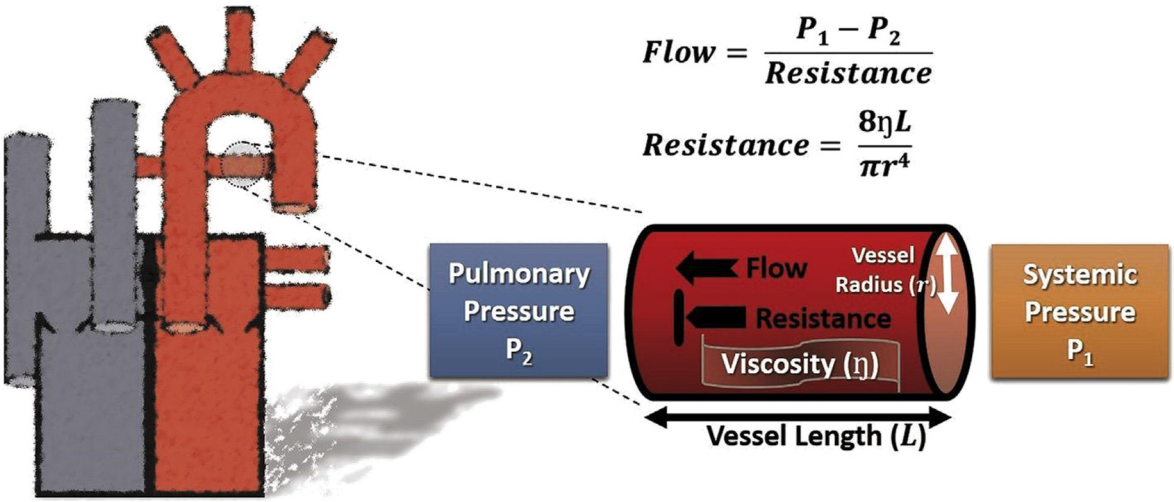
At birth in preterm infants

In preterm infants, especially the most immature group, the normal signals impaired and the mechanisms for ductal closure are delayed .[30,31]It has been shown that the DA in preterm infants is more sensitive to the vasodilating effects of PGE2 as well as NO.[32] This impairs the anatomical closure, as the vasoconstriction of the vessel is not prominent enough to induce the anatomical changes necessary for permanent closure.[19]

Term infant with PDA – there is a deficiency of mucoid endothelial layer and the muscular media of the ductus. Spontaneous closure is rare.

Preterm with PDA – The PDA has a normal structural anatomy in preterm babies.the patency may be due to immaturity and hypoxia.

Determinants of the flow through the duct.. Ref. Smith et al. Seminars in Fetal and Neonatal Medicine. 2018.(23)245-249.



Resistance is dependent on the vessel radius, the length, and the viscosity of the blood that flows through the vessel.[15] For the DA, the pulmonary and systemic pressures are the governing factors for the pressure difference and flow direction through the DA.[20]Furthermore, vasoconstriction and vasodilatation of the DA change the radius.[20] These constantly changing dynamics factors make estimation of the shunt through the duct difficult.

- The postnatal decrease in pulmonary resistance results in changes of ductal flow from purely right to left in utero, to bidirectional during the transitional period, and purely left to right there after.[20]
- In full term infants, smooth muscle cells in the ductal wall react to the oxygen tension changes postnatally, where higher oxygen tension triggers ductal closure.[19]

Infants born extremely and very preterm are often very sick after birth and the postnatal transition can differ from full term infants. Here are a few examples of the dynamic nature of the flow through the duct in this group.

- Directly after birth or during the first hours of life, many preterm infants develop respiratory distress syndrome and are treated with surfactant. As the lung opens and aerates, the pulmonary resistance decreases and the shunt, often bidirectional or right to left, changes to left to right through the duct.[34]The ventilator strategy on invasive and non-invasive ventilation such as continuous positive airway pressure (CPAP) with the degree of positive end expiratory pressure (PEEP) can modulate the ductal shunt, i.e. higher PEEP decreases the shunt from left to right with increased pulmonary pressure.[35]
- Vasoactive mediators affect the ductal constriction.[19] It has been described that in context with infections, the vasoactive inflammatory mediator; tumor necrosis factor alfa (TNF-alfa) is associated with delayed duct closure and even re-opening.

DIAGNOSIS OF PDA

CLINICAL DIAGNOSIS OF PDA

Signs of a significant PDA are not always evident during the first days but appear later. In the definition proposed by McNamara and Sehgal in 2007 a hemodynamic significant PDA fulfills both echocardiographic and clinical criteria.[22]The clinical criteria most often used are:

1. Signs of significant left-right shunt: hyperdynamic pulsatile precordium,bounding peripheral pulses and wide pulse pressure>25mmhg
2. Signs of systemic underperfusion: poor peripheral pulse volume,prolonged CRT,decreased urine output,deranged renal function and hypotension.
3. Signs of pulmonary overperfusion: abnormal weight gain,increase in liver size,new onset or increase in ventilatory requirements that primarily involve PEEP/PIP and Fio2 ,respiratory acidosis,pulmonary crepitations and haemarrhagic pulmonary edema

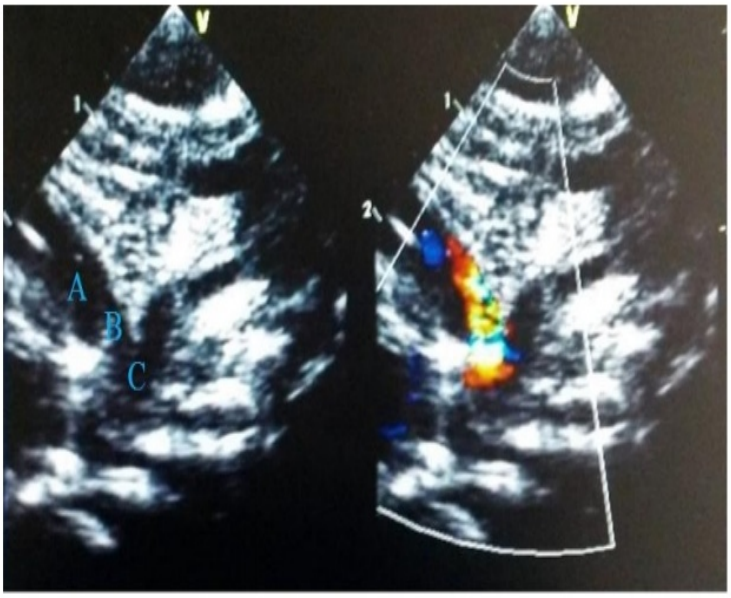
However the diagnosis PDA based on clinical features has mainly two pitfalls i.e.low sensitivity and delay in detection. Moreover these signs were insensitive (sensitivity of 30-40%) and had poor predictive value(60%)

ECHOCARDIOGRAPHIC MARKERS OF PDA

Echocardiography remains the golden standard for confirming the presence of a PDA.[37]Furthermore, by using echocardiographic surrogate markers, it is possible to estimate the excessive pulmonary circulation and systemic hypoperfusion due to the ductal shunt.[36]

Ductal view on two dimensional echocardiography and color Doppler.

2.5 ECHOCARDIOGRAPHIC DIAGNOSTICS OF THE PDA



A. Pulmonary artery
B. Ductus Arteriosus
C. Aorta

The features suggestive of patent ductus arteriosus include:

- 2-D color Doppler –short axis view : direct visualization of the ductus. In 2-D shortaxis view,in the presence of a patent ductus,the appearance is classically described as ‘three legged stool’appearance. In the color Doppler there is a continuous flare in the MPA.
- Short axis view , pulsed Doppler : turbulence in the MPA due to left to right shunt jet flowing into MPA
- Four chamber view: flowing of interatrial septum into right with enlarged left atrium and left ventricle
- Long axis view: LA:Ao ratio > 1.5:1
- Raised left ventricular stroke volume

However these signs only establish the presence of a patent ductus and do not reflect the hemodynamic significance of the ductus. The echocardiographic markers indicating the hemodynamic significance and degree of shunting have been well

described in a recent review by Sehgal,et al.The markers can be categorized into ductal size and flow characteristics, signs of excessive pulmonary circulation and systemic hypoperfusion (end-organ steal).

Table 1: Echocardiographic markers of hemodynamically significant PDA

Echocardiography parameter*	No PDA	Mild	Moderate	Large
Features of ductus arteriosus				
Trans ductal diameter (mm)	0	<1.5	1.5-3.0	>3.0
Ductal velocity Vmax (cm/sec)	0	>2	1.5-2.0	< 1.5
Antegrade PA diastolic flow (cm/sec)	0	>30	30-50	>50
Pulmonary overcirculation				
Left atrial /aortic root width ratio	1.1 ± 0.2	<1.4:1	1.4-1.6	>1.6:1
Left ventricular/ aortic root width ratio	1.9 ± 0.3	-	2.2 ± 0.4	2.27± 0.27
E wave/ A wave ratio	<1	<1	1-1.5	>1.5
IVRT(ms)	<55	46-54	36-45	<35
LVSTI	0.34 ± 0.09	-	0.26 ± 0.03	0.24 ± 0.07
Systemic hypoperfusion				
Retrograde diastolic flow (as % of forward flow)	10	< 30	30-50	> 50
Aortic stroke volume (ml/kg)	≤2.25			≥2.34
Left ventricular output (ml/kg/min)	190-310	-	-	>314
LVO/SVC flow ratio	2.4 ± 0.3	-	-	4.5 ± 0.6

** LVO = left ventricular output, SVC = superior vena cava, LVSTI = left ventricular stroke volume index, IVRT =* isovolumic *relaxation time, PWD = pulse wave Doppler, CWD = continuous wave Doppler, PA =pulmonary artery. (Empty boxes implies data not available)*

BIOMARKERS AS A DIAGNOSTIC TOOL FOR PDA

Recently, the cardiac biomarkers of most interest are N-Terminal fragment-pro-Brain Natriuretic Peptide (NT-proBNP) and cardiac Troponin T (cTnT). The most well-studied biomarkers are the peptide NT-proBNP which is biologically inactive secreted together with the biologically active natriuretic peptide BNP.[38] They are released in response to ventricular and atrial wall stretching and used generally as markers of congestive heart failure.

cTnT is a protein in the cardiac muscle that is secreted in response to myocyte injury.[38]It has been associated with respiratory disease morbidity (pulmonary hypertension, RDS) and circulatory failure in infants, caused by for example PDA, both in term and preterm infants.[39,40]It is used as a marker of perinatal asphyxia in term infants.[41] It has been postulated that the correlation between PDA and cTnT levels stems from myocardial ischemia due to the ductal steal of blood flow affecting the coronary arteries especially in preterm infants.[42]

OTHER : Chest radiograph findings are non specific and features like cardiomegaly and pulmonary plethora occurs when significant PDA leads to congestive cardiac failure.

Postnatal age for PDA treatment

The optimal postnatal age for PDA closure is unclear. The timing of medical treatment has ranged from prophylactic and early treatment at the very first postnatal days to later treatment at several weeks or even months of age.

Prophylactic and early treatment

Prophylactic treatment of PDA refers to closure of the ductus before 12− 24 hours of life and before the onset of symptoms in all at risk preterm infants. Previous trials of prophylactic indomethacin and ibuprofen seemed to decrease the risk of PDA but caused significant side effects and did not decrease overall morbidity and mortality.

Late treatment (symptomatic therapy)

The criteria and postnatal age for late treatment vary, but late treatment refers to treatment after 7 days of life.

PDA AND NEONATAL OUTCOMES

Prolonged condition of PDA in preterm can be associated with important complications, such as severe RDS, prolonged need for assisted ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), renal function damage, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, or death [43,44,45,46]

These conditions depend on the magnitude of left-right shunt volume through PDA, regulated by the balance between PDA dimension and arterial resistance fall in the pulmonary circle during the early hours of postnatal life and resulting in lung hyperflow and development of pulmonary congestion and edema. If this condition persists, deterioration of respiratory function can occur. The impact of this "ductal steal" on systemic circulation causes a reduction in cardiac output increasing, the mechanism that allows facing the rising in systemic resistances of postnatal period. This condition can lead to vital organs perfusion impairment, such as brain, kidney, and bowel[48,49].

IVH

The association of significant ductal steal shortly after birth followed by brain hypoperfusion, with risk of IVH is known.[50]

Pulmonary hemorrhage

Rapid increase in pulmonary blood flow is thought to be the underlying cause of pulmonary haemarrhage.In a randomized trial of early targeted PDA treatment, where an early echocardiography is performed to confirm a PDA there was a decrease in pulmonary hemorrhages in the group receiving early PDA treatment with indomethacin.[51]

NEC

The ductal steal leads to ischemia in the gut of infants with a hsPDA. The association of PDA and later NEC has not been easy to study, but an association has been described.[52,53]

Bronchopulmonary dysplasia (BPD)

BPD is most commonly defined in PDA studes as oxygen need at 36 weeks postmenstrual age (PMA).[54] Previous studies have suggested that early PDA treatment leading to PDA closure is beneficial in terms of decreased pulmonary morbidity and development of BPD.[55,56] . In a randomized trial of early versus later ibuprofen treatment, Sosenko et al. did not find any differences in BPD incidence or mortality between the two groups.[57] Moreover, in the Trial of Indomethacin Prophylaxis in Preterm infants, indomethacin prophylaxis reduced the incidence of PDA, but did not change the BPD incidence[58].

Neurodevelopmental outcome

Various cohort studies have shown an association between PDA treatment and later adverse neurodevelopmental outcome.[10,11,13] PDA surgery, especially, has been associated with adverse neurodevelopmental outcome but this is constantly debated.[61]Neurodevelopmental outcomes are most often determined with Neurodevelopmental Impairment (NDI) as defined by Moore et al[59]. NDI is categorized into none, mild, moderate or severe and includes hearing impairment, visual impairment, presence of cerebral palsy (as defined by Gross Motor Function Classification System) and cognitive assessment according to the appropriate test for age.[59] A common age to investigate neurodevelopmental outcome is 18-24 months using Bayley Scales of Infant Development.[60]

TREATMENT STRATEGIES

The pharmacological basis for medical therapy is the use of non selective cyclo-oxygenase (COX) inhibitors, which inhibits prostaglandin synthesis and causes ductal constriction. The two most widely used non selective COX inhibitors are indomethacin and ibuprofen**.**Treatment success is about the same (70−80%) for both ibuprofen and indomethacin.

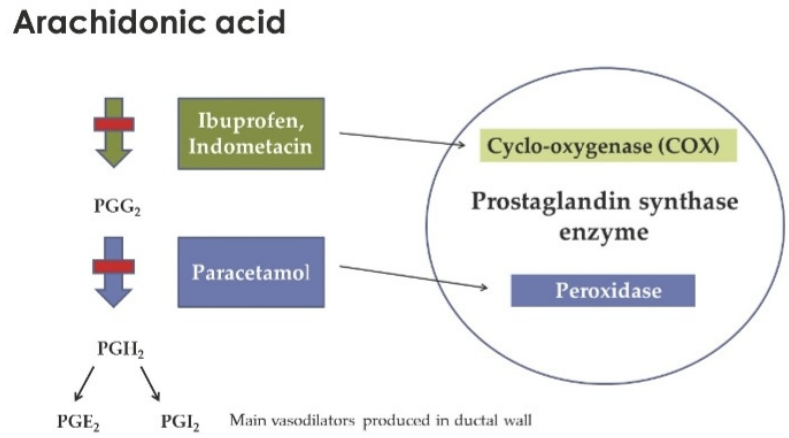


Fig. 1. Ibuprofen, indomethacin, and paracetamol in the arachidonic acid pathway. COX-inhibitors ibuprofen and indomethacin inhibit the cyclooxygenase (COX) part of prostaglandin. Paracetamol inhibits the peroxidase moiety of the enzyme, decreasing prostaglandin synthesis. Both sides must be active in the prostaglandin synthase enzyme to have the catalysing action.

Indomethacin versus Ibuprofen

Among nonselective COX inhibitors, intravenous (iv) indomethacin was the first drug used for PDA treatment, presenting a closure rate of about 70–85% without any other short-term benefits [33] Since indomethacin has been used as a prophylaxis in PDA management, it has been shown to reduce the incidence of intraventricular hemorrhage (IVH ≥grade 3 by 30%) and severe pulmonary hemorrhage by 35%, symptomatic PDA development, and necessity of surgical ligation without effects on mortality or long-term neurodevelopmental outcome .

Instead of this previous evidence, the recent prospective double cohort study of Liebowitz and Clyman [62], published on 2017, has pointed out also a protective effect of prophylactic indomethacin on development of BPD and death, instead of delayed PDA treatment (after 7 postnatal days) in extremely premature neonates.However, for its high vasoconstrictor power, this drug has been associated with several side effects such as impairment in renal function until acute or chronic renal failure, oliguria, proteinuria, hyperkalemia , cerebral white matter damage, NEC, intestinal perforation (especially when coadministered with corticosteroids), and platelet dysfunction

Recognizing these indomethacin related side effects, ibuprofen was subsequently introduced either orally or in iv manner. Ibuprofen shares with indomethacin the mechanism of action and the efficacy in PDA closure , but its lower vasoconstrictor effect leads to a reduced impact on microcirculation and consequent less impairment of renal function; this difference could be partly determined by a preferential effect of indomethacin on COX-1 instead of COX-2 but also by other mechanisms not exactly known .

However, ibuprofen is not free from other significant side effects, such as pulmonary hypertension and hyperbilirubinemia [4,39] .Now it represents the first-choice drug for hsPDA treat-ment, but it is not recommended in prophylaxis because of the lack of efficacy in reducing intraventricular hemorrhage incidence, unlike indomethacin [26,38,39]

The Cochrane meta-analysis[63] comparing ibuprofen with indomethacin in preterm <37 weeks gestation or low birth weight (<2500 gm), involving 20 trials enrolling 1092 infants, there was no difference in the failure of duct closure. The ibuprofen group had significantly lower serum creatinine levels and decreased

incidence of oliguria. There was 32% reduction in NEC in ibuprofen group and no difference in other outcomes like mortality, reopening rate of PDA, need for surgical ligation of PDA, duration of ventilator support, chronic lung disease (CLD), IVH or ROP.

A recent randomized trial of Demir et al.[64], published on January 2017, has evaluated the ibuprofen intrarectal way of administration, which became as effective as the oral way in VLBW neonates with hsPDA. After treatment, in both groups the authors demonstrated higher levels of Cystatin-C, a biomarker of glomerular filtration which can suggest nephrotoxicity, indicating the necessity of a closely clinical observation especially in patients with a damaged renal function.

El-Mashad et al[65] recommend the administration of low ibuprofen doses, underlying its inhibitory effect on hepatic glucuronidation of bilirubin and its high albumin binding affinity, which can increase the risk of bilirubin encephalopathy .

Recommendation on dosage

Dosage of Indomethacin and Iboprufen for pharmacological treatment of a PDA[16]		
Indomethacin	IV Infusion over 30 min	▪ Loading dose: 0.2 mg/kg/dose ▪ Subsequent doses (adjusted as per postnatal age) • <2 days: 0.1 mg/kg/dose 12 hourly x 2 doses • 2-7 days: 0.2 mg/kg/dose 12 hourly x 2 doses • >7 days: 0.25 mg/kg/dose 12 hourly x 2 doses
Iboprufen	IV or oral	▪ Loading dose: 10 mg/kg/dose ▪ Subsequent dose: 5mg/kg/dose 24 hourly x 2 doses
• *Following the first course, a second course with same dosage could be used in case of persistent PDA needing treatment or re-opening of the ductus with symptoms.* • *Failure of medical treatment: Persistence of hemodynamically significant ductus or reopening despite two courses of treatment defines failure of medical treatment.*		

CONTRAINDICATION

- Renal: Urine output< 0.6 ml/kg/h
- blood urea > 40 mg/dL, creatinine >1.8 mg/dL §
- Bleeding: Bleeding from IV sites, skin bleeds, gastrointestinal bleeding, enlarging or evolving intraventricular hemorrhage (IVH),
- platelet count < 60,000/mm3
- Gastrointestinal: necrotizing enterocolitis; blood in stool

NEPHROTOXICITY AND NSAIDS:

Recent data suggest that prematurity incomplete nephrogenesis, in addition to nephrotoxic administered toxins, could predispose to chronic kidney damage (CKD) [66,67,68].The nephrotoxic effect of NSAIDs is related to prostagl-andin important role during kidney and cardiovascular system adaptation after birth

Prostaglandins neonatal circulating levels become higher than in successive life, since these mediators act as afferent arteriolar vasodilators and regulators of renal water clearance, facing the postnatal systemic resistances vasoconstriction. For these reasons, the inhibition of prostaglandin synthesis negatively affects renal blood flow and glomerular filtrate, generally resulting in transient oliguria [69].

Moreover, neonatal kidney, not completely developed, is susceptible to the lack of prostaglandins and its maturation process closely depends on these mediators. This has been demonstrated both prenatally and in the postnatal period but appears more pronounced in preterms, whose urinary excretion of prostaglandin E2 (PGE2) and prostaglandin I2 (or prostacyclin) becomes higher than in neonates born with normal

GA or with a month of postnatal life [70,71] During studies conducted to evaluate NSAIDs renal damage, urinary PGE2 revealed a useful and noninvasive biomarker of nephrotoxicity, becoming significantly decreased in the urine of preterm infants after treatment for PDA closure, both with indomethacin and with ibuprofen [72]

Other sensitive and promising urinary biomarkers of kidney injury are represented by Cystatin-C and Neutrophil Gelatinase-Associated Lipocalin (NGAL); NGAL urinary excretion increases early during AKI and its detection becomes significantly helpful in monitoring nephrotoxicity in newborns [73].

SURGICAL LIGATION OF PDA

Surgical ligation of PDA is effective in definitively interrupting the ductal shunt. While effective, ligation has been associated with both short and long-term adverse neonatal outcomes, including post-ligation cardiac syndrome (PLCS), vocal fold paralysis, pneumothorax, chylothorax, and later neurosensory impairment in early childhood.

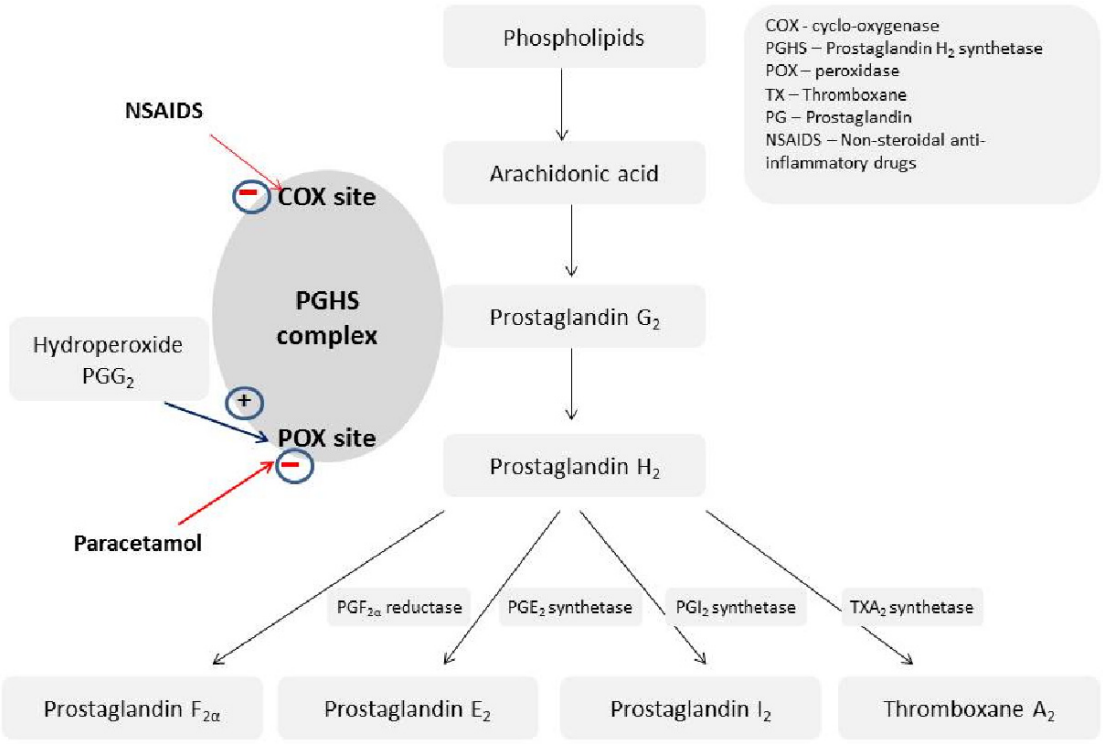
PARACETAMOL IN PDA

Unlike indomethacin and ibuprofen, paracetamol has no peripheral vasoconstrictive effect and has fewer side effects thus providing a more attractive choice for closure of PDA than indomethacin and ibuprofen. Before paracetamol introduction, in case of contraindication for NSAIDs, such as active or recent intracerebral hemorrhage (<48 h), thrombocytopenia (<50,000/mm^3), bleeding diathesis (meaning INR > 1.5 and/or hematuria, blood in the stool, tracheal secretions or at the injection site), sepsis, NEC, intestinal perforation, pulmonary hemorrhage, hepatic damage with severe hyperbilirubinemia, renal dysfunction (oliguria <1 ml/kg/h also after adequate hydration, serum creatinine >110–140 mol, and BUN >14 mmol/l),

and hypersensitivity to ibuprofen [76,77,78] the only available solution was surgical ligation with all the connected risks [76,79,80]

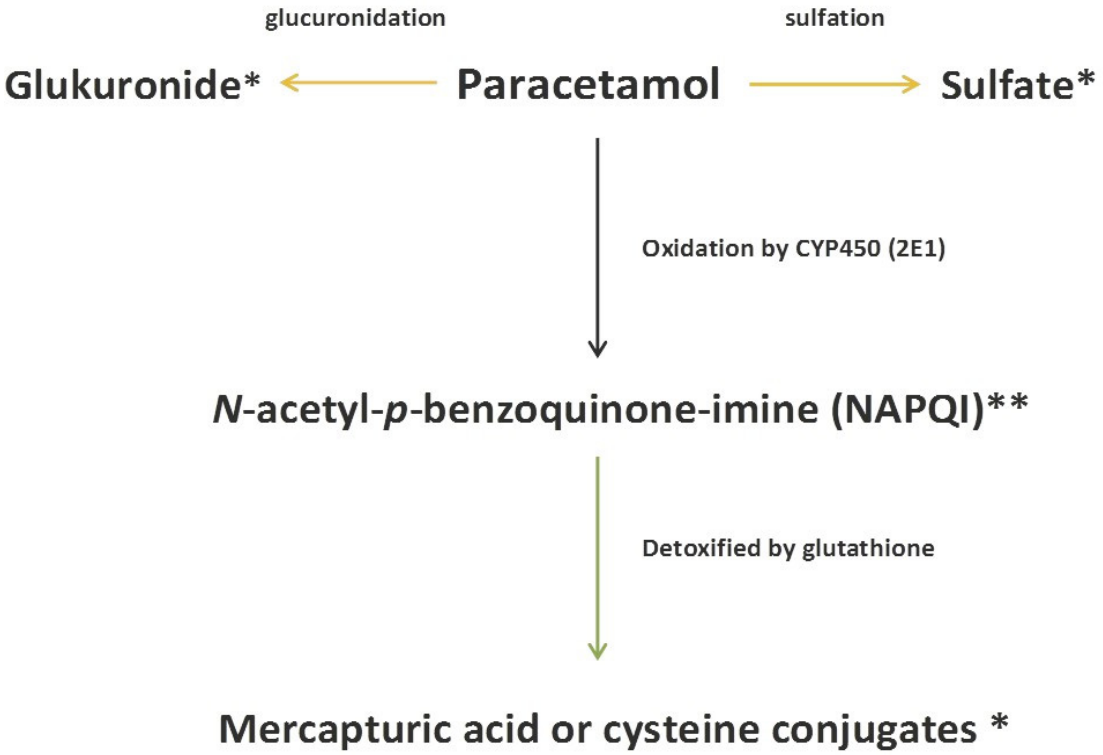
MECHANISM OF PARACETAMOL IN PDA CLOSURE

Paracetamol seems to act at the peroxidase segment of the enzyme. Peroxidase is activated at 10-fold-lower peroxide concentrations than is cyclooxygenase[74,75] Therefore, paracetamol-mediated inhibition is facilitated at reduced local peroxide concentrations (e.g., hypoxia). Theoretically, these differences would permit peroxidase inhibition to be optimally effective under conditions in which cyclooxygenase inhibition is less active or hypothetically, render it ideally suited for treatment in the PDA environment



PHARMACOKINETICS

Paracetamol is primarily eliminated by hepatic metabolism, and hepatic maturation is the key in paracetamol pharmacokinetics.Paracetamol undergoes both sulfation and glucuronidation, and these nontoxic products are excreted renally. In neonates, the sulfation of paracetamol predominates. Paracetamol also undergoes oxidation by cytochrome P450 (CYP) enzymes, predominantly CYP2E1, to form the reactive *N*-acetyl-*p*-benzoquinone-imine (NAPQI), which is detoxified by conjugation with glutathione. Repeated paracetamol administration has no effect on glutathione plasma levels in the preterm infant, potentially reflecting good glutathione stores.



Paracetamol metabolism main pathways. In preterm infants, sulfation predominates, while the proportion of glucuronidation increases later in childhood and adults. It is metabolised primarily in the liver into nontoxic* and toxic** products. Nontoxic products have renal excretion, while toxic NAPQI binds to liver proteins and amino acids. NAPQI production is primarily metabolised by the CYP2E1 pathway, and liver toxicity depends on NAPQI levels, not paracetamol itself.

DOSAGE OF PARACETAMOL:

The general dose used to treat PDA (15 mg/kg/6q) is greater than that used for pain and antipyretics (7.5−10 mg/kg/6q). The efficacy of paracetamol has been compared to COX-inhibitors, and it has been noted to be comparable with indomethacin and ibuprofen. Both IV and oral paracetamol have been compared to placebo and COX-inhibitors (IV indomethacin, IV or oral ibuprofen).

Kessel et al reported that plasma concentration levels of paracetamol did not exceed the recommended level after using a dose of 15 mg/kg/ q6h. Allegaert et al[81] reported that peak level of nearly 25mg/kg are likely to reach after four doses and it could assumed that plasma levels will accumulate with the 15mg/kg /6hr regimen. Paracetamol has been shown to be as effective as COX-inhibitors ibuprofen and indomethacin, but with fewer side effects.

Side effects of paracetamol

Acute and short-term safety of paracetamol is well documented. The drug is known to have possible acute side effects on the liver. Especially when administrated in high doses, elevations of liver enzymes have been seen. Fortunately, the true hepatotoxicity caused by paracetamol is rare in neonates.

It is generated through the production of *N*-acetyl-*p*-benzoquinone-imine (NAPQI) by the hepatic cytochrome P450[81]. Paracetamol-induced hepatotoxicity is not associated with exposure to the drug *per se* but depends more of the amount of exposure to NAPQI and the amount of protecting agent glutathione stores.

One hypothesis for the lack of acute paracetamol toxicity in preterm infants is that, due to their immaturity, the production of toxic metabolites (NAPQI) in the liver is low, while the synthesis of protecting agents such as glutathione in the liver is mature, and thus formation and stores are good despite prematurity.

Intravenous paracetamol has been reported to raise liver enzymes in transiently has been reported to raise liver enzymes and this adverse effect has been already reported in three neonates by Alan et al.,[82]

STUDIES ON PARACETAMOLIN HsPDA:

A prospective study conducted by Mohanty et al.,[83] at Manipal Hospital, Bangalore stated the effect of oral paracetamol in closing hemodynamically significant Patent Ductus Arteriosus in preterm infants (gestational age <32 weeks) where Ibuprofen was contraindicated. 29 of 40 neonates (72.5%) showed successful response while 11 (29.5%) failed to show any response. No major complications were seen.

Sinha et al.,[84] Military hospital ,Pathankot,Punjab reported an interesting findings of ductal closure in 10 preterm neonates (gestational age 27-33 wks) presenting with significant large PDA who had failed or had absolute contraindication with Brufen. These preterm neonates were treated with oral paracetamol in the dose of 15 mg/kg 8 hourly. The PDA closure was achieved within 48 h and there was no complication.

Terrin et al.,[85] performed on 2016 the first meta-analysis and systematic review on the results of the studies published between 2013 and 2014 evaluating paracetamol administration for PDA treatment (2 RCTs and 14 uncontrolled studies); the author reported a similar PDA closure rate of paracetamol instead of ibuprofen and a comparable safety profile, underlying that the analyzed studies included a relatively small number of neonates to consider these results as definition.

Oncel et al.,[85]compared the efficacy and safety of oral paracetamol and oral ibuprofen for the pharmacological closure of patent ductus arteriosus (PDA) in preterm infants. This prospective, randomized, controlled study enrolled 90 preterm infants with gestational age 30 weeks, birthweight 1250 g, and postnatal age 48 to 96 hours who had echocardiographically confirmed significant PDA. After the first course of treatment, the PDA closed in 31 (77.5%) of the patients assigned to the oral ibuprofen group vs 29 (72.5%) of those enrolled in the oral paracetamol group (P = .6). The reopening rate was higher in the paracetamol group than in the ibuprofen group, but the reopening rates were not statistically different (24.1% [7 of 29] vs 16.1% [5 of 31]; P =.43). The cumulative closure rates after the second course of drugs were high in both groups. Only 2 patient (2.5%) in the paracetamol group and 3 patients (5%) in the ibuprofen group required surgical ligation. This randomized, controlled clinical study demonstrated that paracetamol may be a medical alternative in the management of PDA.

According to the reviews of Oncel et al.,[85] and Terrin et al.,[86] paracetamol efficacy would be lower in extremely preterm neonates (<28 weeks of GA), probably for structural limitations in these subjects, which present a higher expression of prostaglandin receptors in the wall of the ductus and a thin-walled DA, with a lower

represented neointimal mounds. In these patients, administration of PG inhibitors can be followed by functional closure but less frequently by the structural ductal closure

Ohlsson and Shah[87] performed meta-analysis on two large RCTs comparing oral paracetamol versus oral ibuprofen. No significant differences were found between closure rate after 1stcourse. Side effects were lower in paracetamol group

Dash et al.,[88] compared between enteral paracetamol and intravenous indomethacin for closure of PDA in preterm neonates. This prospective RCT enrolled 171 preterm infants with birthweight 1500 g, within 48 hours of birth, and with one of the following echocardiographic criteria: duct size >1.5 mm, a left atrium-to-aorta ratio >1.5.,38 preterm neonates were randomized to receive enteral paracetamol and 39 were randomized to receive intravenous indomethacin. PDA closure rates with oral paracetamol and indomethacin were 100% and 95%, respectively. There were no significant differences between two groups for side effects or other co-morbidities. In this study, enteral paracetamol showed a PDA closure rate of 100% and no hepatotoxicity was detected. The PDA closure rates were quite high in both study groups (>95%) which may be related to the high mean gestational age (31.6 weeks). The other striking result of this study is high intestinal bleeding rate in paracetamol group (26.3%) related to the high osmolality of paracetamol solutions used for treatment

Dang et al.,[89] randomized, non-blinded, parallel-controlled, non-inferiority trial in order to compare oral paracetamol and ibuprofen for PDA closure in premature infants. In this study, mean days to closure were shorter in the paracetamol group than in the ibuprofen group (3.22±0.14 days vs. 3.71±0.16 days, P=0.020) subjects born at ≤34 weeks of gestation were chosen for enrollment. It was demonstrated in this trial that paracetamol may be utilized as the drug of choice for PDA in preterm infants with

good efficacy and lower risk of gastrointestinal bleeding or hyperbilirubinemia compared with ibuprofen treatment, and is especially suited for those with hyperbilirubinemia.

Hammerman et al.,[90] first reported the ductal closure with paracetamol in 5 preterm infants (gestational age 26-32 weeks, postanatal age 3-35 days) with large hemodynamically significant PDA who had either failed or had contraindications to ibuprofen therapy.

Al-Lawama 2017 was a single-centre study conducted in the Neonatal Intensive Care Unit of Jordan University Hospital, Amman, evaluated the effectiveness and safety profiles of oral paracetamol versus oral ibuprofen for PDA closure in preterm s with a gestational age of ≤ 32 weeks or birth weight of ≤ 1500 g and a haemodynamically significant PDA. Results A total of 120 premature infants fulfilled the inclusion criteria. Of these 120 infants, 34 fulfilled the treatment criteria and 22 were finally randomized and found no significant difference in the mortality or primary closure rates between the two groups also. There was no significant difference in the short-term neonatal outcomes

Yang et al.,[92] demonstrated a probably higher renal safety of this drug describing a minor incidence of oliguria comparing two groups of infants treated with paracetamol versus ibuprofen. Yang et al. demonstrated a similar PDA closure rate between oral paracetamol and ibuprofen, but less adverse events . In conclusion this study evidenced lower toxicity, also corresponding to lower plasma and urinary PGE2 levels, in paracetamol group.

Cook et al.,[93] performed a population pharmacokinetic model in order to define intravenous paracetamol effects and toxicity determinants and successively evaluated its predictive value with the aim of generalizing this knowledge to the whole neonates population

Serum paracetamol levels were evaluated in three studies of PDA management. In the study of Oncel et al.,[94] these became 7.3 mcg/mL, 15.5 mcg/mL, and 14.7 mcg/mL during the three days of therapy. In the study of Yurttutan et al.,[95] serum paracetamol levels after 24 h from administration became lower than 18 mcg/mL [94,95] Harkin et al.,[96] analyzed 87 serum samples from 21 paracetamol treated patients and detected concentrations lower than 25.2 mg/L, without relevant accumulation. All these values resulted in therapeutic range for children (10–30 mcg/mL)

The effects of prophylactic paracetamol administration on PDA closure have been retrospectively evaluated by Aikio et al.,[98] on 102 neonates born with <32 weeks of GA, demonstrating a reduction in PDA incidence from 30.7% to 14.7% after paracetamol introduction before the age of 72 hours of life, without an increase in adverse effects.

Bagheri et al.,[97] demonstrated comparable global closure rates between oral paracetamol and oral ibuprofen, with only minimal complications in paracetamol group.

Harkin et al.,[96] demonstrated a faster hsPDA closure rate in paracetamol group (95%) than in placebo group. The authors used a different drug dosage, administering 20 mg/kg of paracetamol at 24 hours of life, followed by 7,5 mg/kg every 6 h for 4 days.

The efficacy of paracetamol after ibuprofen failure has been evaluated in two trials by Roofthooft et al.,[76] and Valerio et al.,[78] finding different results. According to

Roofthooft et al.,[76] paracetamol is not effective in hsPDA closure in newborns with a postnatal age >2 weeks, showing a global paracetamol success of 18% in the studied sample, significantly lower than literature data.

In the study of Valerio et al.,[78] comparing the efficacy of paracetamol between a ‘rescue ‘group (after failure of ibuprofen) and a ‘first line; group (contraindication for ibuprofen) no significant difference in PDA closure efficacy was detected. More patients of the first line group underwent PD A surgical ligation and showed PDA reopening.

El-Mashad et al.,[78] performed the first large prospective randomized study comparing the efficacy and side effects of paracetamol, ibuprofen, and indomethacin simultaneously. For this purpose, 300neonates have been enrolled and treated with iv paracetamol (100), iv ibuprofen (100), or iv indomethacin (100). Global PDA closure rate did not show significant differences among the three groups and an improvement in ventilatory setting was also demonstrated after successful PDA closure. In NSAIDs groups the authors detected a significant increase in creatinine and serum blood urea nitrogen levels associated with a significant platelet count and urine output reduction. Among the ibuprofen treated patients was there also a significant increase in bilirubin levels. The effect in platelet reduction is absent after paracetamol treatment and this could be explained, according to the authors, by its lack of action on thromboxane, unlike NSAIDs. In conclusion, in this study, paracetamol has shown the same efficacy of indomethacin and ibuprofen in preterm neonates PDA closure but less side effects, especially for its low impact on renal function, platelet count, and GI bleeding.

In the retrospective cohort study of Weisz et al.,[99] including 26 also demonstrated a positive response in paracetamol treated preterms for hsPDA in 46% in absence of complications, demonstrating that paracetamol could be a safe therapy in such infants.

Sancak et al.,[104] compared the two different administration routes of paracetamol in 18 VLBW newborns; hsPDA closure rate seemed to be higher in those treated with oral compared to iv paracetamol administration after two courses of therapy, but this result was not statistically significant. Both the treatments did not show hepatic toxicity. In the future, larger trials should be performed in order to define the possible differences between the two administration routes.

Safer profile in terms of gastrointestinal bleeding and hyperbilirubinemia after paracetamol administration instead of ibuprofen has been described by Evans [105] and Terrin et al.,[88]

Le et al., agree with the idea that paracetamol seems to be a good alternative in PDA treatment and should be considered, in case of ibuprofen contraindication, before ligation.

El Kuffash et al.,[106] evaluated late treatment with iv paracetamol beyond the 2nd week of life which became effective in hsPDA closure, avoiding PDA ligation

Evans [105] described a similar reopening rate after PDA treatment both in paracetamol and in ibuprofen groups and also concluded underlying the same efficacy of the two drugs, which should be confirmed through other trials

Results in support of conservative PDA treatment have been reported by Slaughter et al.,[107] and Letshwiti et al. [108]. Slaughter et al demonstrated no association between NSAID treatment (performed between 2 and 28 postnatal days) and the odds

of mortality or BPD at 36 weeks of postmenstrual age versus similar not treated preterms.

Janz-Robinson et al.,[109] reported data of a retrospective population-based cohort study attesting the association between PDA treatment (medical or surgical) and risk of developmental delay, cerebral palsy, sensorineural or conductive deafness, or bilateral blindness instead of nontreated patients, at age 2-3 years, especially for neonates <25 weeks' GA

On the contrary, Oncel MY et al.,[110] conducted a study to determine the effects of paracetamol versus ibuprofen treatment given to preterm infants for the pharmacological closure of patent ductus arteriosus (PDA) on neurodevelopmental outcomes at 18 to 24 months' corrected age. A total of 80 infants completed the trial protocol. Of the 75 infants eligible for follow-up, 61 infants (30 in the paracetamol group and 31 in the ibuprofen group) were evaluated. There was no significant difference in neurodevelopmental outcomes between the two groups

AIM OF THE STUDY

To study the efficacy of oral paracetamol in closing hemodynamically significant patent ductus arteriosus in preterm infants where ibuprofen contraindicated

OBJECTIVE.

PRIMARY OBJECTIVE:

The primary objective is to study the efficacy of oral paracetamol for closure of hsPDA in preterm neonates of <34 weeks' with evidence of hsPDA

SECONDARY OBJECTIVE:

The secondary objective is to study the

- Time to closure of PDA
- Duration of mechanical ventilation (in days)
- Duration of any respiratory support(in days)
- Duration of any supplemental oxygen(in days)

OUTCOME

Primary outcome measure:

The primary outcome measure is closure of PDA by the end of the last dose of the study drug or earlier

Secondary outcome measure:

- Closure of PDA following a single course of study drug
- Reopening of PDA following initial closure
- Hepatitis with deranged liver transaminases
- Intraventricular haemarrhage (volpe's grading)
- Sepsis (positive blood culture)

RESEARCH METHODOLOGY

- Study design: Prospective type of observational study
- Study place: Govt : Theni medical college and hospital
- Study period: One year

ELIGIBILITY

- Inborn preterm neonates <34 weeks' gestation
- Presence of a hemodynamicaly significant PDA*

*hsPDA is defined if any one of the below-mentioned clinical /biochemical sign is present in the presence of a PDA with a transductal diameter >1.5mm or in the presence of anyone of the below mentioned echocardiographic sign suggestive of hemodynamic significance even in the absence of any of the below-mentioned clinical/biochemical sign.

1. Signs of significant left-right shunt: hyperdynamic pulsatile precordium, bounding peripheral pulses and wide pulse pressure>25mmhg
2. Signs of systemic underperfusion: poor peripheral pulse volume, prolonged CRT, decreased urine output, deranged renal function and hypotension

3. Signs of pulmonary overperfusion: Abnormal weight gain, increase in liver size, new onset or increase in ventilatory requirements that primarily involve PEEP/PIP and Fio2, respiratory acidosis, pulmonary crepitations and haemarrhagic pulmonary edema.

ECHOCARDIOGRAPHIC FEATURES indicative of hsPDA:

A transductal diameter of >1.5mm plus one of the following:

1. Evidence of left atrial enlargement (left atrium: aortic root diameter ratio >1.4:1
2. Absent or reversed diastolic blood flow pattern in descending thoracic aorta

With brufen contraindication –

- coagulopathy,
- platelet count <60000,
- serum creatinine>1.5mg/dl
- ,necrotising enterocolitis
- bleeding diathesis

Exclusion criteria

1. Antenatally or postnatally diagnosed structural heart disease
2. Presence of major congenital malformations
3. Elevated liver enzymes AST>55U/L or ALT>23U/L
4. Refusal of consent

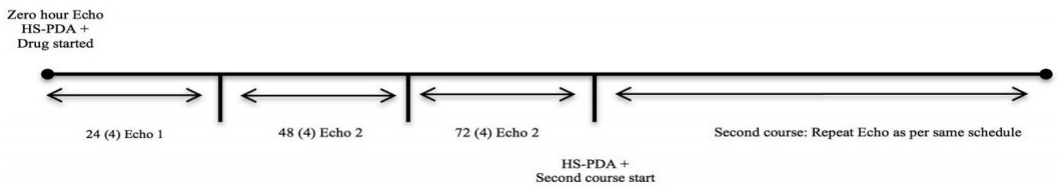
ETHICAL COMMITTEE APPROVAL

Approved

METHODOLOGY

This observational study will be performed at neonatal intensive care unit, government theni medical college and hospital after getting written informed consent from one of the parents' of study population.

- Preterm infants with HsPDA were given oral paracetamol suspension
- Paracetamol oral suspension would be administerd through an orogastric tube in a dose of 15mg/kg/dose at six hourly intervals for three consecutive days.the drug would be filled in a 5ml syringe and would be gently pushed through the orogastric tube followed by a flush of 1ml of sterile water for injection.
- These neonates were monitored temperature changes before and 30 minutes after giving oral paracetamol.
- Repeat Echo (1,2 and 3) done at 24plus or minus 4 hours on 1st,2nd, 3rd day drug dose for closure of PDA
- If ductus still open on echo 3,repeat course of the same study drug of same duration and the echo would be repeated as per the first course schedule.
- The ductus would be finally labelled as failed to close based on echo 6 which would be done at the end of the last dose of the second course of the study.



ine of assessments by bedside echocardiography. hsPDA, haemodynamically significant paten

TECHNIQUE OF TRANSTHORACIC ECHOCARDIOGRAPHY:

- The echocardiographic assessments done using MINDRAY machine. A cardiac probe of 8-12MHz frequency will be used for the study. Before the procedure the probe head will be cleaned and disinfected with 2%glutarldehyde solution. Three standard views would be optimised for visualisation of the ductus arteriosus-subxiphoid,high parasternal and aortic arch views.

- Presence of ductus in 2D would always be cross-checked using a color doppler superimposition. transductal diameter would be measured in 2D in high parasternal view.

- Color doppler would be used to visualise the direction of shunt blood flow.

- M mode would be used to measure the left atrial: aortic root diameter ratio.

STATISTICAL ANALYSIS

Data will be entered in excel sheet; Statistical analysis of the data will be performed by statistical software SPSS. Outcome variables will be categorized as PDA closed or not closed and their prevalence will be expressed as percentage and p value of < 0.05 will be considered significant.

ETHICAL ISSUES

Parents of all babies recruited in the study were explained about the methodology and investigations in detail and consent obtained.

RESULTS AND OBSERVATIONS

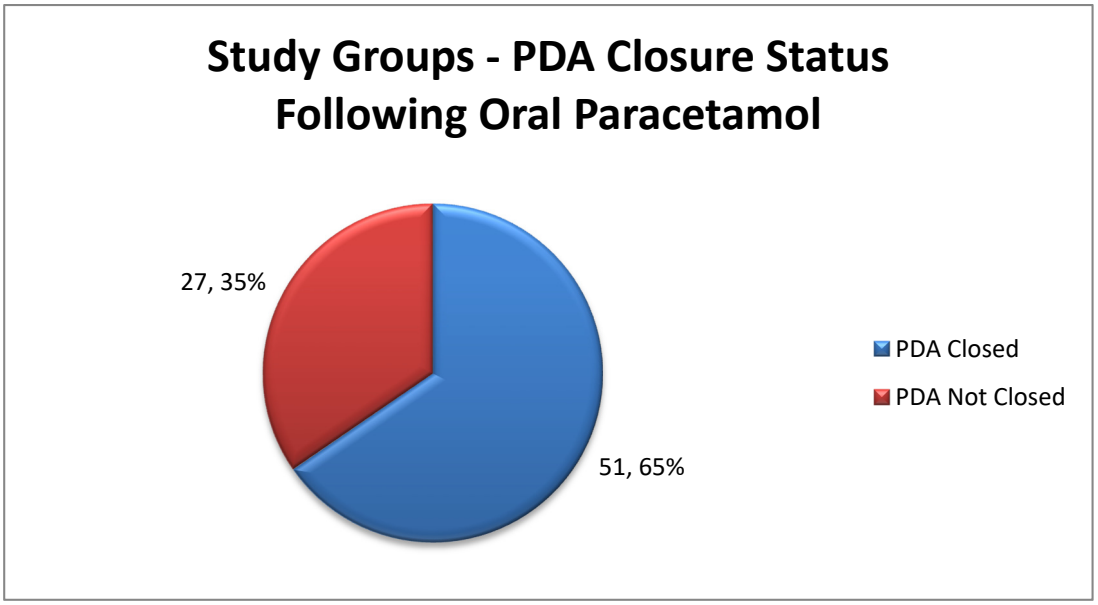
After obtaining Informed consent and institutional approval for the study, seventy eight preterm neonates of <34 weeks' with evidence of hsPDA were recruited to study the efficacy of oral paracetamol in closing hemodynamically significant patent ductus arteriosus in preterm infants where ibuprofen contraindicated during the period of October 2018 to September 2019 after the inclusion and exclusion criteria being applied.

In our study the selected babies with hemodynamically significant PDA are being evaluated for the mode of delivery, birth weight, gestational age (using modified Ballards scoring system) , antenatal steroids intake, APGAR at 5minute , resuscitation required at birth , temperature and LFT changes before and after paracetamol , course of paracetamol , duration of mechanical ventilation and requirement of supplemental oxygen.

Data collected was internally compared, tabulated, analysed and interpreted by using descriptive and inferential statistics based on the formulated objectives of the study

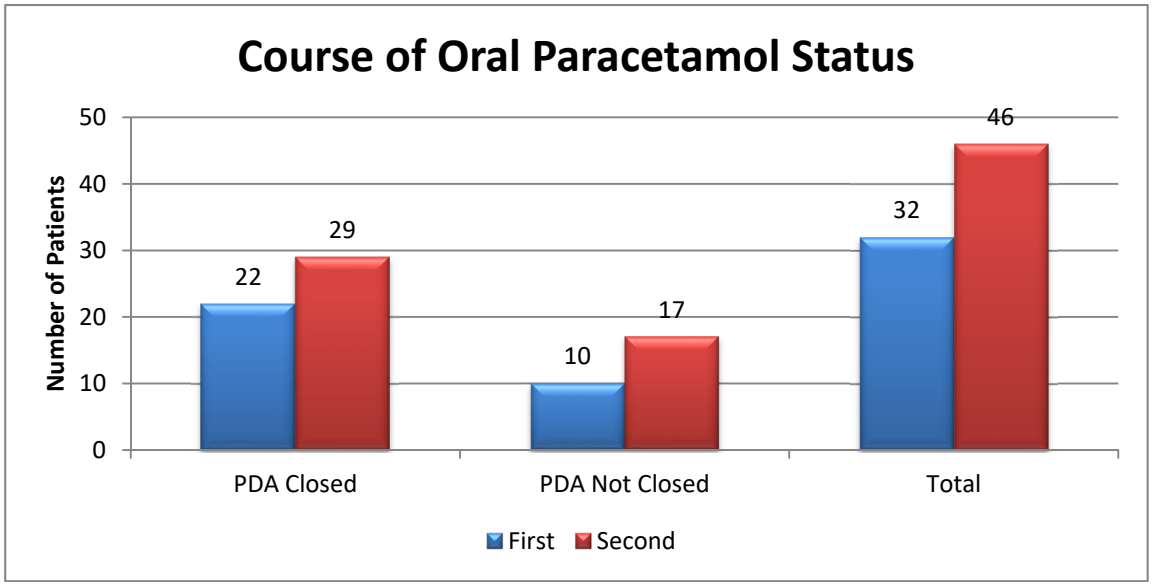
Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Accuracy analysis done to determine sensitivity, specificity, predictive values and AUC. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

Study Groups

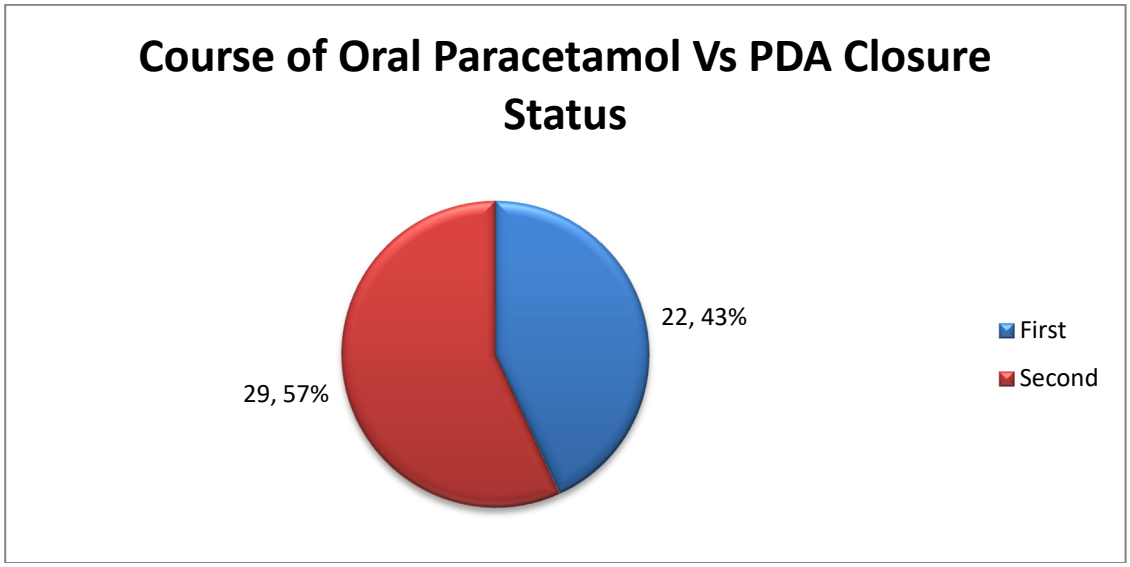


Study Groups - PDA Closure Status Following Oral Paracetamol	PDA Closed	PDA Not Closed	Total
Number	51	27	78
Percentage	65.38	34.62	100.00

Course of Oral Paracetemol



Course of Oral Paracetamol Status	PDA Closed	%	PDA Not Closed	%	Total	%
First	22	43.14	10	37.04	32	41.03
Second	29	56.86	17	62.96	46	58.97
Total	51	100.00	27	100.00	78	100.00
P value Chi Squared Test				0.607		



Course of Oral Paracetemol Vs PDA Closure Status	PDA Closed	%
First	22	43.14
Second	29	56.86
Total	51	100.00

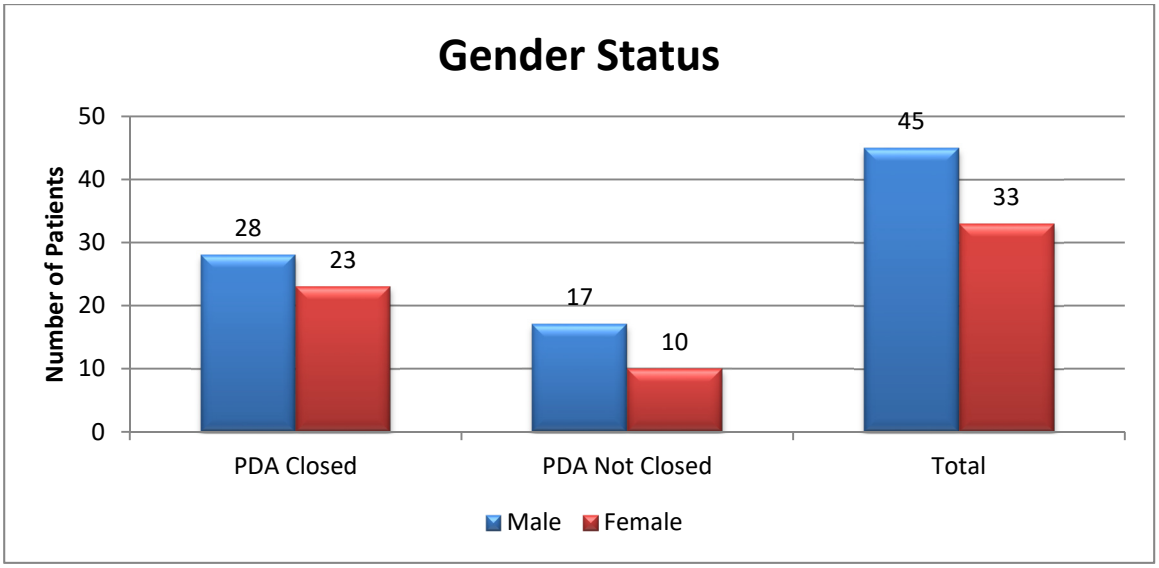
The effectiveness of the closure of the ductus arteriosus with paracetamol reported in our study was 65.38% (n=51). Out of 51 cases of PDA closure, 22 cases (43.14%) had a positive response after one treatment course and 29 cases (56.86%) had a positive response after two treatment courses.

DUCTAL DIAMETER BEFORE AND AFTER PARACETAMOL

	BEFORE PARACETAMOL	AFTER PARACETAMOL	P value
PDA measurement	3.01+/- 0.64	1.10+/-0.52	<0.001

The difference in the mean PDA measurements before and after paracetamol was found to be statistically significant P value <0.001

Gender



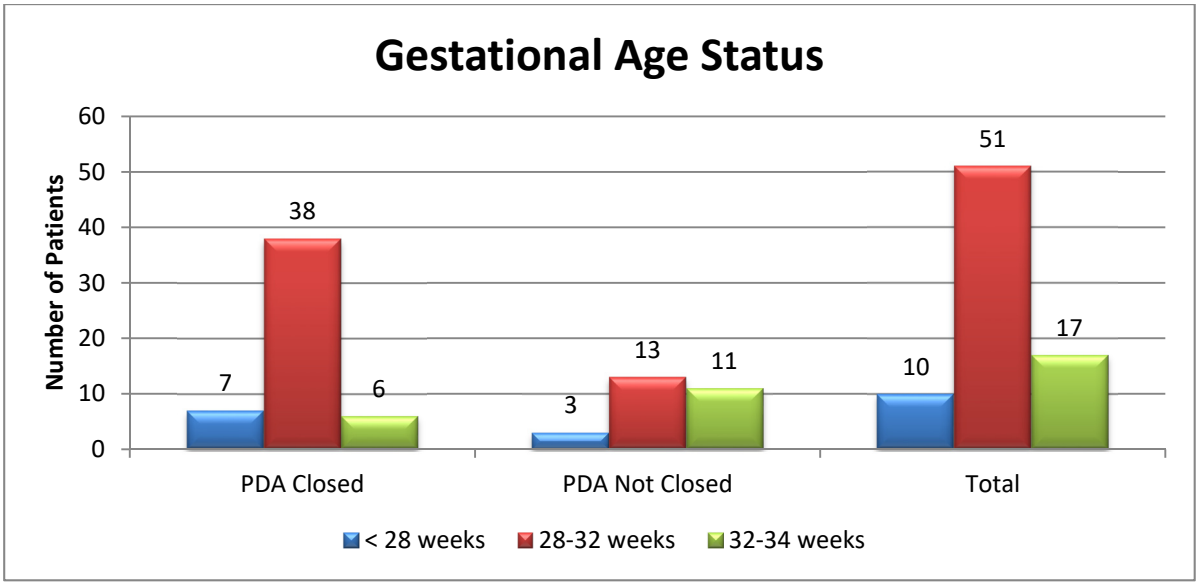
Gender Status	PDA Closed	%	PDA Not Closed	%	Total	%
Male	28	54.90	17	62.96	45	57.69
Female	23	45.10	10	37.04	33	42.31
Total	51	100.00	27	100.00	78	100.00
P value Chi Squared Test				0.497		

While analysing gender status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects belonged to male gender (n=45, 57.69%).
- In PDA closed group, majority of the study subjects belonged to male gender (n=28, 54.90%).
- In PDA not closed group, majority of the study subjects belonged to male gender (n=17, 62.96%).

When statistically comparing gender status between the study groups, the difference in the incidence of gender groups was found to be statistically non-significant ($p > 0.05$).

Gestational Age



Gestational Age Status	PDA Closed	%	PDA Not Closed	%	Total	%
< 28 weeks	7	13.73	3	11.11	10	12.82
28-32 weeks	38	74.51	13	48.15	51	65.38
32-34 weeks	6	11.76	11	40.74	17	21.79
Total	51	100.00	27	100.00	78	100.00

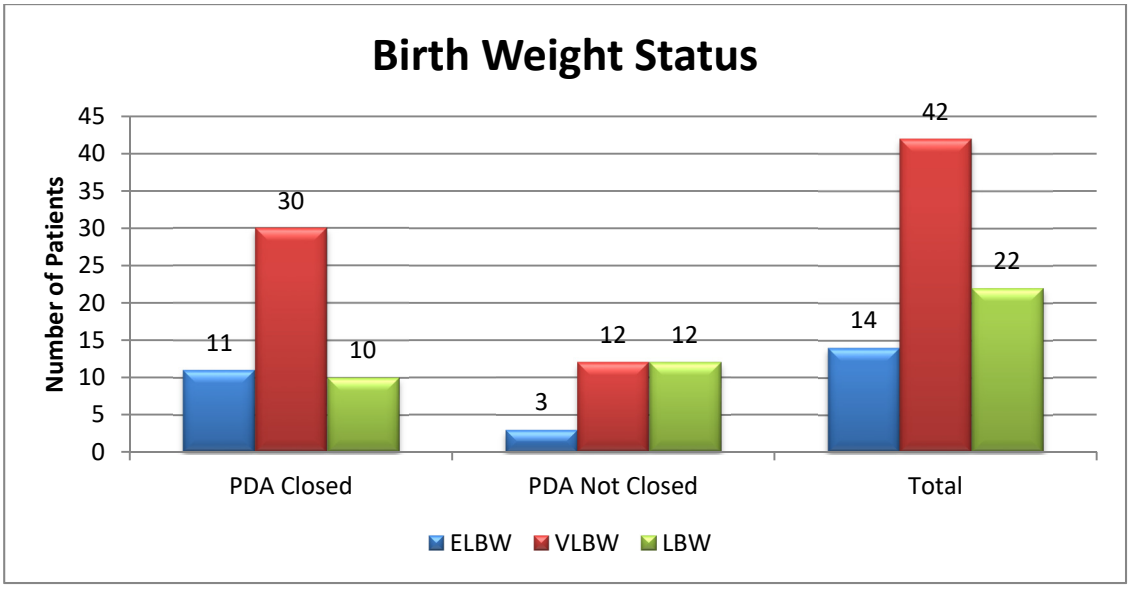
Gestational Age Distribution	PDA Closed	PDA Not Closed	Total
Mean	30.10	31.07	30.44
SD	2.17	2.51	2.33
P value Unpaired t Test	0.094		

While analysing gestational age distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects belonged to 28-32 weeks gestational age class interval (n=51, 65.38%) with a mean GA of 30.44 weeks.
- In PDA closed group, majority of the study subjects belonged to 28-32 weeks gestational age class interval (n=38, 74.51%) with a mean GA of 30.10 weeks.
- In PDA not closed group, majority of the study subjects belonged to 28-32 weeks gestational age class interval (n=13, 48.15%) with a mean GA of 31.07 weeks.

When statistically comparing gestational age distribution between the study groups, the difference in the gestational age was found to be statistically non-significant ($p > 0.05$).

Birth Weight



Birth Weight Status	PDA Closed	%	PDA Not Closed	%	Total	%
ELBW	11	21.57	3	11.11	14	17.95
VLBW	30	58.82	12	44.44	42	53.85
LBW	10	19.61	12	44.44	22	28.21
Total	51	100.00	27	100.00	78	100.00

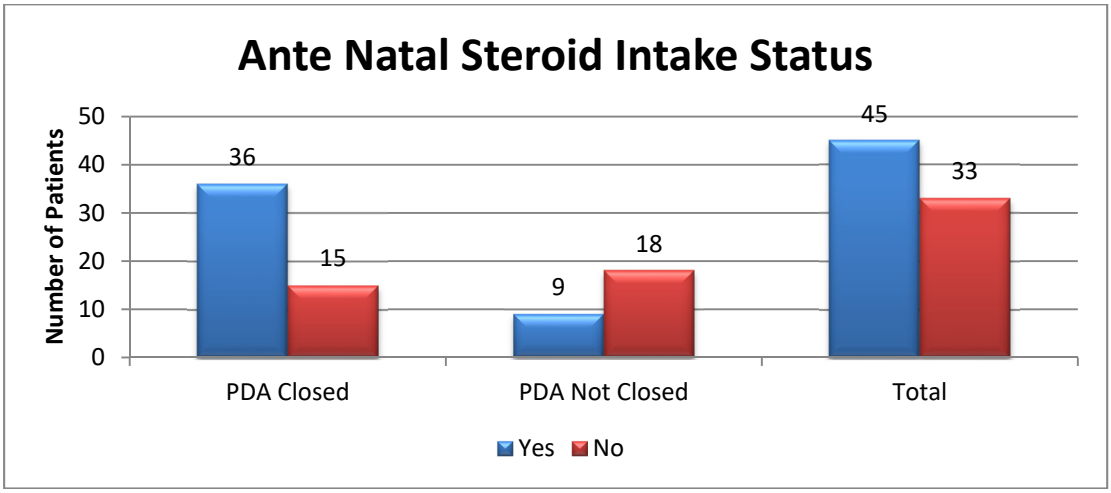
Birth Weight Distribution	PDA Closed	PDA Not Closed	Total
Mean	1.34	1.52	1.40
SD	0.39	0.38	0.40
P value Unpaired t Test	0.065		

While analysing birth weight distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects belonged to very low birth weight class interval (n=42, 53.85%) with a mean BW of 1.40 kgs.
- In PDA closed group, majority of the study subjects belonged equally to very low/Low birth weight class interval (n=12, 44.44%) with a mean BW of 1.34 kgs.
- In PDA not closed group, majority of the study subjects belonged to very low birth weight class interval (n=42, 53.85%) with a mean BW of 1.52 kgs.

When statistically comparing birth weight distribution between the study groups, the difference in the birth weight was found to be statistically non-significant ($p > 0.05$).

Ante Natal Steroid Intake



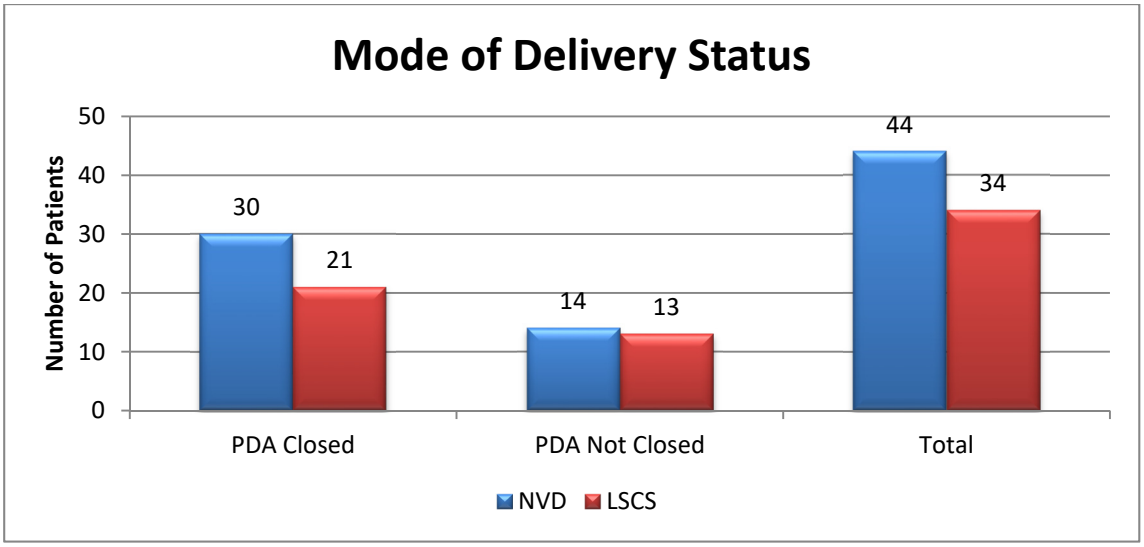
Ante Natal Steroid Intake Status	PDA Closed	%	PDA Not Closed	%	Total	%
Yes	36	70.59	9	33.33	45	57.69
No	15	29.41	18	66.67	33	42.31
Total	51	100.00	27	100.00	78	100.00
P value Chi Squared Test				0.002		

While analysing ante natal steroid intake status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects took steroids during ante natal period (n=45, 57.69%).
- In PDA closed group, majority of the study subjects took steroids during ante natal period (n=36, 70.59%).
- In PDA not closed group, majority of the study subjects did not take steroids during ante natal period (n=18, 66.67%).

When statistically comparing ante natal steroid intake status between the study groups, the difference in the incidence of ante natal steroid intake was found to be statistically significant ($p < 0.05$).

Mode of Delivery



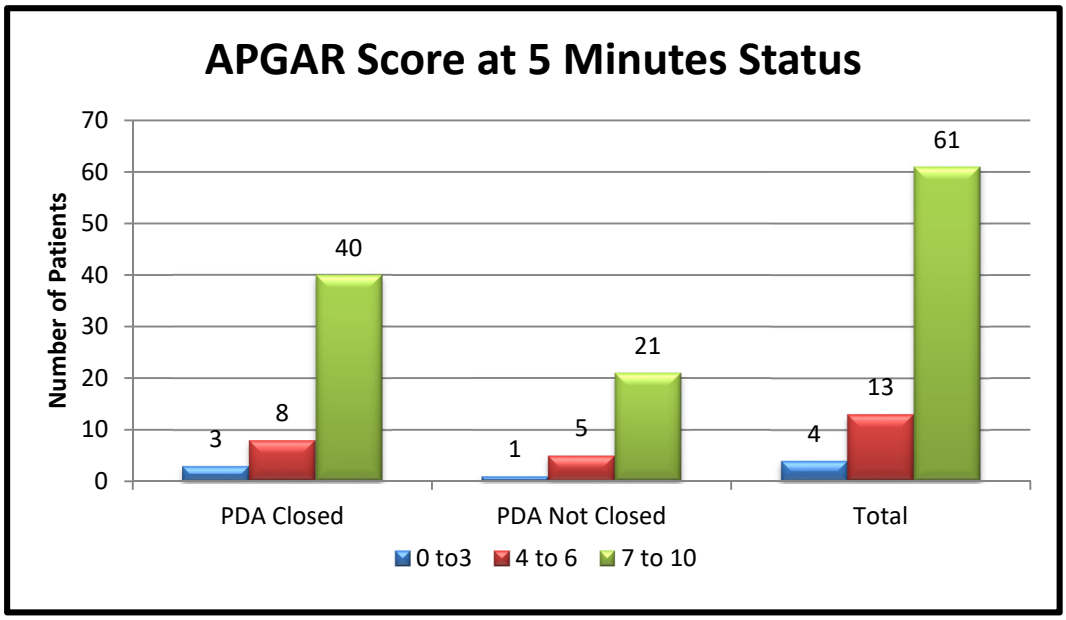
Mode of Delivery Status	PDA Closed	%	PDA Not Closed	%	Total	%
NVD	30	58.82	14	51.85	44	56.41
LSCS	21	41.18	13	48.15	34	43.59
Total	51	100.00	27	100.00	78	100.00
P value Chi Squared Test				0.564		

While analysing mode of delivery status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had normal vaginal delivery(n=44, 56.41%).
- In PDA closed group majority of the study subjects had normal vaginal delivery (n=30, 58.82%).
- In PDA not closed group, majority of the study subjects normal vaginal delivery (n=14, 51.85%).

When statistically comparing mode of delivery status between the study groups, the difference in the incidence of mode of delivery groups was found to be statistically non-significant (p >0.05).

APGAR Score at 5 Minutes



APGAR Score at 5 Minutes Status	PDA Closed	%	PDA Not Closed	%	Total	%
0 to3	3	5.88	1	3.70	4	5.13
4 to 6	8	15.69	5	18.52	13	16.67
7 to 10	40	78.43	21	77.78	61	78.21
Total	51	100.00	27	100.00	78	100.00

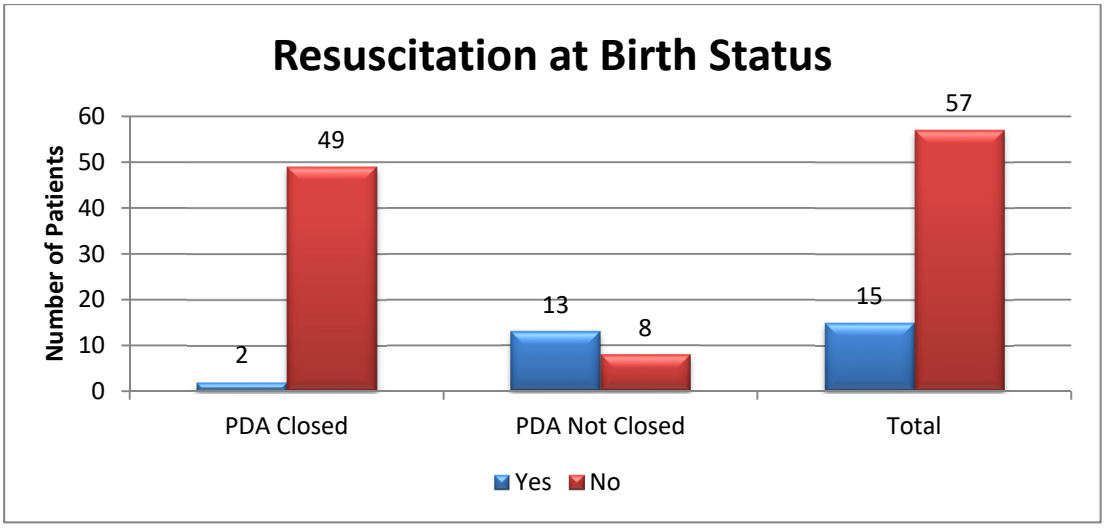
APGAR Score at 5 Minutes Distribution	PDA Closed	PDA Not Closed	Total
Mean	6.75	6.67	6.72
SD	1.43	1.62	1.48
P value Unpaired t Test	0.833		

While analysing APGAR score at 5 minutes distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had APGAR score at 5 minutes between7 to 10 scoring points(n=61, 78.21%) with a mean APGAR score at 5 minutes of 6.72scoring points.
- In PDA closed group, majority of the study subjects had APGAR score at 5 minutes between7 to 10 scoring points (n=61, 78.21%) with a mean APGAR score at 5 minutes of 6.75scoring points.
- In PDA not closed group, majority of the study subjects had APGAR score at 5 minutes between7 to 10 scoring points (n=61, 78.21%) with a mean APGAR score at 5 minutes of 6.67scoring points.

When statistically comparing APGAR score at 5 minutes distribution between the study groups, the difference in the APGAR score at 5 minutes was found to be statistically non-significant ($p > 0.05$).

Resuscitation at Birth



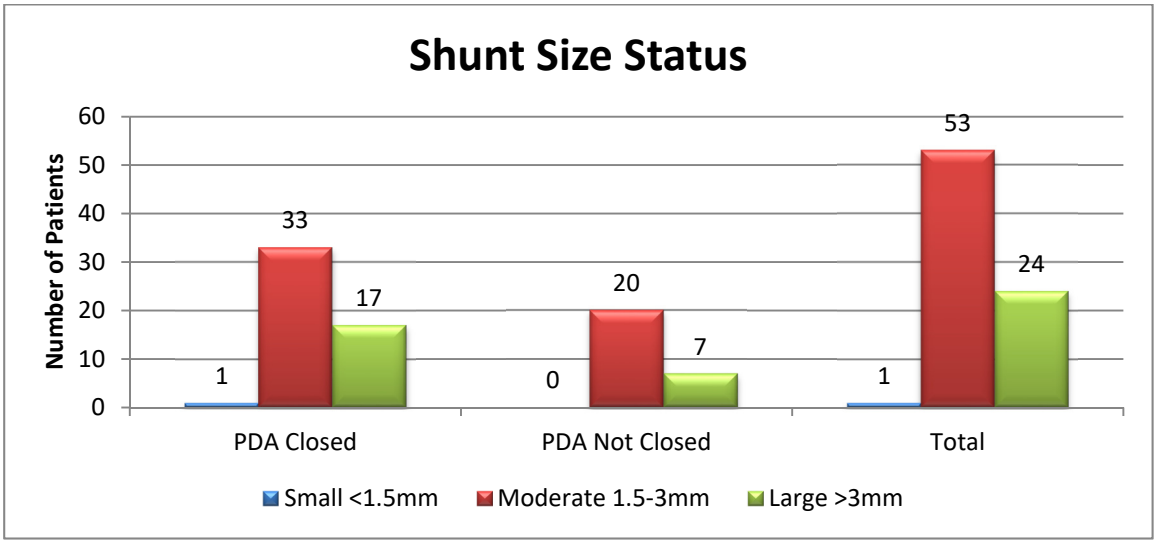
Resuscitation at Birth Status	PDA Closed	%	PDA Not Closed	%	Total	%
Yes	2	3.92	13	61.90	15	20.83
No	49	96.08	8	38.10	57	79.17
Total	51	100.00	21	100.00	72	100.00
P value Chi Squared Test				<0.001		

While analysing resuscitation at birth status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had no resuscitation at birth (n=57, 79.17%).
- In PDA closed group, majority of the study subjects had no resuscitation at birth (n=49, 96.08%).
- In PDA not closed group, majority of the study subjects had resuscitation at birth (n=13, 61.90%).

When statistically comparing resuscitation at birth status between the study groups, the difference in the incidence of resuscitation at birth was found to be statistically significant ($p < 0.05$).

Shunt Size



Shunt Size Status	PDA Closed	%	PDA Not Closed	%	Total	%
Small <1.5mm	1	1.96	0	0.00	1	1.28
Moderate 1.5-3mm	33	64.71	20	74.07	53	67.95
Large >3mm	17	33.33	7	25.93	24	30.77
Total	51	100.00	27	100.00	78	100.00
P value Chi Squared Test				0.628		

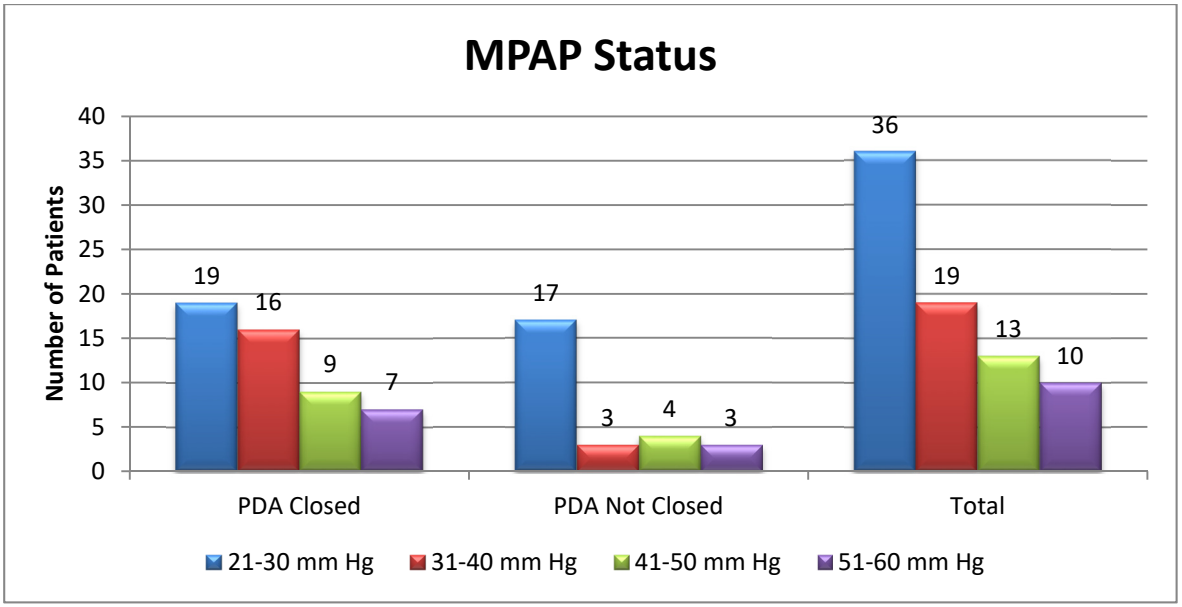
Shunt Size Distribution	PDA Closed	PDA Not Closed	Total
Mean	2.97	3.07	3.01
SD	0.68	0.55	0.64
P value Unpaired t Test	0.470		

While analysing shunt size distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had moderate shunt size (n=53, 67.95%) with a mean shunt size of 3.01 mm.
- In PDA closed group, majority of the study subjects had moderate shunt size (n=33, 64.71%).with a mean shunt size of 2.97 mm.
- In PDA not closed group, majority of the study subjects had moderate shunt size (n=20, 74.07%) with a mean shunt size of 3.07 mm..

When statistically comparing shunt size distribution between the study groups, the difference in the mean shunt size was found to be statistically non-significant ($p > 0.05$).

MPAP



MPAP Status	PDA Closed	%	PDA Not Closed	%	Total	%
21-30 mm Hg	19	37.25	17	62.96	36	46.15
31-40 mm Hg	16	31.37	3	11.11	19	24.36
41-50 mm Hg	9	17.65	4	14.81	13	16.67
51-60 mm Hg	7	13.73	3	11.11	10	12.82
Total	51	100.00	27	100.00	78	100.00

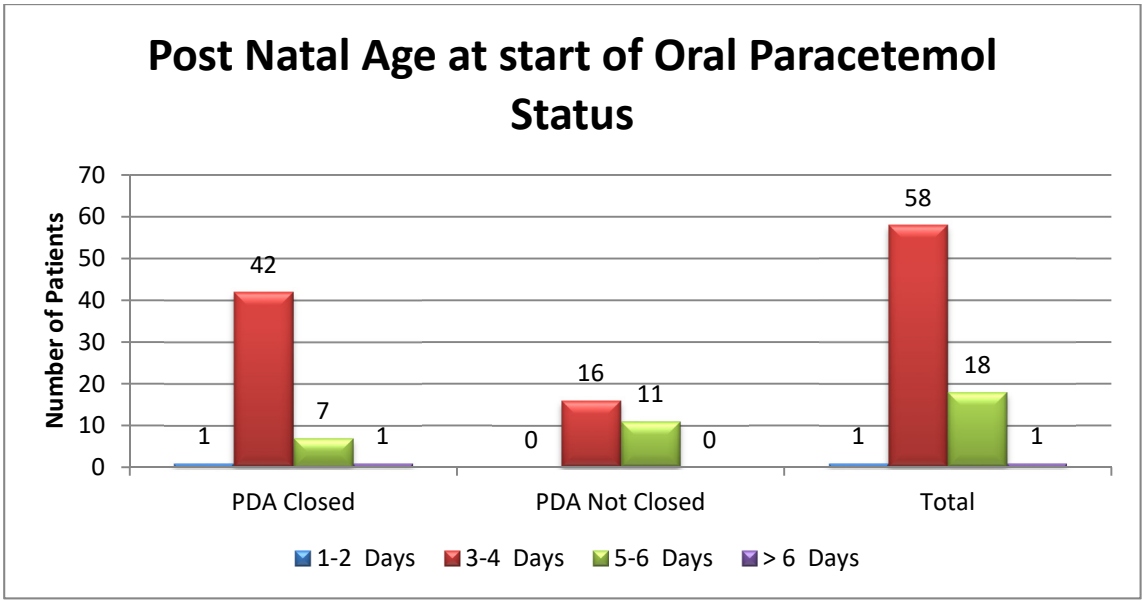
MPAP Distribution	PDA Closed	PDA Not Closed	Total
Mean	37.84	34.81	36.79
SD	10.01	10.05	10.06
P value Unpaired t Test	0.210		

While analysing mean pulmonary artery pressure distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had MPAP between 21-30 mm Hg(n=36, 46.15%) with a mean MPAP of 36.79 mm Hg.
- In PDA closed group, majority of the study subjects had MPAP between 21-30 mm Hg(n=19, 37.25%) with a mean MPAP of 37.84 mm Hg.
- In PDA not closed group, majority of the study subjects had MPAP between 21-30 mm Hg(n=17, 62.96%) with a mean MPAP of 34.81 mm Hg.

When statistically comparing mean pulmonary artery pressure distribution between the study groups, the difference in the mean pulmonary artery pressure was found to be statistically non-significant ($p > 0.05$).

Post Natal Age at start of Oral Paracetamol



Post Natal Age at start of Oral Paracetamol Status	PDA Closed	%	PDA Not Closed	%	Total	%
1-2 Days	1	1.96	0	0.00	1	1.28
3-4 Days	42	82.35	16	59.26	58	74.36
5-6 Days	7	13.73	11	40.74	18	23.08
> 6 Days	1	1.96	0	0.00	1	1.28
Total	51	100.00	27	100.00	78	100.00

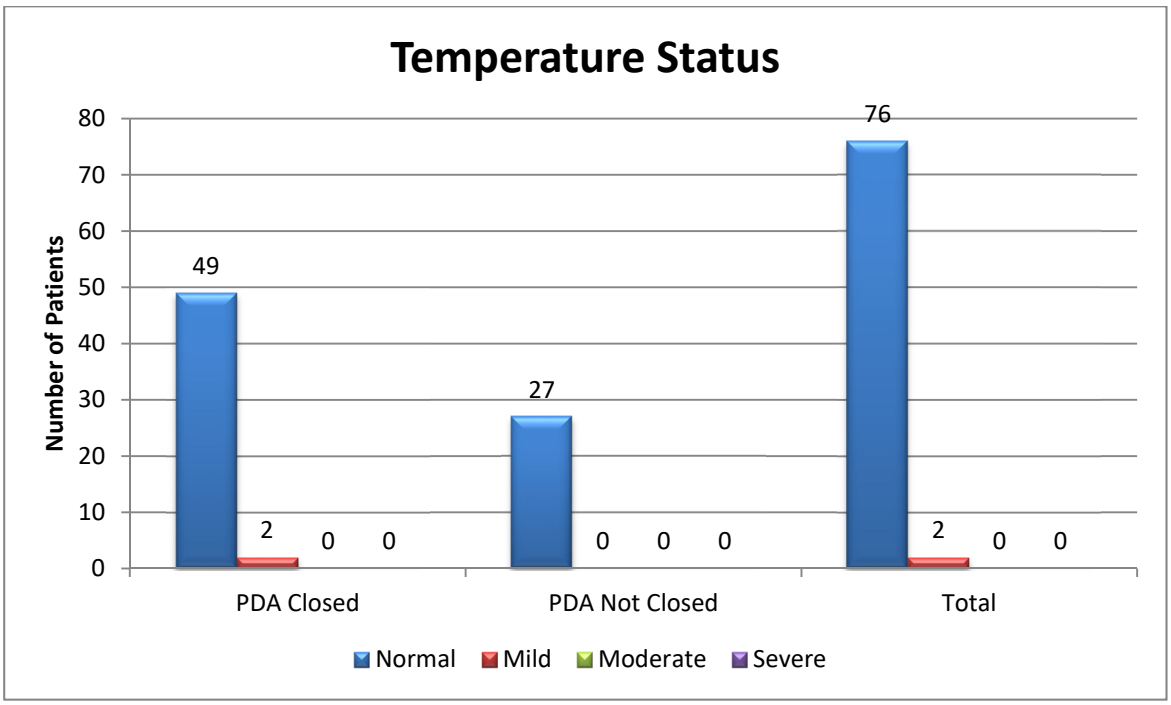
Post Natal Age at start of Oral Paracetamol Distribution	PDA Closed	PDA Not Closed	Total
Mean	3.73	4.26	3.91
SD	1.00	0.71	0.94
P value Unpaired t Test	0.008		

While analysing post natal age at start of oral paracetamol distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had post natal age at start of oral paracetamol between 3-4 days (n=58, 74.36%) with a mean post natal age at start of oral paracetamol of 3.91 days.
- In PDA closed group, majority of the study subjects had post natal age at start of oral paracetamol between 3-4 days (n=43, 82.35%) with a mean post natal age at start of oral paracetamol of 3.73 days..
- In PDA not closed group, majority of the study subjects had post natal age at start of oral paracetamol between 3-4 days (n=16, 59.26%) with a mean post natal age at start of oral paracetamol of 4.26 days..

When statistically comparing mean post natal age at start of oral paracetamol distribution between the study groups, the difference in the mean post natal age at start of oral paracetamol was found to be statistically significant ($p < 0.05$).

Temperature



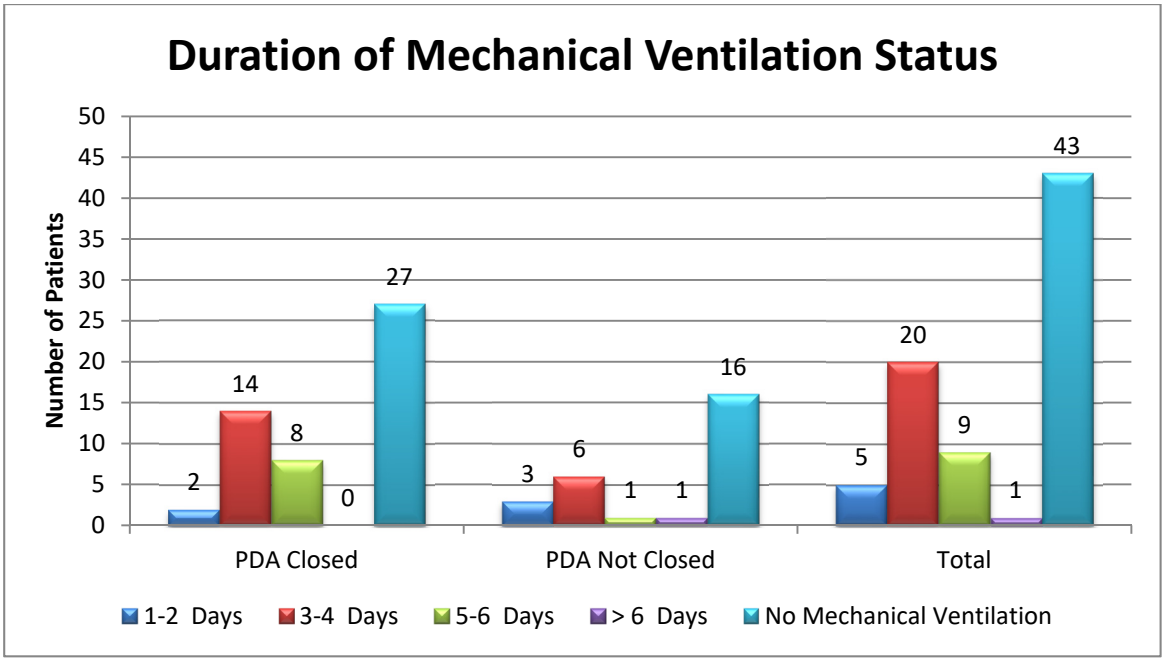
Temperature Status	PDA Closed	%	PDA Not Closed	%	Total	%
Normal	49	96.08	27	100.00	76	97.44
Mild	2	3.92	0	0.00	2	2.56
Moderate	0	0.00	0	0.00	0	0.00
Severe	0	0.00	0	0.00	0	0.00
Total	51	100.00	27	100.00	78	100.00
P value Chi Squared Test				0.703		

While analysing temperature status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had normal temperature (n=76, 97.44%).
- In PDA closed group majority of the study subjects had normal temperature (n=49, 96.08%).
- In PDA not closed group, majority of the study subjects had normal temperature (n=27, 100%).

When statistically comparing temperature status between the study groups, the difference in the incidence of temperature groups was found to be statistically non-significant ($p > 0.05$).

Duration of Mechanical Ventilation



Duration of Mechanical Ventilation Status	PDA Closed	%	PDA Not Closed	%	Total	%
1-2 Days	2	3.92	3	11.11	5	6.41
3-4 Days	14	27.45	6	22.22	20	25.64
5-6 Days	8	15.69	1	3.70	9	11.54
> 6 Days	0	0.00	1	3.70	1	1.28
No Mechanical Ventilation	27	52.94	16	59.26	43	55.13
Total	51	100.00	27	100.00	78	100.00

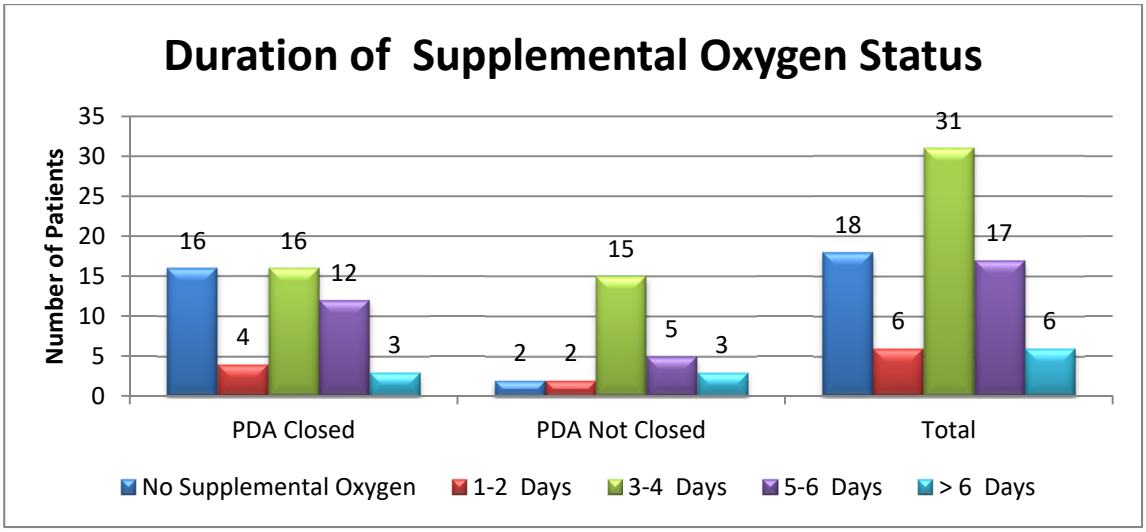
Duration of Mechanical Ventilation Distribution	PDA Closed	PDA Not Closed	Total
Mean	3.92	3.64	3.83
SD	1.14	1.50	1.25
P value Unpaired t Test	0.590		

While analysing duration of mechanical ventilation distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had duration of mechanical ventilation between 3-4 days (n=20, 25.64%) with a mean duration of mechanical ventilation of 3.83 days.
- In PDA closed group, majority of the study subjects had duration of mechanical ventilation between 3-4 days (n=14, 27.45%) with a mean duration of mechanical ventilationof 3.92 days..
- In PDA not closed group, majority of the study subjects had duration of mechanical ventilation between 3-4 days (n=6, 22.22%) with a mean duration of mechanical ventilationof 3.64 days.

When statistically comparing duration of mechanical ventilation distribution between the study groups, the difference in the mean duration of mechanical ventilation was found to be statistically non-significant ($p > 0.05$).

Duration of Supplemental Oxygen



Duration of Supplemental Oxygen Status	PDA Closed	%	PDA Not Closed	%	Total	%
No Supplemental Oxygen	16	31.37	2	7.41	18	23.08
1-2 Days	4	7.84	2	7.41	6	7.69
3-4 Days	16	31.37	15	55.56	31	39.74
5-6 Days	12	23.53	5	18.52	17	21.79
> 6 Days	3	5.88	3	11.11	6	7.69
Total	51	100.00	27	100.00	78	100.00

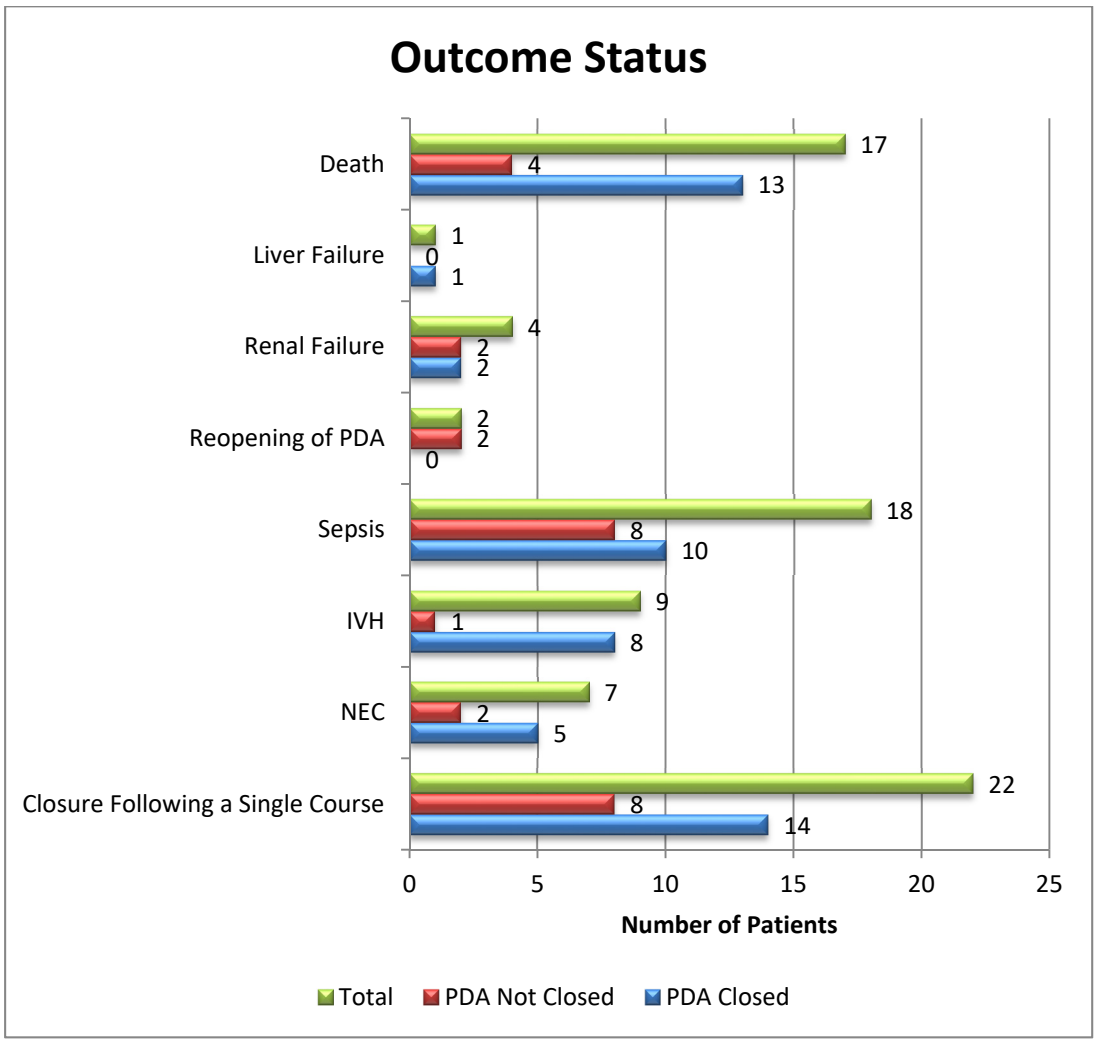
Duration of Supplemental Oxygen Distribution	PDA Closed	PDA Not Closed	Total
Mean	4.35	4.00	4.30
SD	1.66	0.00	1.52
P value Unpaired t Test	0.135		

While analysing duration of supplemental oxygen distribution among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had duration of supplemental oxygen between 3-4 days (n=31, 49.74%) with a mean duration of supplemental oxygen of 4.30 days.
- In PDA closed group, majority of the study subjects had duration of supplemental oxygen between 3-4 days (n=16, 31.37%) with a mean duration of supplemental oxygen of 4.35 days..
- In PDA not closed group, majority of the study subjects had duration of supplemental oxygen between 3-4 days (n=15, 55.56%) with a mean duration of supplemental oxygen of 4.00 days.

When statistically comparing duration of supplemental oxygen distribution between the study groups, the difference in the mean duration of supplemental oxygen was found to be statistically non-significant ($p > 0.05$).

Outcome


Outcome Status
Death
17
4
13
Liver Failure
1
0
1
Renal Failure
4
2
2
Reopening of PDA
2
2
0
Sepsis
18
8
10
IVH
9
1
8
NEC
7
2
5
Closure Following a Single Course
22
8
14
0
5
10
15
20
25
Number of Patients
Total
PDA Not Closed
PDA Closed

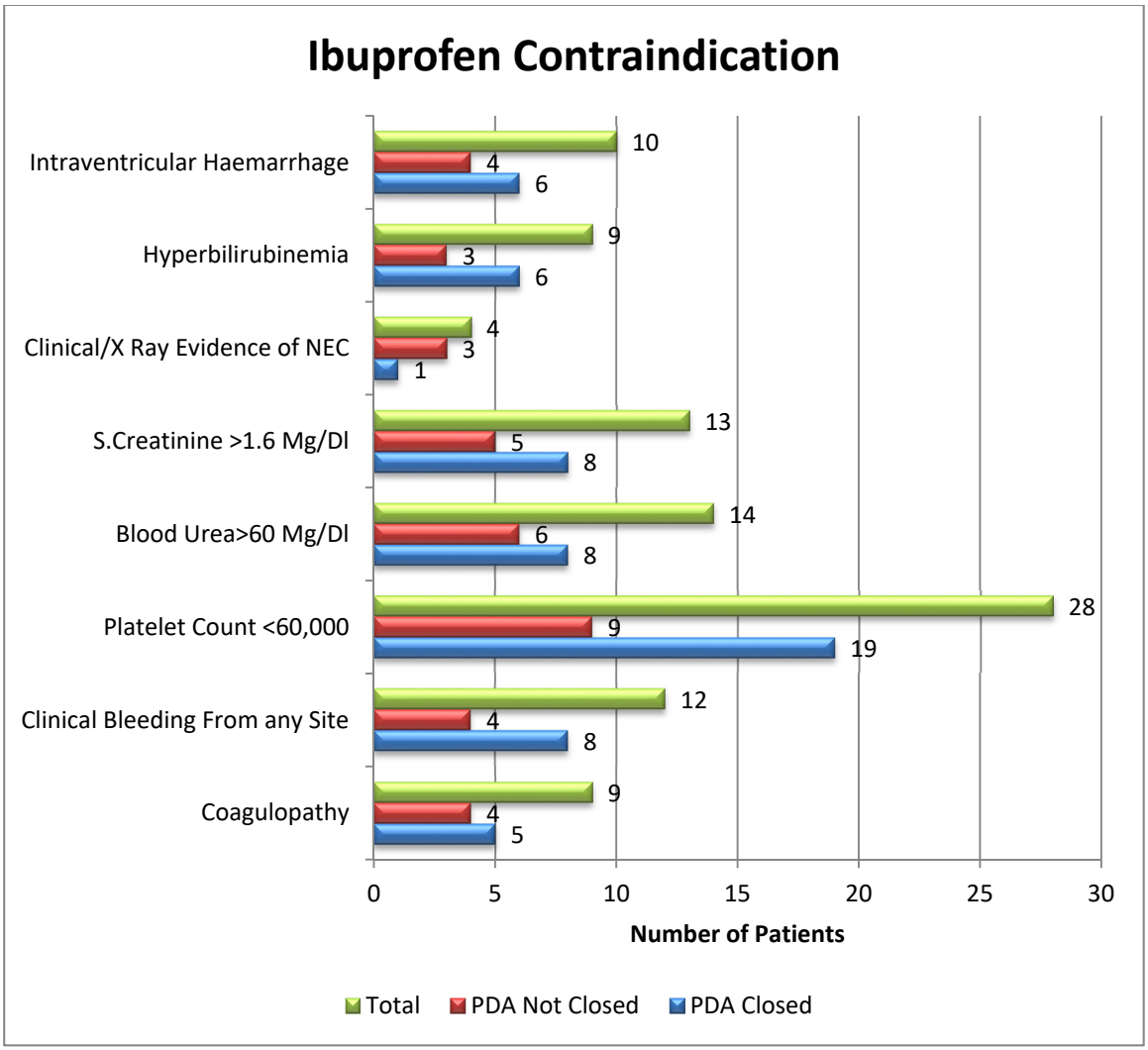
Outcome Status	PDA Closed	%	PDA Not Closed	%	Total	%	P value Chi Squared Test
Closure Following a Single Course	14	28.00	8	28.57	22	28.21	0.957
NEC	5	10.00	2	7.14	7	8.97	0.672
IVH	8	16.00	1	3.57	9	11.54	0.099
Sepsis	10	20.00	8	28.57	18	23.08	0.389
Reopening of PDA	0	0.00	2	7.14	2	2.56	0.056
Renal Failure	2	4.00	2	7.14	4	5.13	0.546
Liver Failure	1	2.00	0	0.00	1	1.28	>0.999
Death	4	26.00	13	14.29	17	21.79	0.299

While analysing outcome status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had sepsis as outcome (n=18, 23.08%) followed by death (n=17, 21.79%)
- In PDA closed group,majority of the study subjects had sepsis as outcome (n=10, 26.00%) followed by IVH (n=8, 20.00%)
- In PDA not closed group, majority of the study subjects had death as outcome (n=13, 28.57%) followed by sepsis (n=8, 14.29%)

When statistically comparing outcome status between the study groups, the difference in the incidence of outcome groups was found to be statistically non-significant ($p > 0.05$).

Ibuprofen Contraindication



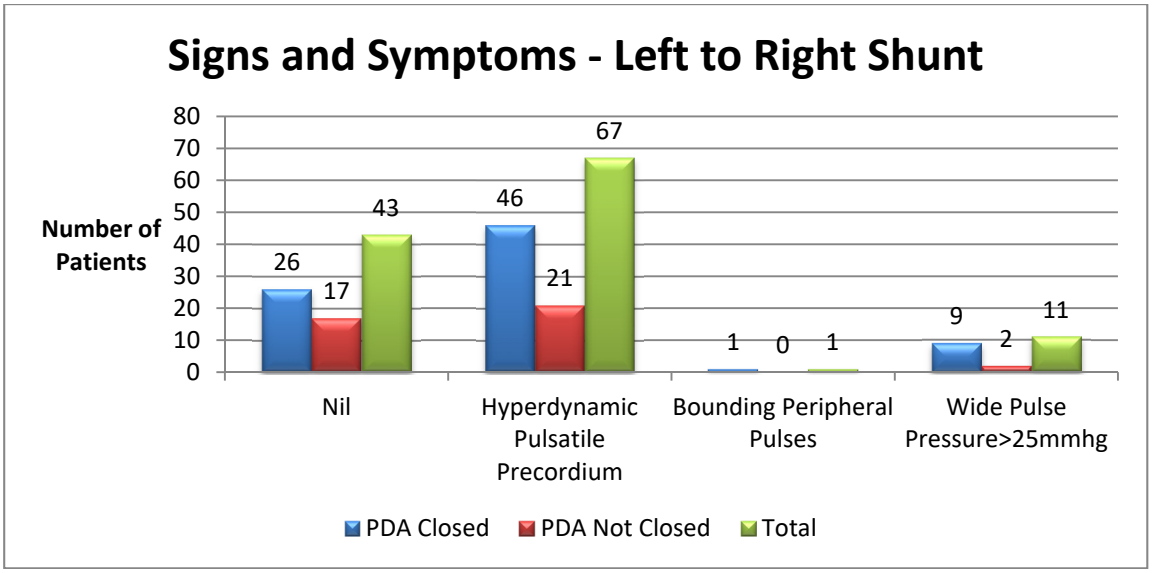
Ibuprofen Contraindication	PDA Closed	%	PDA Not Closed	%	Total	%	P value Chi Squared Test
Coagulopathy	5	9.80	4	14.81	9	11.54	0.247
Clinical Bleeding From any Site	8	15.69	4	14.81	12	15.38	0.148
Platelet Count <60,000	19	37.25	9	33.33	28	35.90	0.312
Blood Urea>60 Mg/Dl	8	15.69	6	22.22	14	17.95	0.968
S.Creatinine >1.6 Mg/Dl	8	15.69	5	18.52	13	16.67	0.483
Clinical/X Ray Evidence of NEC	1	1.96	3	11.11	4	5.13	0.557
Hyperbilirubinemia	6	11.76	3	11.11	9	11.54	0.557
Intraventricular Haemarrhage	6	11.76	4	14.81	10	12.82	0.334

While analysing ibuprofen contraindication status among study patients, it was observed that;

- Among the total study subjects, majority of the study subjects had platelet count <60,000 as sign of ibuprofen contraindication (n=28, 35.90%) followed by blood urea>60 Mg/dl(n=14, 17.95%)
- In PDA closed group, majority of the study subjects had platelet count <60,000 as sign of ibuprofen contraindication (n=19, 37.25%) followed by blood urea>60 Mg/dl/clinical bleeding from any site/S.Creatinine >1.6 Mg/dl(n=8, 15.69%)
- In PDA not closed group, majority of the study subjects had platelet count <60,000 as sign of ibuprofen contraindication (n=9, 33.33%) followed by blood urea>60 Mg/dl(n=6, 22.22%)

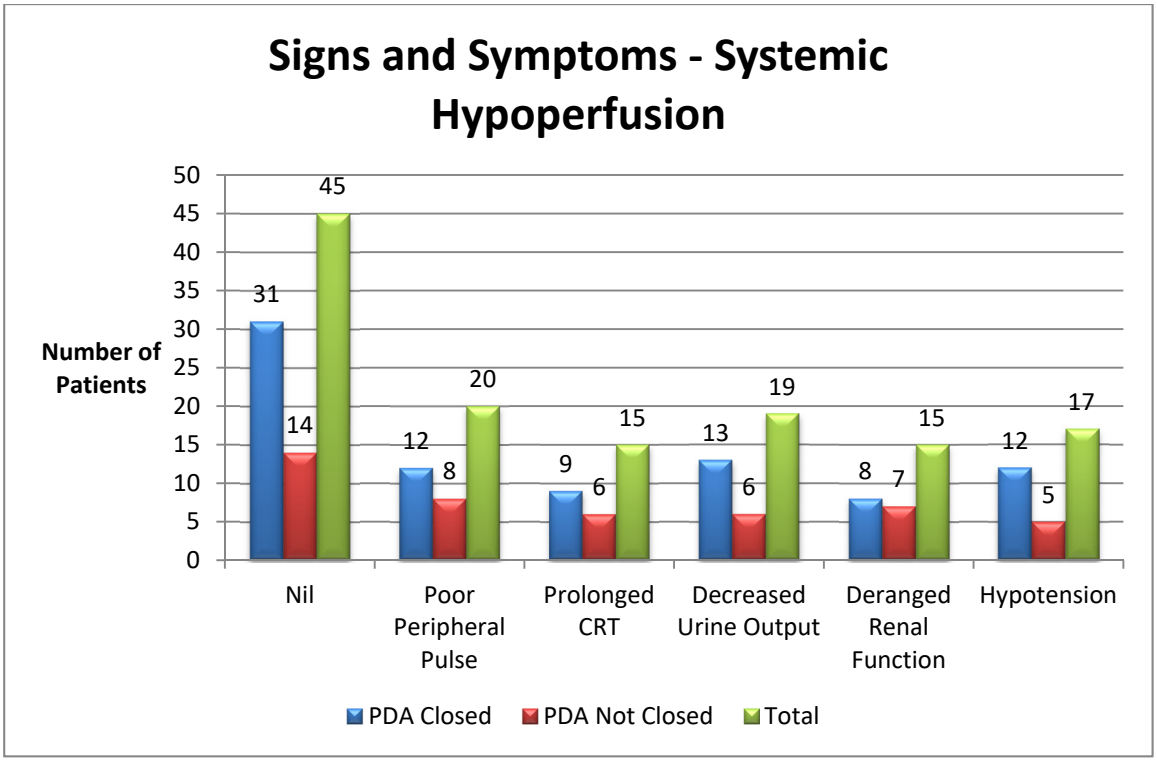
When statistically comparing ibuprofen contraindication status between the study groups, the difference in the incidence of outcome groups was found to be statistically non-significant (p >0.05).

Signs and Symptoms - Left to Right Shunt



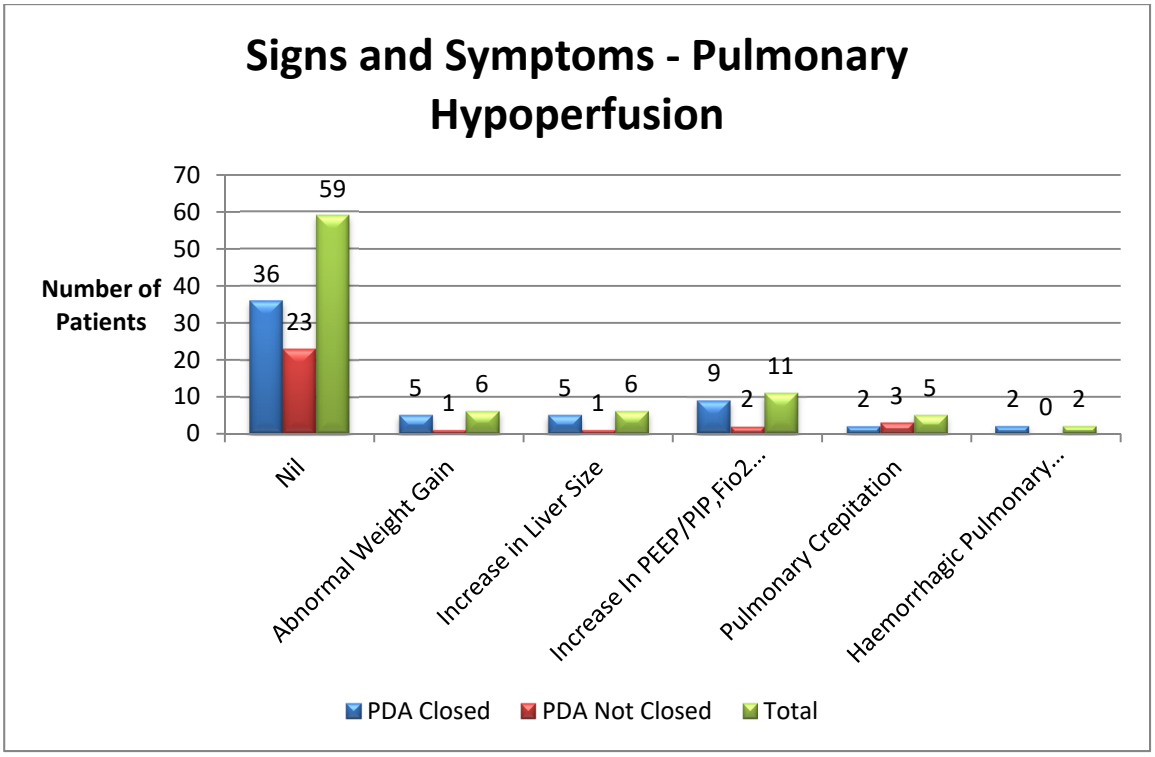
Signs and Symptoms - Left to Right Shunt	PDA Closed	%	PDA Not Closed	%	Total	%	P value Chi Squared Test
Nil	26	50.98	17	62.96	43	55.13	0.889
Hyperdynamic Pulsatile Precordium	46	90.20	21	77.78	67	85.90	0.988
Bounding Peripheral Pulses	1	1.96	0	0.00	1	1.28	0.749
Wide Pulse Pressure>25mmhg	9	17.65	2	7.41	11	14.10	0.633

Signs and Symptoms - Systemic Hypoperfusion



Signs and Symptoms - Systemic Hypoperfusion	PDA Closed	%	PDA Not Closed	%	Total	%	P value Chi Squared Test
Nil	31	60.78	14	51.85	45	57.69	0.142
Poor Peripheral Pulse	12	23.53	8	29.63	20	25.64	0.506
Prolonged CRT	9	17.65	6	22.22	15	19.23	0.349
Decreased Urine Output	13	25.49	6	22.22	19	24.36	0.307
Deranged Renal Function	8	15.69	7	25.93	15	19.23	0.232
Hypotension	12	23.53	5	18.52	17	21.79	0.085

Signs and Symptoms - Pulmonary Hypoperfusion



Signs and Symptoms - Pulmonary Hypoperfusion	PDA Closed	%	PDA Not Closed	%	Total	%	P value Chi Squared Test
Nil	36	70.59	23	85.19	59	75.64	0.722
Abnormal Weight Gain	5	9.80	1	3.70	6	7.69	0.942
Increase in Liver Size	5	9.80	1	3.70	6	7.69	0.853
Increase In PEEP/PIP,Fio2 Requirements	9	17.65	2	7.41	11	14.10	0.960
Pulmonary Crepitation	2	3.92	3	11.11	5	6.41	0.940
Haemorrhagic Pulmonary Edema	2	3.92	0	0.00	2	2.56	0.704

Effect of Paracetemol on PDA

Variable	Before Paracetamol	After Paracetamol	P value
SGOT (U/L)	31.15±4.26	31.79±7.39	0.508
SGPT (U/L)	29.79±5.03	31.67±8.33	0.092
LFT Abnormal Changes	0 (0.00%)	1 (1.28%)	0.316
PDA measurement (mm)	3.01±0.64	1.10±1.52	<0.001
Temperature Variation	0 (0.00%)	0 (0.00%)	>0.999

While analysing effect of paracetamol on PDA among study patients, it was observed that;

- Before administration of paracetamol, study subjects mean SGOT levels of 31.15 U/L, SGPT levels of 29.79 U/L, mean PDA measurement of 3.01 mm and no LFT abnormal changes and temperature variation
- After administration of paracetamol, study subjects mean SGOT levels of 31.15 U/L, SGPT levels of 31.67 U/L, mean PDA measurement of 1.10 mm and 1.28% LFT abnormal changes and no temperature variation

When statistically comparing effect of paracetamol on PDA between the study groups, the difference in the mean SGOT and SGPT measurements and incidence of LFT abnormal changes and temperature variation was found to be statistically non-significant ($p > 0.05$). But the difference in the mean PDA measurements was found to be statistically significant ($p < 0.05$).

DISCUSSION

Several RCTs and observational studies have been conducted for the treatment of HsPDA in preterm neonates to date. In the first case series by Hammerman et al demonstrated that oral paractamol was effective in patients who did not respond to ibuprofen.

In our study a total of 78 preterm neonates with hemodynamically significant PDA with ibuprofen contraindication were included. Ductal closure was observed in 51 babies accounting for 65.38%. This is in accordance with the study conducted by Al - Lawama at al at the university of Jordan in preterm neonates <32weeks. The primary closure rate was 69% in the paracetamol group with no adverse effects.

In a study conducted by Sunil et al at Kempagowda Institute of Medical sciences,Bangalore among 36 babies who received paracetamol PDA closure was evident in 27 babies accounting for 75% with no significant side effects.

In a study conducted by Mohanty et al at Manipal hospital,Bangalore in preterm neonates <32 weeks where ibuprofen was contraindicated reported a closure of 72.5% with no major complications.

According to Terrin G et al reported a case series of neonates with HsPDA closure rate of 70%. The mechanism by which paracetamol can close ibuprofen refractory PDA might lie in the different site of action on prostaglandin synthetase of the two drugs.

Closure rates of PDA in Oncel et al were 72.5% in in the paracetamol group after the first course of treatment. Furthermore closure rates were 81.2% in acetaminophen group by Dang et al.

In the observational study by Sinha et al at Military hospital, Punjab , 10 neonates with HsPDA and brufen contraindication were given paracetamol and ductal closure achieved in all these babies.

Dang et al studied 160 infants with gestational age <34 weeks treated with15mg/kg every 6hr for 3days of paracetamol and found that ductus was closed in81.2% of paracetamol group compared with 78.8% of infants in the ibuprofen group and the incidence of hyperbilirubinemia or gastrointestinal bleeding was significantly lower in the paracetamol group.

Vaidya et al conducted a study at university of Massachusetts medical school-Baystate ,out of 43 infants 25 were with acetaminophen and 18 with indomethacin. Successful PDA closure rate was slightly lower for acetaminophen (40%) compared to indomethacin (55.5%) although statistically significant (p=0.31).

Guimaraes et al at university of Minas Gerais , Brazil conducted a retrospective study in 87 preterm newborns with a postnatal age of 3 to27 days received acetaminophen for 3 to 7 days. A second cycle was administered in case of reopening of ductus. The ductal closure rate after one or two cycles was 74.4% and the recommendations for surgical ligation was reduced to 50% and concluded that acetaminophen showed to be an effective alternative for the closure of ductus arteriosus for preterm neonetes in whom indomethacin or ibuprofen was contraindicated.

In the study conducted by Dash et al.,comparing the use of oral acetaminophen to intravenous indomethacin obtained a ductal closure rate of 100% with a 7 day treatment of acetaminophen.

BEFORE AND AFTER PARACETAMOL- DUCTAL DIAMETER

On comparison of PDA measurements distribution between the study groups, the difference in the mean PDA measurements among patients in after paracetamol group compared to before paracetamol group was 1.90mm lower.. This trend of significantly lower mean PDA measurements after paracetamol group compared to before paracetamol group was found to be in the range of 63% decrease.

In the study conducted by Rizky Adriansyah et al at University of Indonesia Medical school babies aged 2 and 7 days received intravenous paracetamol for 3 days. Preintervention PDA diameter assessed at 24 hours after the intervention and at 14 days of life. Mean duct diameters before ,24 hours after the intervention and at 14 days of life were 3.0,0.9 and 0.6mm respectively (p value<0.0001). There was a significant reduction in the ductal diameter following paracetamol administration.

In the study conducted by Harkin et al,a randomized trial the ductal caliber was significantly reduced with a p-value of 0.016

The same view was echoed by Gianluca Terrin et al.,where there was significant reduction in median ductal diameter.

It can be concluded that treatment with oral paracetamol is associated with PDA closure. Babies with treatment on oral paracetamol are 3.54 times more likely to have closure of PDA. The use of paracetamol for ductus arteriosus closure could be effective, economical and with fewer side effects than current treatments, Our data on the effectiveness of paracetamol in the treatment of PDA merits for conduction of further well designed and robust randomized control trials, to confirm the usefulness of paracetamol as first choice agent in management of PDA due its lesser side effect

profile. It may also be considered as an alternative to surgical ligation in whom ibuprofen is either contraindicated or resistant.

ANTENATAL STEROIDS:

On comparison of ante natal steroid intake distribution between the study groups, the difference in the incidence of ante natal steroid intake among patients in PDA closed group compared to PDA not closed group was 37.25 percentage points higher.. This trend of significantly higher incidence of ante natal steroid intake in PDA closed group compared to PDA not closed group was found to be in the range of 53% increase.According to Ramesh et al lack of antenatal steroids is one of the risk factor for PDA and antenatal steroids decreases the incidence of RDS and invariably the need for mechanical ventilation and oxygen therapy.

COURSE OF TREATMENT:

In our study closure following first course was 22 neonates. Second course were given for 56 neonates out of which 29 babies had complete ductal closure accounting for 56.86% . This is in accordance with study conducted by Mohammed et al at Kerman institute of medical sciences where PDA closure rate after the second course was found to be 50%.

In the study conducted by Dang et al in China reported a overall closure rate of paracetamol about 81.2% with secondary closure accounting for about 25%.

El-khuffash et al have compared long days(7) to short days (2) courses of oral paracetamol and obtained better results with the long course.

In the study of Guimaraes et al the efficacy of paracetamol after the first cycle was 62% (54/87) and a second cycle was performed in 15 patients with a success rate of 73.3% (11/15).

RE-OPENING AFTER CLOSURE.

In our study two cases (3.9%) had re-opening of PDA following ductal closure.This is comparable with the study conducted by Dang et al at China where the rate of re-opening after closure in the paracetamol group was 5(7.7%) out of 65 neonates.

In contrast the study conducted by Oncel et al the re-opening rate was higher in the paracetamol group than in the ibuprofen group but the re-opening rates were not statistically significant.

RESUSCITATION REQUIRED AT BIRTH

On comparison of resuscitation at birth distribution between the study groups, the difference in the incidence of resuscitation at birth among patients in PDA closed group compared to PDA not closed group was 57.98 percentage points lower.. This trend of significantly lower incidence of resuscitation at birth in PDA closed group compared to PDA not closed group was found to be in the range of 94% decrease. Hypoxia were associated with increased incidence of PDA according to Nizarali et al., Tsai M-L et al.

It can be concluded that resuscitation at birth is associated with PDA non-closure. Babies with resuscitation at birth are 15.79 times more likely to have non-closure of PDA than those without resuscitation at birth.

POST NATAL AGE OF TREATMENT

On comparison of post natal age at start of oral paracetemol distribution between the study groups, the difference in the mean post natal age at start of oral paracetemol among patients in PDA closed group compared to PDA not closed group was 0.53 days lower.. This trend of significantly lower mean post natal age at start of oral paracetemol in PDA closed group compared to PDA not closed group was found to be in the range of 13% decrease.The same view was echoed by Oncel et al. In this study the infants treated were <30 weeks and before 96 hrs with PDA closure rate of 77.5%.

SHUNT SIZE

There is no statistical significance between rate of PDA closure and shunt size in our study.

However in the study of Guimaraes et al a decreased rate of PDA has been observed in greater ductal diameter.

TEMPERATURE VARIATION

In our study there was no significant temperature changes before and after paracetamol. This is in accordance with the study by Sinha et al where no differences in temperature noted.

LIVER FUNCTION TEST:

In this study only one baby had elevation of transaminases attributed by sepsis related neonatal cholestasis. This is in accordance with study conducted by Oncel et al., Al-Lawama et al., Sinha et al., Terrin et al., Guimaraes et al.,Dang et al.,where no significant transaminitis seen.

LIMITATION

- There was no control group in this study
- Spontaneous closure could have confounded the results
- Long term follow up including neurodevelopmental outcome could not be done
- This study enrolled preterm infants <34 weeks who needed treatment for HsPDA but further studies are needed for the comparison of treatment in a group of infants <1000g who are likely to have a PDA that is unlikely to close spontaneously for several weeks and who are most likely to benefit from the treatment.

CONCLUSION

Unlike ibuprofen and indomethacin paracetamol has no peripheral vasoconstrictive properties and has fewer side effects thus providing an attractive choice for the treatment of HsPDA. Previously in case of ibuprofen or indomathacin contraindication surgical ligation is the only option but now paracetamol serves as an effective alternative in indomathacin or ibuprofen contraindicated cases. In conclusion these results showed that paracetamol may particularly suitable for early closure of ductus as it appears additionally to be safe

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PROFORMA

- Mother name:
- age:
- Baby sex:
- Date of birth
- Presenting complaints

ANTENATAL HISTORY

- Obstetric score:
- LMP:
- EDD:
- Booked &immunised-
- Anemia/PIH/GDM
- Antepartum haemorrhage/Leaking PV/Maternal fever
- AN USG

BIRTH DETAILS

- Mode of delivery
- cried immediately after birth-yes/no
- Birth weight-

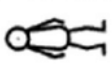
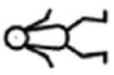
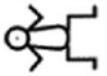
EXAMINATION

Vitals:

- HR
- RR
- SpO2
- NIBP Pulse pressure
- CRT
- Peripheral pulse
- Temp
- U/O
- Cry,activity
- Weight gain

- NEW BALLARDS SCORING

Neuromuscular Maturity

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)	 >90°	 90°	 60°	 45°	 30°	 0°	
Arm recoil		 180°	 140°–180°	 110°–140°	 90°–110°	 <90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior ⅔	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

SYSTEMIC EXAMINATION:

- CVS
- RS
- P/A
- CNS

-

- Mechanical ventilation
- Supplemental oxygen

INVESTIGATION

- Platelet count
- RFT
- CRP/NEC
- PT/APTT
- ECHO FINDINGS-

Shunt

Size

MPAP

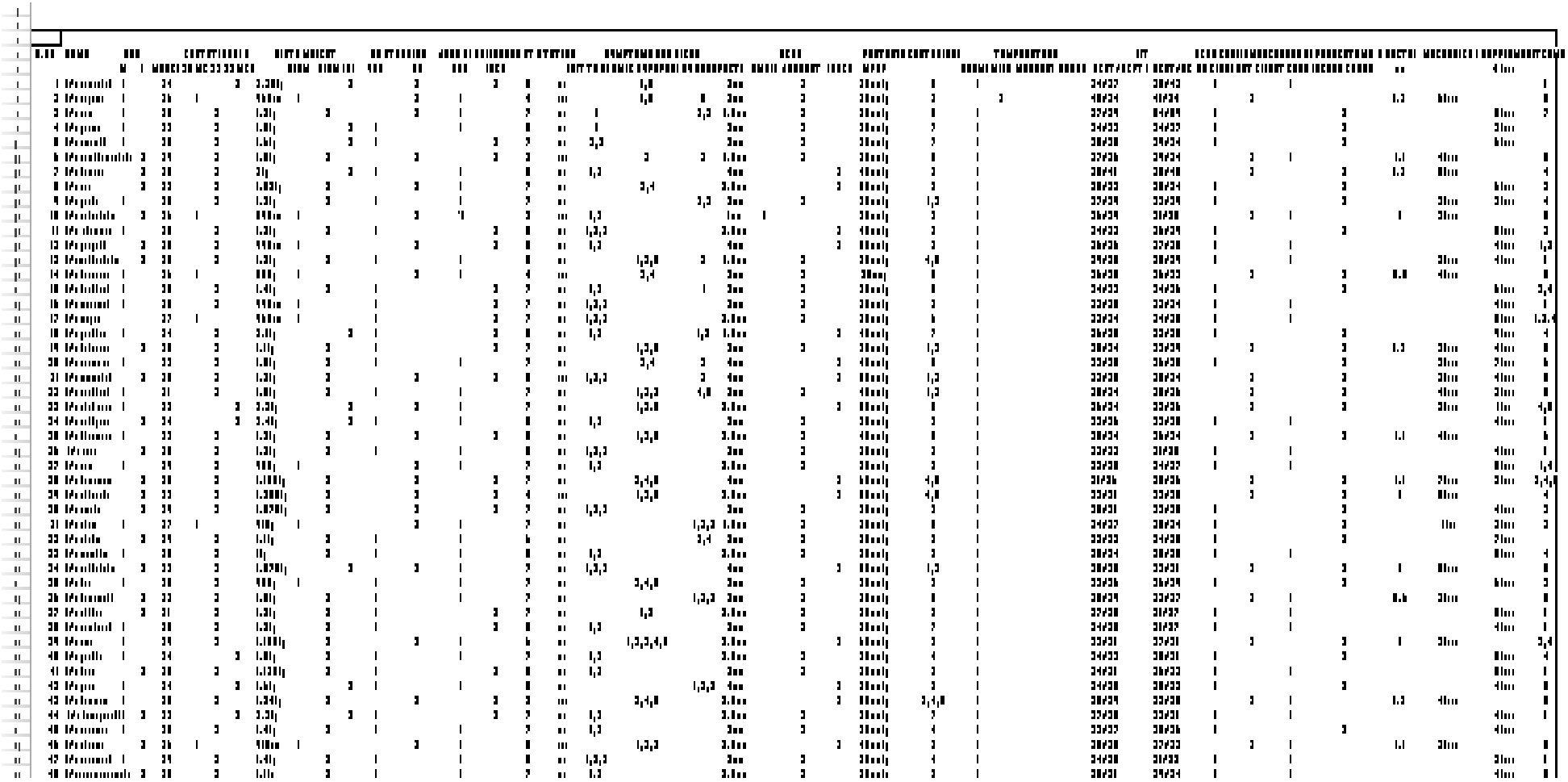
- Brufen contraindication

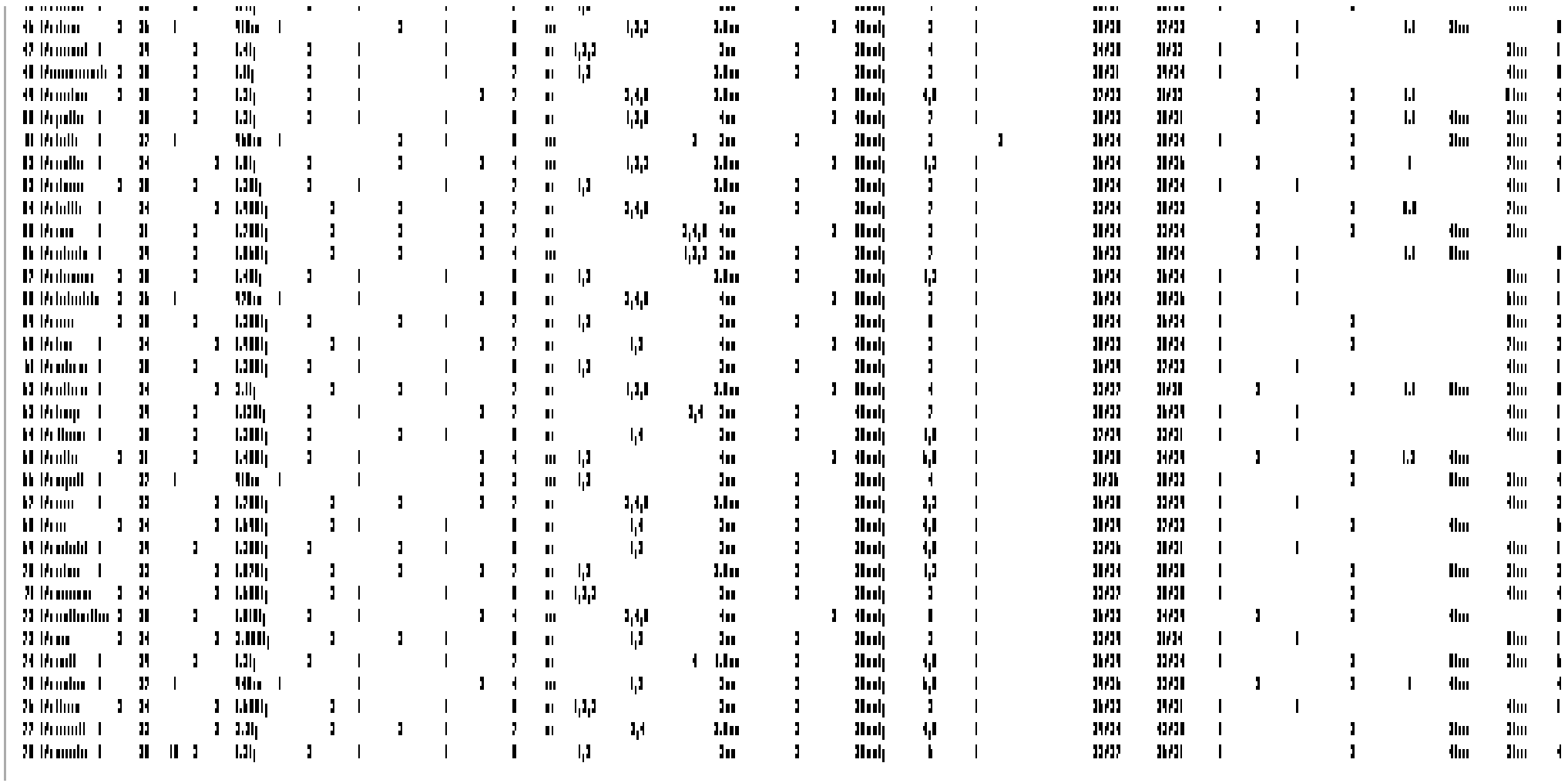
Thrombocytopenia	☐
Azotemia/oliguria	☐
Bleeding diathesis	☐
NEC	☐

- ORAL PARACETAMOL 15mg/kg

- COMPLICATIONS POST ADMINISTRATION
- REPEAT ECHO
- RESULTS

MASTER CHART





ABBREVIATIONS

DA- Ductus arteriosus

PDA- patent ductus arteriosus

HsPDA- hemodynamically significant patent ductus arteriosus

NT proBNP- N terminal pro Brain Natriuretic Peptide

CTnT- Cardiac Troponin

COX- cyclo oxygenase

NSAIDS- Non Steroidal Anti-Inflammatory Drugs

NEC-Necrotising Enterocolitis

CLD- Chronic Lung Disease

IVH- Intraventricular haemarrhage

ROP- Retinopathy Of Prematurity

PVL- periventricular leuckomalacia

BPD- bronchopulmonary dysplasia

GA- gestational age

VLBW- very low birth weight

PGE2- Prostaglandin E2

NO- nitric oxide

CPAP-continuous positive airway pressure

PEEP- peak end expiratory pressure

FiO_2- fraction of inspired oxygen

CKD- chronic kidney disease

AST- aspartate aminotransferase

ALT- alanine aminotransferase

MPAP- mean pulmonary artery pressure

SGOT – serum glutamic oxaloacetic transaminase

SGPT- serum glutamic pyruvic transaminase

NAPQI- N-acetyl-p-benzoquinone imine