"COMPARISON OF EFFICACY AND SAFETY OF ORAL IBUPROFEN VERSUS INTRAVENOUS PARACETAMOL IN THE CLOSURE OF PATENT DUCTUS ARTERIOSUS IN PRETERM NEONATES, A ONE YEAR RANDOMISED CONTROL TRIAL"

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With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF EFFICACY AND SAFETY OF ORAL IBUPROFEN VERSUS INTRAVENOUS PARACETAMOL IN THE CLOSURE OF PATENT DUCTUS ARTERIOSUS IN PRETERM NEONATES, A ONE YEAR RANDOMISED CONTROL TRIAL ",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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LIST OF ABBREVIATIONS

DA	-Ductus arteriosus
PDA	-Patent ductus arteriosus
HsPDA	-Hemodynamically significant patent ductus arteriosus
WHO	- World Health Organisation
BPD	- Bronchopulmonary dysplasia
IVH	-Intraventricular Haemorrhage
PVL	-Periventricular Leukomalacia
ARF	-Acute renal failure
NEC	-Necrotizing enterocolitis
COX	-cyclooxygenase
EC	-electrocardiogram
ECHO	-Echocardiogram
PGE2	-Prostaglandin E2
NSAIDS	-Non steroidal anti inflammatory drugs
VLBW	-Very low birth weight
PCT	-Paracetamol

LSCS	-Lower segment caesarean section
NVD	-Normal vaginal delivery
PLT	-Platelet
Hb	- Haemoglobin
TLC	-Total leukocyte count
SGOT	-Serum glutamic-oxaloacetic transaminase
SGPT	- Serum glutamic-pyruvic transaminase
Creat	-Creatnine
mg/kg/d	- milligram per kilogram per day
gm/dl	- Grams per decilitre
OD	-Once daily
BD	-twice a day
TID	-three times a day
QID	-four times a day
IV	-Intravenous

ABSTRACT

INTRODUCTION-

Ductus arteriosus (DA) is a communication between thepulmonary artery and the aorta.Generally ,the functional closure of the ductus arteriosus occurs in the first 72 hours of life and anatomical closure occurs within first 2-3 weeks of life.It is one of the most common problems in the preterm infants and accounts for about 10% ofcongenital heart lesions.

A small PDA remains asymptomatic and is diagnosed by a murmur whereas , a large DA may result in heart failure. Clinical criteria for hsPDA are Tachycardia, bounding pulse with wide pulse pressure, hyperdynamic precordium with continuous murmur on auscultation, hepatomegaly, and the failure of respiratory distress syndrome to improve within 2–7 days.

AIMS AND OBJECTIVE

PRIMARY OBJECTIVE:

To compare the efficacy of oral Ibuprofen and IV Paracetamol in the closure of hsPDA in preterm neonates.

SECONDARY OBJECTIVE:

To determine the safety and adverse effects of both ibuprofen and paracetamol.

MATERIAL AND METHODOLOGY

All the neonates who are diagnosed clinically with PDA and confirmed by 2D-echo will be enrolled randomly assigned into 2 groups in the ratio of 1:1.Each of the groups will receive treatment alloted to them.

IV PARACETAMOL-Group A, 15 mg/kg every 6 hourly for 3 consecutive days)

ORAL IBUPROFEN-Group B- 10 mg/kg ibuprofen followed by 5 mg/kg/day for 2 days)

The patients will undergo repeat 2Decho to assess the closure of PDA after 3days.If the PDA is still persistant,a repeat dose of the same drug will be given for another 3 days.

Repeat echo cardiographical examination will be done with in 24 hours of last dose.

RESULTS –

According to our research, the most common symptom was fast breathing (80.77%), followed by rapid heart rate (71.15%), implying that the majority of them complained of fast breathing.The most common findings in our study were murmur and oxygen desaturation (84.62% each), followed by bounding pulse (82.69%).

The majority of babies (40.38%) showed complete closure after the first dose, followed by a significant reduction in size (38.46%).After the second dose, 30.77% of the infants had complete closure. After the second dose, approximately 19.23% of the patients were still open. After receiving the first dose of treatment, 15 (57.69%) of the 26 patients in the ibuprofen group had significant reductions in the size of their PDA, while 7 (26.92%) had complete closure. In the paracetamol group, 14 (53.8%) of the 26 patients had complete closure and 7 (26.92%) had a significant reduction in the size of the PDA. After receiving the second dose of treatment, 11 (42.3%) of the 26

patients in the ibuprofen group had complete closure, while 6 (23.0%) remained unclosed. In the paracetamol group, 5 (19.2%) of the 26 wounds were completely closed, while 4 (15.3%) remained open. In our study, 19 patients (73.07%) had complete closure after paracetamol treatment, and 18 patients (69.23%) had complete closure after ibuprofen treatment.

CONCLUSION-

We concluded from this study that both drugs are equally effective in closing the hemodynamically significant PDA. However, when compared to Oral Ibuprofen, the closure rate of PDA with intravenous paracetamol was higher after the first course of the drug. In addition, paracetamol has fewer side effects than ibuprofen. Thus, the use of any of the drugs is effective in the closure of hsPDA, reducing the need for the baby to be subjected to unnecessary surgical procedures.

KEYWORDS-Patent ductus arteriosus, Paracetamol, Ibuprofen,2D Echo.

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INTRODUCTION

A insistent opening among the two main blood arteries that branch off of the heart is known as patent ductus arteriosus (PDA for short). This opening, known as the ductus arteriosus, is a normal component of a newborn's circulatory system while it is still in the mother's womb. It typically closes soon after the baby is born. In the event that the ductus does not close, the patient will have what is known as a patent (or "open") ductus arteriosus. The PDA enables the mixing of oxygen-rich blood coming from the aorta with oxygen-poor blood coming from the pulmonary artery. Due to this, an excessive amount of blood is pumped into the lungs and stresses heart and raises the blood pressure in the pulmonary arteries (1).

When the PDA (ductus) is not too large, there is no additional strain placed on the heart and lungs as a result. It's possible that surgery and other therapies won't be necessary. Within the first several months of their lives, little PDAs frequently stop working on their own. Medicine can frequently assist for the closing of ductus in premature newborns. Medicine, catheter-based procedures, and surgery are the three therapeutic modalities that are available for patients with PDA. A physician will recommend the closure of a PDA if it is determined that there is a substantially large PDA which overburdened the lungs with blood and inurn enlarges the heart. A physician might also close a PDA in order to lessen the likelihood of the patient acquiring endocarditis (infection of tissue that lines blood arteries and the heart). Endocarditis is a dangerous condition that must be treated with antibiotics administered intravenously (IV) (1).

The existing treatment for PDA consists of two phases: the first phase is the treatment with NSAID (pharmacological), and the second phase is the surgical ligation. Medical professionals always make sure to prevent surgical ligation because it has serious side effects. Ibuprofen or indomethacin is typically used as the primary medication in the standard medical treatment for PDA closure. Both have a success rate of between 70 and 80 percent in cases of encouraging ductal closure. These medications have the potential to induce serious adverse effects, such as gastrointestinal perforations, acute renal failure, and bleeding disorders. Ibuprofen has found to have lesser side effects as compared to indomethacin seems to be preferred drug for PDA closure pharmacologically. But it cannot be an ideal drug due to its inadequate safety profile and 30% rate of failure in the treating PDA closure pharmacologically. In a number of preterm newborns, PDA closure using paracetamol was shown to be successful in randomised controlled trials. In addition, it has been discovered that Paracetamol has a superior safety profile than the above mentioned drugs. Paracetamol has demonstrated lesser rate of renal and gastrointestinal adverse effects and no damaging effect on oxygenation of cerebral. These findings have been published in the journals. According to Hammerman et al., (2011) (2), use of paracetamol as PDA treatment in five neonates had contraindications to ibuprofen medication. These neonates were treated for PDA with paracetamol. This method was described for the first time. There were no adverse effects recorded despite the fact that the rate of ductus closure was 100%. Additional case reports and clinical trials assessing the efficacy of this novel therapeutic approach have been published in the years that followed.

However, recently, concerns have been raised about paracetamol's effectiveness. This is due to the fact that only one randomised controlled trial investigated the efficiency of paracetamol. Retrospective studies have showed less effective in PDA closure or constriction in contrast with indomethacin.

The two drugs that are frequently used as the initial treatment for PDA are ibuprofen and indomethacin. However, because of the risk of possibly fatal adverse effects connected with their use, medical professionals are looking at other treatment possibilities. Usage of paracetamol to treat PDA as an alternative to ibuprofen is currently based on an insufficient amount of clinical data. As a result, additional clinical trials are required to demonstrate a therapeutic function of the drug for managing the disease. These additional clinical trials should take into account both the short-term and the long-term outcomes of safety and efficacy. As a result of these considerations, we came to the conclusion that additional research was required to either validate or refute past findings about the effectiveness of paracetamol and to acquire additional information regarding the drug's potential adverse effects. As a consequence, the drive of this study was to evaluate the effectiveness and safety of ibuprofen versus intravenous paracetamol in treatments of PDA in preterm newborns.

OBJECTIVES

PRIMARY:

To compare the efficacy of oral Ibuprofen and IV Paracetamol in the closure of hsPDA in preterm neonates.

SECONDARY:

To determine the safety and adverse effects of both ibuprofen and paracetamol treatment in the closure of hsPDA in preterm neonates.

REVIEW OF LITERATURE

2.1. Patent ductus arteriosus

According to González MDR (2008) (3), the ductus arteriosus (DA) is a vital vascular shunt that develops throughout the embryonic stage of life and connects the aorta and the pulmonary artery. Because they are receiving oxygen from their mother while they are still inside their mother's womb, babies do not require lungs to supply oxygen while they are in the womb. Because a baby's lungs cannot produce oxygen, it is not necessary for the heart to pump blood to the lungs in order for the baby to breathe. The DA is a blood vessel that is present in all babies while they are still inside the mother's womb. It is responsible for allowing blood to travel around the lungs and get directly to the heart. After the umbilical cord has been severed and the baby has been delivered, the infant's lungs must begin to provide oxygen to the rest of the body. Within the first few hours of a newborn's existence, the ductus arteriosus typically closes, the lungs expand, and the blood vessels relax to allow for a greater flow of blood through them. Sometimes the ductus arteriosus may not seal on its own after a certain amount of time has passed. This condition is referred to as a patent (sometimes written as "open") ductus arteriosus. Although this illness is more common in preterm children, full-term infants are not immune to the possibility of developing it.

The DA shuts on its own a few hours after birth under physiological conditions, resulting in the total independence of the systemic and pulmonary circulations. This occurs in the first few hours of life. The success rate of the DA to close after delivery has an incidence that is directly proportional to GA (gestational age), with the occurrence from 80 to 90% in newborns who were born after 32 weeks of gestation to 40% in those who were born after 28 weeks of gestation (4,5,6) the ductus is not closed, a portion of the blood volume that would normally be carried through the complete circulation is carried through the pulmonary circulation. The amount of pulmonary overflow and reduced end-organ perfusion that results from the flow being diverted is directly proportional to the size of the ductus (hemodynamically significant PDA), and it is characterised by the presence of an open ductus arteriosus (hsPDA). HsPDA is linked to an increased likelihood of possibly life-threatening clinical consequences, including bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), acute renal failure (ARF), necrotizing enterocolitis (NEC), and death (7). Therefore, detecting the symptoms of hsPDA and treating it in an appropriate manner is an essential part of the therapy of premature new-borns. Due to turbulent blood flow, a PDA results in a heart murmur (distinct sounding) which can be heard on physical exam.

Presence of a murmur, in conjunction with other indications of heart failure, almost always results in the diagnosis of PDA. An X-ray of the chest will reveal that the patient has an enlarged heart as well as indications of a high volume of blood flow in the lungs. In order to verify the diagnosis, an echocardiography is performed. Your physician will be able to examine the size of the DA. This will determine whether or not the heart chambers have become larger as a result of the increased blood flow.

X-ray of the chest, instead, is normally normal in adolescents and adults. In order to confirm the diagnosis, an echocardiography is often performed. This test reveals whether or not blood is flowing via the PDA.

In the event that the PDA does not close by itself, healthcare providers are able to make the necessary adjustments. Babies and children with moderate and large sized PDAs who are not treated within the appropriate timeframe may have an increased chance of having heart issues as adults. This risk is increased if treatment is delayed. Have a conversation with your baby's healthcare practitioner to determine whether or not your child requires follow-up care.

PDAs can be closed by surgery. When a baby is less than six months old and has a significant birth defect that is accompanied by symptoms such as low weight gain and rapid breathing, surgical closure is frequently recommended. Surgery could be postponed till the baby is from 6 to 12 months old if the infant does not exhibit any symptoms. The cardiologist who treats your child will provide guidance regarding the optimal time for the surgery. Your youngster will be put under general anaesthesia and put to sleep for the procedure. During surgery, sutures or clips are used to seal the PDA. The additional blood is prevented from entering the lungs as a result of this. These procedures are required to be performed on premature infants.

Ibuprofen or indomethacin is the two medications that are typically used as the initial treatment for persistent ductus arteriosus (PDA). However, because of the risk of possibly fatal adverse effects connected with their use, medical professionals are looking at other treatment possibilities. In the PDA treatment, the usage of the drug paracetamol as a substitute to ibuprofen is currently based on an insufficient amount of clinical data. As a result, additional clinical tests are required to determine whether or not paracetamol can play a therapeutic role in PDA management. These tests must take into account both the short-term and the long-term efficacy and safety outcomes.

2.2. History

An insistent opening between a couple of major blood arteries that branch off of the heart is known as PDA. This opening is a regular component of a newborn's circulatory system from the mother's womb itself and is known as DA. It typically closes soon after the baby is born. If it does not close, it is meant to refer as a PDA.

In spite of the numerous randomised clinical trials that have been carried out from past three decades, there is no widespread agreement regarding the most effective therapeutic strategy to bring about ductal closure in preterm newborns. It is well proven that medicinal treatment with cyclooxygenase (COX) inhibitors (indomethacin, ibuprofen) can be just as effective as resorting to surgical ligation in closing the PDA as can closing the PDA with the use of surgical ligation (8).

For over hundred years, medical professionals have hard time to understand the significance of a PDA and discussed if it has to be treated it or not. This dilemma about the treatment has continued today (9-14). Because he was unable to carry out physiological tests, he had to rely on his keen observation abilities in order to get information from cadavers and animal dissections. Galen has been called out by traditional historians for making mistakes, but more contemporary historians have given Galen credit for coming to the right conclusions (15). Galen was aware of the unidirectional nature of blood flow and made the astute observation that breathing carried "vital spirits" into the body. Though, he was unclear on the nature of the so-called "vital spirits" and how they became entwined in the blood, he was fundamentally correct in stating that a significant portion of the blood did not flow through the foetal lungs since the foetus did not breathe.

Claudius Galen from c 130 to 200 CE, was the first to describe the foramen ovale, its valve, and the DA in foetal cadavers (16). He said that since the fetal lungs 'cannot move' as do the 'perfected' lungs of adults, nature has anastomosed the pulmonary artery with the aorta and the left and right atria (17).

He was unable to conduct physiological investigations; therefore he had to rely on his keen eye for detail in animal dissections and cadavers. While modern historians have recognised Galen for his accurate conclusions by the reinterpretation of ancient Greek, classical historians have condemned Galen for his faults (15). Galen accurately observed that breathing got in "vital spirits" and the unidirectional blood flow. He wasn't sure what the "vital spirits" were or how they got into the blood, but he was essentially right when he indicated that because the foetus wasn't breathing, a lot of the blood didn't go through the foetal lungs.

A saying by him goes, "all who drink of this remedy recover in a short time, except those in whom it does not help, who all die. Therefore, it is obvious that this fails only in incurable cases" (18).

In 1543, Andreas Vesalius (1514–1564) published De Humani Corporis Fabrica (The Fabric of the Human Body). His colleagues as well as followers rediscovered the DA (15). The followers of Leonardo Botallo (circa 1519–1587) accredited him for the finding of the ductus (19) and called it Ductus Botalli (as illustrated in Figure 1) - a word that is present for 400 years and 40 references in a 1918 textbook (20)

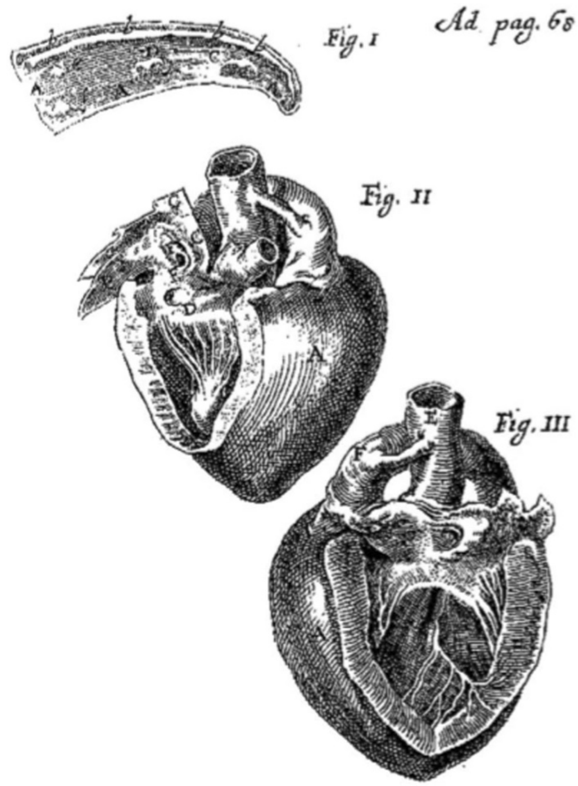

Figure 1: A ductus arteriosus joining the aorta and pulmonary artery as illustrated by Botallo in the book of Opera Omnia (20)

PDA was described as bacterial endocarditis or congenital heart defects by morbid anatomists during the 16th and 19th century, in autopsies of patients. During the time period described above, the concerns that plagued the scientific community were the reason for open ductus in few people and not in the others, and the function of this anatomy was. Before the 20th century, it was unknown what role DA had in the developing foetus and how long its effects lasted after birth.

The advent of cardiac ultrasonography in the mid-1970s through the 1980s brought with it increased sophistication for the exact anatomic identification of heart abnormalities. At first, cardiac ultrasonography was performed in M mode; later, imaging and Doppler techniques were utilised.

The earliest recorded “idea” for ligating the ductus to improve health dates back to 1888 (17,19,21). The Boston surgeon John Cummings Munro (1856–1910) believed that he could ligate the ductus in patients who were still alive at the time. In a lecture he gave to the Philadelphia Academy of Surgery in 1907, he recalled an incident from 19 years earlier when he had observed an infant who was suffering from severe cardiac failure and who passed away a few weeks later. Munro discovered a PDA during the autopsy, and he ligated it to demonstrate that it was possible to do so. Then he continues by saying that he "...tried in vain to influence my paediatric specialist with my views..." (19) This is the first disagreement that has been documented between a surgeon who is willing to ligate a PDA and his paediatric colleagues who are against it. Robert Gross (1905–1988) is credited with recording the first effective heart surgery (15, 17,23).

On 26th August of 1938, Gross successfully ligated a 7-year-old girl named Lorraine Sweeny's patent ductus arteriosis, launching him onto the stage of paediatric surgery all around the world. At that time, William E. Ladd, the surgeon in chief, served as his chief resident in surgery at Children's. Gross had meticulously prepared for this risky procedure by performing it in the animal lab and postmortem room. Ladd was on summer vacation when he carried it out. Gross's surgical coup was never forgotten by Ladd. Gross felt positive that if Ladd had been in town, he would not have permitted him to do it.

On the same day he ligated the patent ductus arteriosus of Lorraine Sweeny who was weakened from cardiac failure. This daring expedition served as the first piece in the surgically correcting congenital heart abnormalities. 75 years old now, Lorraine. She is still in very good health. Gross remarked that if she had not done well, he would probably be a farmer in some part of New England when they were later reminiscing together. More than 1,400 patent ductus arteriosus's had been distributed by Gross and his residents at the time of his retirement.

On 7th of August (1962), Mostyn Powell reported of cardiac failure signs due to PDA in 6 preterm infants. 5 out of 6 six babies (age -6 weeks to 5 months), the PDA was recorded to be spontaneously closed spontaneously.

An infant who weighed 1416 g during surgery was reported to have had a case of PDA ligation in 1963 by Decanciq, who was a paediatric resident at the time. According to him, this was the "smallest" infant that had been operated on up until that point.

Widespread availability of exogenous surfactant in the late 1980s also led to newer concerns. These concerns included the following questions: did a sudden improvement in pulmonary compliance and drop in pulmonary vascular resistance increase the risk for earlier manifestations of significant patent ductus arteriosus? Did surfactant therapy increase the risk for pulmonary haemorrhage in presence of a significant patent ductus arteriosus?These factors led to a greater interest in treating a PDA.

In the mid of the 1970s, pharmacological intervention as a treatment for PDA emerged (24); as a result, there was now an additional alternative to surgical intervention. Concerning patent ductus arteriosus therapy, the results of the carefully carried out TOLERATE trial (25) have, in point of fact, prompted more questions than they have answered.

It was not until the development of transcatheter ablation of the PDA technique (26) and the approval of Amplatzer Piccolo TM by the United States FDA on January 11, 2019 that intervention cardiologists were able to occlude the PDA even in tiniest premature infants.

2.3. Patent ductus arteriosus condition and mechanism

Even today, patent ductus arteriosus, also known as patent ductus arteriosus, is one of the most frequent paediatric heart disorders found in premature newborns. Not closing of DA before the initial 4 days of a person's life is the medical definition of PDA. PDA is diagnosed in around 80% of children whose birth weight is less than 1200 g and in approximately 45% of newborns whose birth weight is less than 1750 g. patent ductus arteriosus is more common in infants whose birth weight is less than 1750 g. It has been discovered that 15% of premature newborns with a birth weight of fewer than 1750 g have major PDA with CHF. Additionally, between 40% and 50% of premature infants with a weight of less than 1500 g during birth, have significant patent ductus arteriosus with CHF.

Significant pulmonary artery dissections are linked to high rates of morbidity and mortality, which can reach as high as 30 percent in some cases. This is of particular concern in preterm neonates, as these infants are already at increased risk for a variety of severe life-threatening problems.

The ductus arteriosus frequently fails to close in preterm neonates, and these infants require either medication or surgical closure of PDA. It is absolutely necessary, in order to attain successful outcomes, to have an awareness of the mechanisms involved, an early detection of PDA, and knowledge of the therapeutic alternatives.

The majority of the time, a minor PDA won't create any difficulties and may never require treatment. However, if a big PDA is left untreated, it may allow blood that is deficient in oxygen to stream in the opposite way of what it should, which leads to weakening the heart muscle and heart failure as well as other issues.

During life's initial days, the PDA will naturally contract and close in the vast majority of infants who are born with an otherwise normal heart. If it remains open for a longer period of time, it may result in an increased flow of blood to the lungs. If the PDA is too big, there is a greater chance of encountering issues. By the time the child is 1 year old, some of the smaller PDAs that don't shut early will have sealed themselves on their own (1,27).

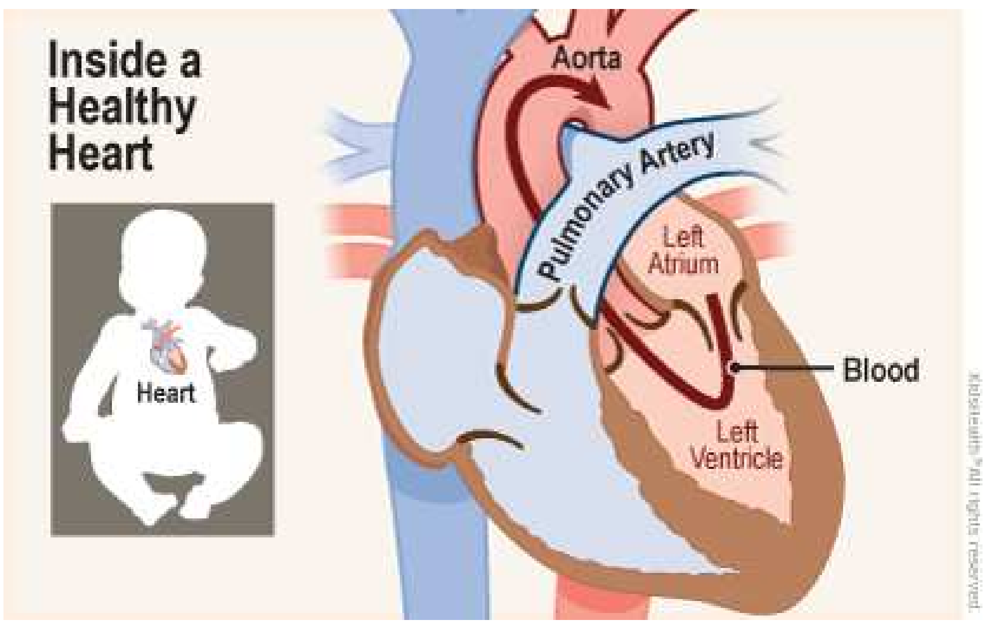

Figure 2: The Healthy Heart

It is more probable for a PDA (PAY-tent DUK-tus are-teer-ee-OH-sus) to remain open in a premature infant, especially if the infant has lung problems. When anything like this occurs, medical professionals might be required for PDA closure.

2.3.1. What Occurs When Someone Has Patent Ductus Arteriosus?

The DA is a regular blood vessel that joins two main arteries, the pulmonary artery and the aorta, that carry blood away from the heart. The aorta and the pulmonary artery are responsible for carrying blood away from the heart.

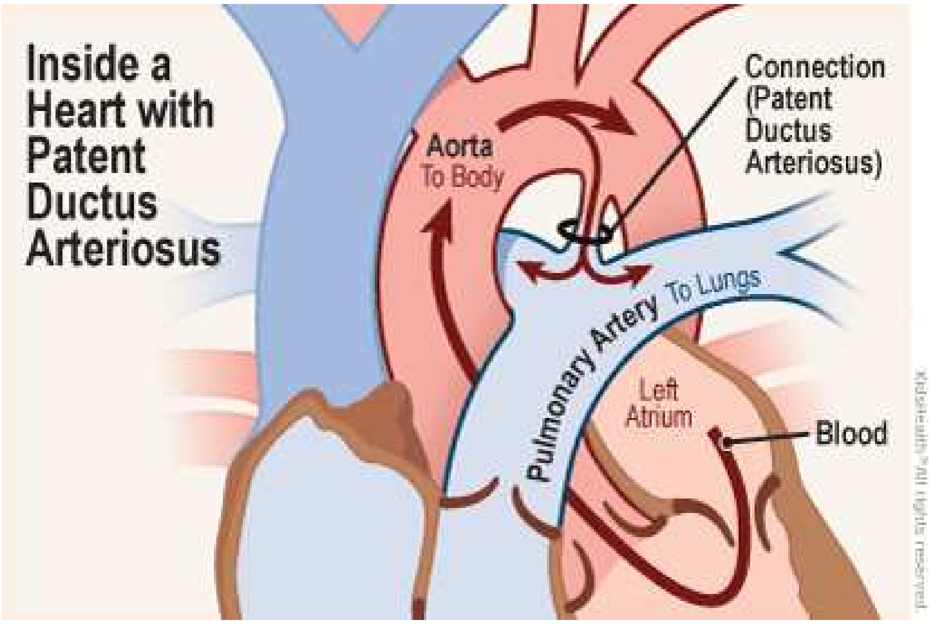

Figure 3: Inside a Heart of PDA patient

Since the foetus receives oxygen directly from the placenta, it does not need lungs while it is still in the mother's womb because it does not need to breathe. The DA is responsible for carrying blood away from the lungs and delivering it straight to the body. The ductus is rendered unnecessary as a child begins to breathe and makes use of their lungs; as a result, it typically closes on its own within the first two days following delivery.

If the ductus doesn't shut, the consequence is a patent ductus arteriosus, which literally translates to "open." Oxygen-rich blood (blood that is high in oxygen) from the aorta is allowed to mix with oxygen-poor blood (blood that is low in oxygen) from the pulmonary artery thanks to the PDA. As a consequence of this, an excessive amount of blood flows into the lungs, which places stress over the heart as well as raises the blood pressure in the pulmonary arteries.

There are a few cardiac conditions that can affect children at birth. These conditions either restrict the passage of blood from the heart to the lungs or the flow of blood that is rich in oxygen to the body. In such circumstances, the PDA may in fact be of assistance, and the attending physician may decide to administer medication to maintain an open ductus arteriosus .

2.4. Prevalence

2.4.1. Epidemiology

It is not fully understood what variables contribute to the ductus arteriosus being open beyond the first 24 to 48 hours of a newborn's life, but researchers are working to figure it out. There is no doubt that premature birth raises the risk of ductal atresia, and this is attributable to physiological reasons connected to premature birth rather than an anomaly that is inherent to the ductus itself (28). In term infants, cases most commonly appear to occur sporadically, however there is increasing evidence that hereditary factors play a role in the development of patent ductus in a number of patients. [Cases of patent ductus occur most often in term infants.] Additionally, it seems that additional factors such as prenatal infection play a role in certain occurrences of the disease.

2.4.2. Incidence

The reported incidence of PDA varies due to methodological variances linked to the demographic group that was examined, the age that was taken into consideration, and the method that was used to detect it (29,30). Even though the ductus arteriosus is normally fully closed within the first 48 hours of a newborn's life, some medical professionals don't consider a patent ductus to be abnormal until the child is at least three months old (31). It has been observed that the incidence of PDA in children who were born at term is less than one in every two thousand births. This accounts for somewhere between five and ten percent of all cases of congenital cardiac disease. On the other hand, if we include children who have a patent ductus that is "silent" (meaning that it was discovered by accident during an echocardiogram that was performed for another reason), the incidence has been estimated to be as high as 1 in 500. According to most of the reports, The ratio of male to female is roughly 1:2 (32).

The reported incidence of PDA in term neonates is only 1 in 2,000 births; it accounts for 5%–10% of all congenital cardiac disease (4). The prevalence of PDA is significantly higher in preterm neonates, with figures varying from 20% to 60% (depending on the demographic and diagnostic criteria) of affected babies (33). The lack of normal closure mechanisms due to immaturity is to blame for the greater prevalence of PDA in preterm babies. PDA has been found to have a strong correlation with both gestational age and weight. To be more specific, PDA is occur in 80% of newborns weighing less than 1,200 g at birth, but it is present in just 40% of children weighing less than 2,000 g at birth (2,25). In addition to this, symptomatic patent ductus arteriosus can be seen in 48 percent of infants who were born weighing less than one kilogramme (34). Table 1, which includes findings from the National Institute of Child Health and Human Development's (NICHD) Neonatal Research

Network, provides a summary of this negative association between birth weight and the occurrence of PDA (35).

Table 1: Association of PDA occurance with birth weight for infants born in the NICHD by epoch (%)

Birth weight	**Epoch**		
	1987-88	**1993-94**	**1999-2000**
501-750g	32	55	50
751-1000g	41	46	37
1001-1500g	17	17	17

It is estimated that approximately 80 percent of preterm newborns who arrive with respiratory distress syndrome (RDS) also have a PDA. This is possibly because RDS is related with elevated circulating prostaglandins (PGE2). There are a few birth variables that have been demonstrated to rise in the risk of PDA development. These birth factors include high altitude during birth, genetic factors, and exposure to rubella while in utero. PDA is found in a higher proportion of female infants than male infants (2:1) which was not been fully explained (36).

PDAs that are hemodynamically significant have been linked to considerable morbidity and death rates, which can reach as high as thirty percent in some cases (37). This is of particular concern in premature neonates, as these infants are already at increased risk for a variety of severe life-threatening problems. It is absolutely necessary, to have an awareness underlying mechanism, to be able to identify PDA early on, and to be familiar with the therapeutic alternatives to succeed with positive outcomes (36).

2.5. Evaluation of the condition

2.5.1. Diagnosis

The physician may believe that you or your child has a PDA based on the rhythm of the heartbeat or the heartbeat of your child. PDAs have been linked to the development of cardiac murmurs, which can be detected by a clinician using a stethoscope.

If the doctor suspects a heart defect, he or she might request one or more of the following tests:

- **Echocardiogram.** A clinician can recognise a PDA, determine if there is enlargement in heart chambers, and assess the pumping efficiency of heart by using sound wave images produce. The doctor can use this test to assess the valves of heartand look for other potential cardiac problems.

- **X-ray of a chest.** Image produced from X-ray aids in examining the condition of heart and lungs.

- **Electrocardiogram.** This test captures the heart's electrical activity, which can assist the doctor in diagnosing cardiac or/and rhythm defects.

- **Cardiac catheterization.** This examination may be carried out to look for further congenital heart problems discovered during an echocardiography or if a catheter treatment is being explored to treat a PDA. It is not often required to diagnose a PDA alone.

In order to reach the heart, a catheter is placed into a blood artery in the arm or groyne of mother or child. Catheterization may allow the doctor to perform operations to close the PDA.

2.5.2. Clinical Features

Patients who have PDA may well have any number of different clinical histories, ranging from having no symptoms at all to having severe congestive heart failure or Eisenmenger syndrome. A sizeable proportion of individuals present with what initially sounds like an asymptomatic heart murmur. Some are found by accident during an echocardiogram that was performed for another reason on patients who did not display any evident clinical indications. Some are found by accident during an echocardiography that was performed for another reason. Even though a person might give the impression that they are in good health, there is still a possibility that they might have an intolerance to physical activity or be diagnosed with reactive airways disease. Even though the majority of patients with PDA are able to compensate well, even with a moderate left-to-right shunt, and continue to be asymptomatic during childhood, many years of chronic volume overload may lead to symptoms of congestive heart failure in adulthood. This is the case despite the fact that the majority of patients with patent ductus arteriosus are able to recompense well even with an adequate left-to-right shunt. If the noise overload persists into adulthood, this is something that could happen. Atrial fibrillation is a condition that develops as a result of persistent and gradually growing expansion of the atrium (left). The onset of symptoms may coincide with the onset of atrial fibrillation, which is a condition that develops due to persistent and gradually growing expansion of the atrium (left). When its effects are coupled with those of an acquired illness, such as ischemic heart disease or calcific aortic stenosis, a patent ductus arteriosus that was previously well-tolerated may now provide a clinically substantial risk to the patient. This is because the patient is most likely to suffer from the two conditions in combination.

2.5.3. Physical Examination:

The observations form physical examination are just as variable as the patient's medical history. Patients who have a patent ductus that is so little that it was only discovered by accident have no abnormal physical results. A persistent murmur can be heard at the upper left sternal boundary; this murmur is commonly known as a "machinery" murmur. This murmur is the most distinctive physical finding associated with this condition. A thrill might also be present in addition to the murmur, which typically travels down the left side of the sternum and into the back. Patients who have moderate or large ductal shunts may occasionally hear a diastolic rumble at the cardiac apex. This rumble is heard when the heart is contracting during the diastolic phase. When the shunt is either moderate or big in size, the impulse from the left ventricle will be more noticeable, and the pulse pressure will be higher. The pulses at the periphery can be very conspicuous or quite bounding. Even in patients who have a larger shunt, rales are uncommon, with the exemption of older patients who have congestive heart failure.

Cyanosis is present in patients who have Eisenmenger syndrome, and these patients may also have differential cyanosis (cyanosis and clubbing of the toes but not the fingers because the right-to-left ductal shunting is distal to the subclavian arteries). Cyanosis may become more severe under situations in which the systemic vascular resistance is reduced, such as when the temperature is high or after vigorous exercise. Because there may be no shunting, there may be no murmur during either systole or diastole. An auscultation may reveal a high-frequency diastolic decrescendo murmur of pulmonary regurgitation and/or a holosystolic murmur from tricuspid valve regurgitation. Both of these murmurs indicate that the pulmonary and/or tricuspid valves are leaking. There is a possibility the pulmonic component's volume of the second heart sound will be raised. Late in the disease course, when right ventricular failure is established, peripheral edoema may be present.

2.5.3.1. Chest Radiograph:

The chest radiograph may show no abnormalities at all if there is no ductal shunting at all, or it might show enlargement of heart (especially enlargement of left atrial and left ventricle) with increased markings of pulmonary vascular. This depends on the ductal shunting amount that is present. It is not uncommon for the major pulmonary artery to be dilated, and ducts' calcification may be visible in some patients, particularly older adults who suffer from pulmonary hypertension.

2.5.3.2. Electrocardiogram

In addition to enlargement of left atrial and hypertrophy of left ventricule, atrial fibrillation or sinus tachycardia may be seen on the electrocardiogram (ECG) of patients who have moderate to large shunts. Electrocardiograms, also known as ECGs, are typically completely normal in individuals who have smaller ductal shunts. Patients who have a enormous DA as well as raised pulmonary artery pressure frequently show signs of enlargement of right atria as well as biventricular hypertrophy. Both of these conditions are linked with an amplified risk of developing heart failure. The fact that either one of these conditions has the potential to raise the blood pressure found in the pulmonary artery.

2.5.3.3. Echocardiogram

The preferred method for determining the presence of a PDA and defining its characteristics is an echocardiogram (Figure 4). When combined with the clinical data, the echocardiogram frequently aids in categorizing the PDA (silent, small, moderate, or large). The echocardiogram often help to find and assess other defects linked to heart in addition to assessing the DA. This is carried out concurrently with the DA assessment.

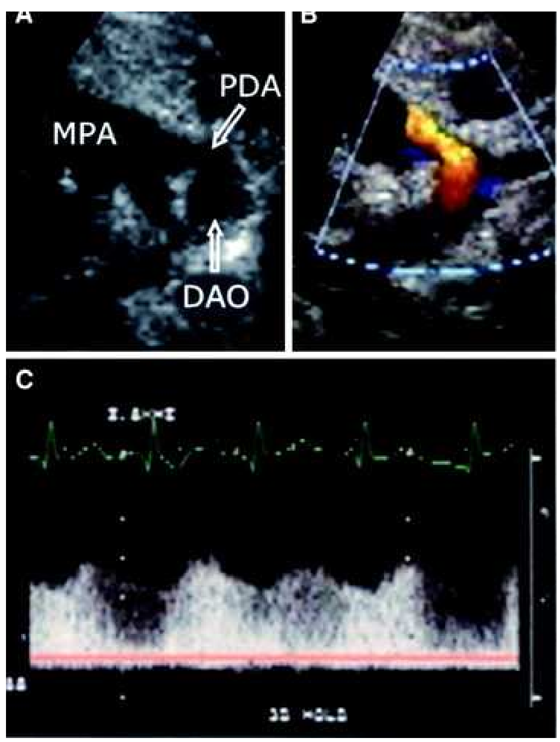

Figure 4: Demonstration of the study of Echocardiogram

M-mode echocardiography is utilised in order to determine the diameters of the cardiac chambers and quantify the left ventricular systolic chamber's function. Chamber diameters are typically normal in a patient who has a small ductus arteriosus; nevertheless, a slight left atrial and/or left ventricular enlargement may be seen. Enlarged left atrium and the left ventricle can be noticed when there is a moderate or big patent ductus present. The shape of the ductus can be seen in two dimensions using imaging technology. Color Doppler is a modality that has a high degree of sensitivity when it comes to finding PDA. It is also widely used to determine the degree of ductal shunting. A colour flow signal that is entering the pulmonary artery close to the origin of the left pulmonary artery can detect a patent ductus of any size, even one that is exceedingly minute. Even if the ductus arteriosus is large, this is not easy to reveal with colour flow Doppler in patients who have high pulmonary vascular resistance and PDA, and those who have low velocity or flow from right to left. This is the case regardless of whether the DA is large. A thorough assessment for a PDA should be prompted by results such as septal flatness, unexplained right ventricular enlargement, and high-velocity pulmonary regurgitation. Intravenous injection of agitated saline causes the formation of microbubbles in the descending aorta, but these bubbles do not form in the ascending aorta. Contrast echocardiography may be beneficial in this situation.

The spectral Doppler signal of ductal flow can be used to build a systematic pulmonary artery pressure curve. If tricuspid regurgitation is present, the peak velocity of the jet that it creates can be utilised to determine the pressure inside the right ventricle. If pulmonary regurgitation flow is present, then the Doppler velocity of that flow can be employed to determine the pressure in the pulmonary artery during the diastolic phase. It is possible to determine the degree of left-to-right shunt by using the cross-sectional areas of the outflow tract in conjunction with the Doppler-derived mean flow velocities.

2.5.3.4. Cardiac Catheterization

The majority of children who have PDA are candidates for therapeutic catheterization, which is the therapy of choice at most facilities at this time. In these patients, it is crucial to completely analyse the pulmonary vascular resistance and the degree of shunting before any intervention is performed. Evaluation of pulmonary vascular resistance and its reaction to vasodilating drugs such as oxygen, nifedipine, prostacyclin, sildenafil, and nitric oxide may be useful in deciding whether or not it is advisable to close the ductus in individuals who have an increased pulmonary artery pressure. Evaluation of the patient's hemodynamic status with a balloon catheter during a short-term occlusion test is another potentially useful method for determining whether or not a closure should be performed.

Angiography is the technique that is used to define the structure of the DA. Prior to performing a transcatheter closure, it is necessary to perform an in-depth the ductal anatomy study, in order to select the appropriate device as well as the appropriate device size for the intervention. The lowest diameter, the maximum diameter (which is typically found at the aortic ampulla), the length, and the proximity of the ductus to the anterior boundary of the tracheal shadow are all important parameters that assist guide device positioning.

2.6. Treatment

PDA is a birth defect that affects roughly 20-50% of newborns who are born before 32 weeks gestation and up to 60% of newborns who are born before 29 weeks gestation (38,39). The decision of whether or not to treat patent ductus arteriosus is still debatable at this time due to the presence of the chance of the PDA spontaneously closing. Conservative therapy, pharmaceutical treatments, surgical ligation, and a transcatheter approach to ductal closure are the treatment options available for patients with hemodynamically significant ductal atresia (hsPDA). A consensus on PDA management strategies has not yet been reached. Surgical ligation is an option that is typically considered after other medical therapies have either been unsuccessful or have been ruled out as inappropriate (40). Recent research has suggested that surgical closure of the PDA may be linked to an elevated risk of neonatal mortality, short-term morbidity, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and neurodevelopmental damage in early childhood. (41,42). According to the findings of other research, there is a potential for bias to occur when treating infants with the most severe symptoms with the most intensive PDA therapy. There is a possibility of confounding effects, which is hinted at by the clinical efficacy of ligation as a treatment of rescue in the event that medicinal or conservative treatment is unsuccessful. According to the findings of a meta-analysis, surgical ligation of the defect is related with a lower newborn death rate; nevertheless, infants who survive the procedure face a severe risk of neurodevelopmental disability (43). Surgical ligation of the PDA is still indicated in the current neonatal therapy for infants who have extensive shunts that cause respiratory insufficiency and whose propensity for spontaneous closure is low (43). When compared to conservative treatment, the dangers and advantages of surgical ligation for PDA are not entirely recognised. Conservative treatment, on the other hand, is more common. After the publication of a Cochrane Review in 2008, prophylactic and early ligation techniques are no longer considered to be appropriate. In preterm newborns, the trend in PDA treatment strategy has been shifting toward adopting a more cautious strategy as opposed to using aggressive methods. This is in contrast to the previous tendency, which favoured treating with aggressive means (44). Nevertheless, this cautious approach has its drawbacks when it comes to the treatment of high-risk patients who require prompt interventions for PDA, and this is the case even when taking the potential adverse effects of the medication into account. Due to the lack of conclusive proof of a causal association between the severity of PDA and unfavourable outcomes to guide management, as well as reports of both short-term and long-term effects from treatment, there was a large amount of heterogeneity in hospital practises. This was observed (45).

According to the findings of a study that was carried out by Joonsik Park et al. 2021(45) The annual incidence rate raised from 70 newborns per 10,000 babies (2015) to 94 babies per 10,000 babies (2018). The occurance of PDA in infants was 81 babies per 10,000 newborns. The diagnosis of PDA was shown to be prevalent in very low birth weight (VLBW) newborns at a rate of 45.2%; this rate increased by 5.6% over the course of the four years that were analysed. The prevalence of surgical ligation decreased considerably from one year to the next among the 2571 infants who were treated with surgical ligation; 4202 infants were treated with medication resulting in considerable decrease from 2015 to 2018, majorly in VLBW newborns, where it went from 62% to 53%. patent ductus arteriosus ligation was also performed on 23% of newborns whose birth weight was 2,500 grammes or more, 11% babies whose birth weight ranged from 1,500 to 2,500 grammes, and 22% newborns whose birth weight was less than 1,500 grammes. The percentage of prematurely born infants that were tiny for their gestational age ranged from 3.8 to 5.9% over the course of the study's four years. This percentage was 4.0% in 632 newborns. Figure 1 depicts the percentage of patients in both the overall study group and the VLBW subgroup that received therapy using the various approaches.

There were a total of 2522 infants who underwent surgical procedures (20.4%), 2247 infants who received intravenous (IV) ibuprofen (24.4%), and 1326 infants who were given oral medicine (10.7%). Out of a total of 4,854 infants diagnosed with VLBW, 1078 underwent surgery (22.2%), 2247 children (46.3%) were treated with IV ibuprofen, and 688 infants (14.2%) were given oral medicine. In all, 45 newborns (0.36%) were treated with a combination therapy that included surgery, IV medicine, and oral medication. In the VLBW subgroup, 37 infants (0.76%) were given this type of treatment. There is still a great deal of uncertainty and debate over the treatment of PDAin premature infants, which has led to a considerably amount of variation in clinical practice. A shift away from a forceful PDA closure strategy and toward a more anticipatory attitude has been noticed in latest years, which allows for spontaneous closure and, as a result, eliminates the requirement for therapeutic measures. It is still not obvious how the effect of active therapy compares to the effect of non-intervention. Monitoring, the use of medicines, and DA closure through cardiac catheterization or surgery are all potential treatment choices for a PDA

2.6.1. Methods of PDA treatment

Medicine, catheter-based techniques, and operations are the three therapeutic modalities that are available for patients with PDA. A physician will recommend the closure of a patent ductus arteriosus if it is determined that the opening size is substantial enough to cause the lungs to become overburdened with blood. This is a condition can cause enlargement of heart.

A physician might also close a PDA in order to lessen the likelihood of the patient acquiring endocarditis, which is an infection that affects the tissue that lines the heart and the blood arteries. Endocarditis is a dangerous condition that must be treated with antibiotics administered intravenously (IV).

Despite being the most frequent cardiac ailment affecting preterm newborns, the PDA continues to be difficult to manage for neonatologists and paediatric cardiologists. This is despite the fact that it is the most common cardiac disorder. Even after fifty years of research and the publication of thousands of articles in the scientific community, there is still no consensus on the definition of a hemodynamically significant PDA or the most effective way to treat it. Despite this, there have been a lot of clinical lessons that have been discovered, and we can't disregard them. It is common knowledge that standard PDA closure shortly after birth does not reduce the morbidities that are linked with a PDA.

In addition, surgical ligation has been linked time and again to an increased risk of birth defects such as BDP and ROP, as well as to inferior outcomes for neurodevelopment. When it comes to the medical treatment of the PDA, we have found that various drugs have had favourable results; however some of these treatments have had more negative side effects than others. We have the potential to be less intrusive thanks to the introduction of percutaneous PDA closure; but, as is the case with the majority of treatment methods, there are still dangers involved. Pharmacogenetics appears to be the next frontier as we continue to ponder the questions of who needs intervention for their hsPDA and how best to achieve this while minimising the morbidity and mortality, particularly in the premature infant population. As we continue to explore, our theories about the PDA and its effects continue to evolve as we learn more.

2.6.2. Fetal Ductal Patency and Closure regulation

Figure 5A illustrates the factors required for the dilation to patency in utero. Nitric oxide is the main tranquillizer, and it works through the cyclic guanosine monophosphate (cGMP)/protein kinase G signalling in the initial fatal development (25). Prostaglandin E2 functions as a calming agent at the end of the gestational period and is mediated by prostaglandin E2 receptor 4. (EP4). This causes the activation of series of singnals of cyclic adenosine monophosphate (cAMP)/protein kinase A (46). All of the aforementioned pathways, along with signalling molecule activation, reduce intracellular calcium levels, which prevents DA smooth muscle contraction during foetal life (47).

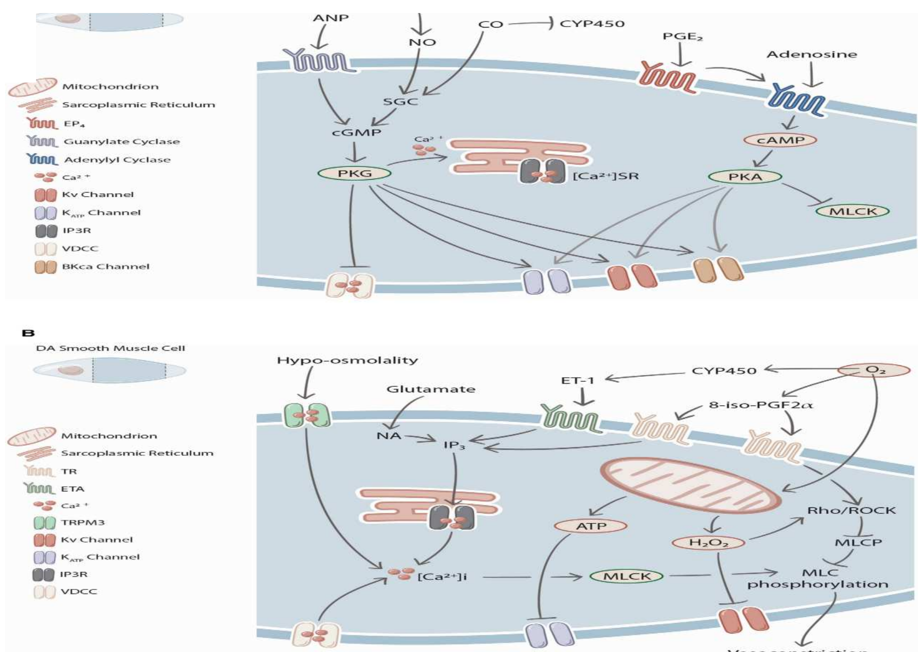

Figure 5: Illustrations of Relaxation of intrauterine ductus arteriosus (DA) (A) and postnatal DA constriction (B)

2.6.3. Normal Postnatal Ductal Closure regulation

Functional postnatal closure of the DA results in remodelling into the fibrous ligamentum arteriosum, which is influenced by maternal environmental factors, molecular, structural, and hemodynamic factors. DA closure is aided by a dramatic reduction in dilating factors and an increase in intracellular calcium levels. The closure of DA is regulated by an increase in alveolar PaO2. Premature biochemical oxygen sensing mechanisms are known to maintain the ductal patency in premature newborns (48). Premature babies will not have internal cushions, will have less contractile smooth muscle cells, and will not have vasa vasorum. All of these structural elements enable preterm infants' sustained ductal patency. According to a recent study, premature babies' PDA might have been controlled by biochemical factors. The relationship between thrombocytopenia and delayed ductal closure has been established (49). Even after platelet transfusions, there was a delay in the closure of PDA in infants with thrombocytopenia. This may be the case because the condition may have been controlled by platelet function rather than quantity (50). Prenatal teratogens (51), Zika virus infection, and congenital rubella syndrome (52) have all been suggested as possible causes of PDA.

2.6.4. PDA Treatments in Preterm Infants

Indomethacin has been the drug most thoroughly investigated as a treatment for PDA in infants. It inhibits cyclooxygenase and interferes with the production of prostaglandins (53). Death, BPD, necrotizing enterocolitis, and neurodevelopment are the main drawbacks to indomethacin's effectiveness (6). Oliguria and elevated serum creatinine levels, which are known to lead to spontaneous intestinal perforation, are side effects of this medication treatment (54). Ibuprofen, on the other hand, showed comparable effectiveness to indomethacin, but it was less likely to cause oliguria and necrotizing enterocolitis . Recent studies have revealed that acetaminophen, often known as paracetamol, may be a safer option to other drugs for the initiation of PDA closure. This is the case despite the fact that it may be just as effective. There are very few randomised controlled trials, and the majority of the findings are anecdotal with no controls. The two randomised trials that compared acetaminophen with a placebo (55) or with no treatment with 80 patients.it was found that after 4 to 5 days of treatment, risk ratio of ductal patency reduced by 51%. In addition, treatment increased the RD of ductal patency. There were no discernible changes found in terms of death, oxygen usage at 36 weeks postmenstrual age, or any other outcomes. There was no significant difference in the rates of ductal closure between the therapies, according to the findings of several short trials comparing acetaminophen to ibuprofen or indomethacin , which suggests that the treatments are therapeutically equivalent. It was discovered that the timing of treatment for PDA in causing ductal closure (Early Treatment Versus Delayed Conservative Treatment) did not significantly differ .

The unexpected reactions to pharmaceutical PDA therapies (such as indomethacin and ibuprofen, for example) may mirror variances in the ontogeny, genetic diversity of enzyme that metabolise drug as well as drug targets, according to recent findings . For instance, the weight-based dosing system that is currently used for indomethacin results in varied exposure to drugs, with up to a 14-fold variance in drug concentrations 24 hours after receiving the same amount of the drug intravenously (57). To this purpose, genetic variability in the metabolism of indomethacin may explain the observed heterogeneity in drug exposures. The cytochrome P450 enzymes, in particular CYP2C9, as well as the uridine 5'-

diphospho-glucuronosyltransferase (UGT) enzymes are responsible for the metabolism of indomethacin. During the foetal and early neonatal stages of development, infants have low expression levels of CYP2C9, and UGT enzymes are also expressed at relatively low levels (58). During childhood, the expression of both enzymes develops quickly into their mature forms.

Additionally, responsiveness to indomethacin in preterm infants diagnosed with PDA has been linked to the CYP2C9 genotype in several studies. In the case-control study, having the G allele of rs2153628 was related with an increased likelihood of responding to indomethacin (odds ratio [OR], 1.918; 95% confidence interval [CI], 1.056–3.483). In addition, the CYP2C92 polymorphism was found to be related with medication failure in a multicenter cohort study of preterm children who were receiving indomethacin for the treatment of PDA. The mechanisms by which variations in these and other genes modify NSAID responses have not been established. However, it is possible that these mechanisms are related to the complex molecular network that regulates ductal patency before and after birth (27).

Surgical ligation of the ductus, which is often carried out by applying a surgical clip via a left posterolateral thoracotomy incision, has the benefit of almost always resulting in successful ductal closure. Only four patent ductus arteriosus - closure trials have been carried out on premature newborns so far practically (25). All of the trials were performed prior to the 1980s and evaluated open surgical ligation rather than the minimally invasive transcatheter closure. This was done before the advent of modern advances in intensive neonatal care, such as antenatal corticosteroids and surfactant, which have helped a significant number of preterm infants with PDAs survive. Prophylactic closure of the ductus on the day of birth was related with decreased rates of necrotizing enterocolitis, more frequent oxygen use and mechanical ventilation at 36 weeks, and no change in death for infants weighing less than 1000 grammes at birth. Despite the obvious variations in ductal patency, symptomatic patent ductus arteriosus patients who underwent ligation did not show a demonstrable reduction in any unfavourable outcome (6). When ligation was compared to indomethacin for the treatment of persistent patent ductus arteriosus, the landmark National Collaborative Study found that ligation was more likely to produce ductal closure (relative risk - 0.04(0.01–0.27)). However, ligation was associated with higher rates of pneumothorax and retinopathy of prematurity, without affecting mortality, chronic lung disease, or other outcomes by study design, the (59).

It is common for ductal ligation to be followed within hours by cardiorespiratory deterioration, also known as postligation syndrome. This condition is thought to be caused by an altered afterload, which in turn leads to an impaired left ventricular systolic performance (60). This complication is more likely to occur in infants who undergo ligation at a younger age than 30 postnatal days. Additionally, there is a link between surgical ligation and an increased risk of both neurodevelopmental impairment and BPD. Left vocal cord paresis and scoliosis are two of the long-term problems that might result after surgical ligation. In light of these findings, the percentages of surgical ligations performed in hospitals

The best treatment to achieve definitive ductal closure in preterm newborns is still a mystery because there have been no direct comparisons made between the various approaches. The longer-term outcomes following transcatheter PDA closure are unknown, despite the fact that the short-term statistics are encouraging. It is still unknown whether the higher likelihood of establishing ductal closure with this method will be associated with improved advantages to infants who are treated (as compared with NSAID medication or conservative management, which will be discussed further below) (43).

2.6.6. Prevention

There is no preventative measure that can stop a pregnancy from giving birth to a child with a PDA. Nevertheless, it is critical to take every measure within one's power to ensure a healthy pregnancy. Before try to get pregnant, patient should discuss with doctor, the possibility of giving up smoking, lowering stress levels, and discontinuing the use of birth control. Having healthy diet, doing regular exercise, avoiding harmful substances like drinking alcohol, consuming tobacco products and using saunas and hot tubs as well, updating vaccinations to avoid infections and keeping the diabetes under control before and during the pregnancy are some of the measures to minimize the risk of having preterm babies with PDA.If there is a history of congenital heart disease or any other genetic disorder in the family, one should consult with a genetic counsellor before attempting to conceive a child.

2.7. Outcomes

The preterm infants may experience severe consequences as a result of persistent ductal patency. The outcomes of the various studies that were examined to determine whether surgical or medical ductus closure is preferable and what the ideal timing for surgical intervention is could not be determined with certainty.

The authors Ibrahim et al., 2015 performed a retrospective study on the outcomes of surgical ligation of PDA from January 2010 to June 2014 at 2 Saudi neonatal intensive units at 2 tertiary care centres. The authors compared the outcomes of early ligation (before 3 weeks) to the outcomes of late ligation (after 3 weeks) with regard to various hemodynamic, ventilatory, and nutritional parameters.

The study included 120 premature babies in total (75 preemies with early ligation and 45 with late ligation of PDA). The average length of assisted ventilation in the group that underwent early ligation was 10 (8–37) days, whereas the average length in the group that underwent late ligation was 37 (26–90) days (P 0.05). At 24 hours after surgery, the late ligation group had a higher median fraction of inspired oxygen [0.29 (0.21-0.70)] than the early ligation group [0.23 (0.21-0.55), which is necessary to maintain good oxygen saturation in patients. In the early ligation group, full oral feeding was accomplished at 29 (15-73) days of age as opposed to 53 (34-118) days of age (P 0.05). The early group had a higher body weight at 36 weeks postconceptional age (2100 (1350-2800) g) than the late group (1790 (1270-2300) g) (P 0.05).

The study proved that preterm infants who have their patent ductus arteriosus surgically ligated earlier have better nutritional and ventilatory outcomes.

There has been a discernible rise in the number of births that occur before their due date in many countries over the past four decades. Approximately one percent of infants with birth weights ranging from 500 to 1500 grammes, account for more than sixty percent of all deaths of neonates (61). The skill and knowledge required to care for extremely premature infants have progressed to the point where it is not unusual for infants weighing less than 500 grammes to make it to their first birthday (28). Those preterm infants who are diagnosed with moderate to large left-to-right shunts through the patent ductus arteriosus (PDA) have a higher mortality rate compared to those preterm infants who are not diagnosed with a patent ductus arteriosus (36). They also have a higher risk of developing pulmonary edoema and haemorrhage, as well as BPD, and their perfusion and O_2 transfer to organs is reduced. There is no doubt that the huge differences in the occurrence that are reported by various institutions are caused by a combination of factors, including the kind and length of ventilatory support, drug therapy, blood transfusions, phototherapy, and diuretics (48).

In premature neonates, the treatment options for PDA comprise three distinct methods: conservative management, which only involves supportive therapy; pharmacologic closure, which involves the use of cyclooxygenase inhibitors; surgical ligation, which involves closing the ductus surgically .

In the conservative management, the use of surgical or trans catheter closure which results in definitive closure has been avoided as both pharmacological and surgical methods linked to the poorer outcomes(such as death)without any long term advantages (6). More strategies have been adopted in conservative management for the spontaneous closure of PDA in preterm babies. It has been found that use of diuretics and fluid restrictions, systemic afterload reduction, maintenance of higher hematocrits and increase in positive airway pressure are few among many strategies adopted to manage PDA (6).

There are currently insufficient data available on the after discharge from hospital results of neonates with a PDA. According to the findings of Herrman and colleagues, spontaneous closure occurred in 86% (18/21) of the 21 newborns who were discharged from the hospital with an open ductus. This corroborates the findings of a recent study which found that spontaneous closure occurred 76% of 52 infants (63). In a recent study, out of 201 preterm babies with a PDA it was observed that spontaneous closure of PDA occurred at the ages of 12 and 18 months respectively among 94 and 117 of infants. The study was conducted on premature infants who were born < 32 weeks gestation and followed up for 18 months at every months intervals. It is currently unknown what the most effective method of outpatient surveillance is for premature infants who have been discharged with a PDA.

There have been no studies that directly compare the results of the three distinct techniques using a randomised controlled trial format. As a result, it is still not obvious which strategy offers the most benefits to premature newborns, nor is it known whether certain clinical factors or environments may favour one strategy over another. Because of this lack of knowledge, the treatment of PDA in premature newborns might vary not just from one neonatal intensive care unit (NICU) to another, but also, frequently, even within the same NICU (54).

Your child's growth may cause a tiny PDA to shut on its own over time. When a PDA is symptomatic, it needs to be treated medically, by cardiac catheterization, or surgically. In order to determine whether or not the PDA is closing on its own, the cardiologist will perform periodic checks. In order to prevent lung issues, any PDA that does not close properly will be repaired.

There is no general agreement on the best timing to perform surgical intervention, and there are no clear indications for the optional surgical closure of PDA in preterm infants that would point to a positive outcome in this high-risk group (38).

PDA ligation was successfully performed on 120 preterm newborns in the study that Ibrahim, 2015 published. These children had failed medical treatment or had a contraindication to receiving medical treatment. The short-term cardiorespiratory and nutritional outcomes of the early ligation group were compared with those of the late ligation group in an effort to identify the key distinctions that account for the early approach's superior results to those of the late approach.

In the study (64)patients who had early PDA closure by surgery had superior nutritional status as measured by weight and length of time since restarting oral feeding. This supports the hypothesis that ductus arteriosus patency reduces blood flow to the intestines while increasing blood flow to the lungs (a phenomena known as the diastolic steal phenomenon). Cassady et al. discovered that early prophylactic PDA ligation in newborns with extremely low birth weight can significantly reduce the incidence of feeding intolerance and NEC, which can be caused by impaired intestinal blood flow in premature infants. This idea was supported by Cassady et al., who discovered that in premature infants, impaired intestinal blood flow may contribute to feeding intolerance and NEC. This may help to explain why we discovered that early closure of PDA led to a shorter time of total parenteral feeding, hence saving the major problems associated with it.

Timely surgical closure of the DA has been shown by Jaillard et al., 2006 to be linked with speedy achievement of enhanced body growth and complete oral feeding (nutritional status)when paralleled to late surgical closure. This was revealed to be the case when early surgical closure was performed. According to the findings of Ibrahim (2015), early surgical ligation is related with superior short-term results, such as less time spent in the hospital and lower mortality. Prompt surgical closure of symptomatic PDA in patients who had failed to respond to medicinal treatment demonstrated progress in nutritional status and ventilatory status but withot any favorable effect on major outcomes.

Lot of studies have revealed no difference between mortality after either procedure (65). The smaller cohorts in the studies are possibly underpowered to detect mortality. Ahmadi et al, 2014, in their cohort of 201 patients, reported 2 in-hospital deaths after SL and none after TC. Sathanandam et al, 2019, comparing a group of 80 extremely low-birth-weight infants undergoing TC with 40 infants undergoing SL by propensity score matching, reported 4 deaths in the SL group and 1 death in the TC group. Similarly, Ogando et al discovered a higher mortality rate for patients undergoing SL up to 36 weeks post-conceptual age; the mortality difference was gone by the time the patient was discharged from the hospital.

2.7.4. Symptoms

Symptoms of PDA differ with the size of the PDA and the term of the new born(fll term or preterm). It is possible that a small PDA will not cause any symptoms and will remain undetected for a considerable amount of time, possibly even until adulthood. A large PDA can cause symptoms of heart failure to appear within a short period of time after birth.

If a large PDA is discovered during childhood, it may cause the following symptoms or conditions:

- Poor growth due to poor eating
- Sweating when crying or eating
- Rapid heart rate
- Poor growth

- Breathlessness or Insistent fast breathing
- Easy tiring.

2.7.5. Risk factors for a PDA include:

- **Preterm birth.** A PDA happens more frequently in infants who are born premature than in infants of full term born.
- **Family history and other genetic conditions.** A PDA increases incase of having other genetic conditions like Down syndrome and heart defects in the family.
- **Rubella infection at the time of pregnancy.** If pregnant ladies get German measles, also known as rubella, during pregnancy, the unborn child's possibility of having a heart problem is increased. The rubella virus is transmitted from mother to child through the placenta, where it then travels through the circulatory system and causes damage to blood vessels, organs, and even the heart.
- Babies born at > 8,200 feet have a greater possibility of a PDA than babies born at lower heights.

2.7.6. Complications

A Larger, untreated PDA could cause pulmonary hypertension, heart failure and /or Heart infection. Pulmonary hypertension can result from an abnormally large amount of blood flowing through the main arteries of the heart because of a PDA, can lead to lung damage that is irreversible. It is possible for someone to get Eisenmenger syndrome form of pulmonary hypertension, if they have a big patent ductus arteriosus. A PDA can ultimately cause the heart to enlarge and weaken, leading to heart failure. Patients with PDA are at a higher risk of an infection of the heart's inner lining (endocarditis).

2.7.7. What are possible complications of PDA?

There is certain proof that the drug indomethacin can help close the PDA in preterm new born. It is administered by intravenous means (intravenously). The action of indomethacin causes the muscles contained within the PDA to contract. The connection is severed as a result of this. Your child's cardiologist is the best person to address any concerns or queries you may have regarding this treatment. It's possible that some infants will need medication to help their hearts and lungs function more effectively. There are occasions when a child requires medication, such as diuretics (water pills). The kidneys are assisted by diuretics in their removal of excess fluid from the body. When the heart is not functioning properly, it is probable that this will be necessary. Alternately, it can be necessary if the blood veins in the lungs need to make way for additional blood flow, as is the case with a PDA.

In the absence of treatment, PDA can cause long-term damage to the lungs, and it can also harm other organs. To ensure that your child is comfortable after undergoing PDA repair, the doctor may prescribe pain medication such as acetaminophen or ibuprofen before discharging them from the hospital. Before your child is discharged from the hospital, the cardiac team will have a discussion regarding pain management. Infants who were not well-nourished prior to surgery typically have more energy once they have fully recovered. They start eating more healthily, which speeds up their weight gain. Older children typically make a full recovery and are able to resume their regular activities within a matter of weeks following surgical procedures. The prognosis following PDA surgical repair varies depending on the gestational age of the new-born as well as the infant's general state of health in premature babies. Early detection and treatment of PDA in children born full-term enables these children to live normal, healthy lives. It is expected that levels of activity and hunger, as well as growth, will return to normal. Antibiotic treatment may be recommended for your child by the paediatric cardiologist in order to reduce the risk of infection in the heart's lining and valves (bacterial endocarditis).

The prognosis is not assured for children who were diagnosed with a big PDA very late or whose PDAs were never corrected. They have an increased likelihood of developing pulmonary hypertension. These youngsters need to have their follow-up care completed at a medical facility that specialises in the treatment of congenital cardiac disease.

2.7.8. Treatment may include the following.

Most infants with PDA eat and grow normally. Infants with large PDAs may get tired when feeding. They may not be able to eat enough to gain weight. Nutrition choices include:

2.7.8.1 High-calorie supplements.

Special nutritional supplements may be added to formula or pumped breast milk to increase the number of calories.

2.7.8.2 Supplementary tube feedings.

Through a thin, flexible tube, supplemental feedings are given to the patient. The tube enters the stomach after passing via the nose, travelling down the food pipe and then into the stomach. The feedings can either be used in conjunction with the bottle-feedings or serve as a replacement for them. Babies who are only able to swallow a portion of their bottles may have the remaining liquid administered to them through a feeding tube. Babies who are too exhausted to be bottle-fed could have their entire diet of formula or breast milk administered through a feeding tube instead.

2.7.8.3. Cardiac catheterization (therapeutic cardiac cath)

In order to make the baby more relaxed for the examination, healthcare provider will give them drugs (sedation). The healthcare provider will insert a catheter, which is a thin, flexible tube, into a blood vessel in the groyne area of the patient. It will be manoeuvred by him or her so that it passes through the big blood vessel in the groyne and into the region of the patent ductus arteriosus. The patent ductus arteriosus will be prepared for the insertion of the catheter. At this point, the physician may choose to provide a dye injection in order to more easily position the catheter in the appropriate location. After this step, a coil or another closure device that is already attached to the catheter will be put in the PDA, due to which blood will no longer be able to flow through the PDA. After the coil or gadget has been moved into the appropriate location, it will be disconnected from the catheter. Then the catheter will be removed typically this method is used if a child:

- Is older than 6 months
- Is at least 22 pounds
- Has defects that are not too large

After receiving therapy for PDA, the majority of children are able to enjoy normal levels of health and functioning (PDA). As long as there are no additional congenital heart problems, the child who has PDA treatment will most likely have normal activity levels, appetite, and growth after the treatment, provided that the child was born at full term.

If your child was born prematurely, the outlook after PDA treatment depends on other factors, such as:

- How early he or she was born
- Whether he or she has other illnesses or conditions, such as other congenital heart defects

Children who have PDA are at slightly increased risk for infective endocarditis (IE). Surgery for patent ductus arteriosus may be done if:

- A infant develops health problems due to PDA and is too tiny to have a catheter-based technique
- A PDA isn't effectively closed by a catheter-based technique
- Surgery is intended for treating congenital heart defects

Surgical complications are extremely uncommon and often only last for a short period of time. Hoarseness, a paralysed diaphragm (the muscle below the lungs), infection, haemorrhage, or fluid accumulation around the lungs are some of the potential complications that can arise.

Following the procedure, the youngster will have to recover in the hospital for a few days. Medicines to alleviate the patient's discomfort and stress will be administered to them. The majority of children are discharged home two days following surgery. Because of the additional health problems they face, premature newborns are typically required to remain in the hospital for a longer period of time.

How to care child who has a PDA problem at home-

- Activities of the child should be limited during recovery period
- Follow-up appointments with doctors
- Administration of medicines at home, if needed

Even though the child may have some discomfort in the immediate aftermath of surgery, it is likely that child will feel quite fine when it is time to go home from the hospital. The child needs to immediately begin eating healthily and put on weight as soon as possible. Surgeries only infrequently result in complications that persist for an extended period of time. However, you should be aware that there is still a risk of complications such as narrowing of the aorta, partial closure of the patent ductus arteriosus, and reopening of the patent ductus arteriosus.

PDA transcatheter closure is an effective and safe procedure; however, to prevent the complication rate, a case-by-case approach is required. This involves taking into consideration the patient's condition, the ducts' anatomy, the experience of the operator, the appropriate device selection, and the availability of surgical backup.

A murmur can be used to diagnose a minor PDA, which is asymptomatic. A large DA, however, may lead to heart failure. Hepatomegaly, bounding pulse with wide pulse pressure, hyperdynamic precordium with continuous murmur on auscultation, tachycardia, and the inability of respiratory distress syndrome to recover within 2–7 days are the clinical criteria for hsPDA. NSAIDs (ibuprofen or indomethacin), are the first line of treatment for haemo-dynamically significant PDA (hsPDA), which is defined as internal duct width >1.5 mm, diastolic turbulence on Doppler in the pulmonary artery, and reversed end-diastolic flow in the descending aorta. Ibuprofen works by inhibiting prostaglandin production through COX, which causes vasoconstriction and the closure of PDA. Prostaglandin H synthase is inhibited by paracetamol, which works on the peroxidase area by lowering prostaglandin synthesis. Surgery can be used to ligate patients who do not respond to medicinal therapy. Complications from surgical ligation can occasionally include infection, haemorrhage, and pneumothorax. In India, there are surprisingly few researches contrasting the effectiveness of paracetamol and ibuprofen. In the north of India, one similar study was carried out, but there was none in the south.

Ibuprofen increases cerebral blood flow, auto regulation, and has neuroprotective benefits after exposure to oxidative stress in a piglet model, according to studies. In an RCT comparing oral vs. IV Ibuprofen in 80 preterm new-borns, Erdeve *et al.*, discovered that oral Ibuprofen had a greater first closure rate. The effectiveness of oral and IV Ibuprofen was evaluated in a meta-analysis, which found that oral Ibuprofen had a greater PDA closure rate than IV but no significant difference in side effects. Despite having a comparable profile of side effects, intravenous ibuprofen is neither widely accessible nor cost-effective for usage in newborn care. When paracetamol was used instead of ibuprofen, a systematic review conducted in 2016 by Terrin et al. found no change in the rate of ductal closure. It also yielded results that were comparable for these two medicines' safety characteristics. Thus, the present study assessed the efficacy and safety of paracetamol in comparison with ibuprofen for the treatment of PDA in preterm infants.

MATERIAL AND METHODS

The study was conducted in the department of pediatrics, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2021 to December 2021.

Study design

Open label Randomized control trial.

Study duration and period

One year from January 2021- December 2021

Place

KLE'S Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi, a teaching hospital affiliated to Jawaharlal Nehru Medical College, Belagavi.

Source of data

All the preterm babies born with PDA in KLE's Dr Prabhakar Kore Hospital, Belagavi, Karnataka.

Sample size

Estimation of sample size was carried out using following formula

$$n = \frac{2(Z\,\alpha/2 + Z\beta)^2}{d^2}$$

Where, $d = \frac{|\mu_1 - \mu_2|}{\sigma}$

$\mu 1$ = the mean change from pre-test to post test of the first group

$\mu 2$ = the mean change from pre-test to post-test of the second group

$\sigma 2$ = the common error variance, for 95% confidence level.

$Z\alpha/2$ = 1.96

$Z\beta$ = 0.84 (At power 80%)

Here we assume d as large, i.e., d = 0.8

Substituting the above values in the formula, the minimum sample size required was calculated to be 26 per each group

Ethical clearance

Prior to the commencement, study was approved by the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belagavi.

Selection Criteria

Inclusion Criteria

All the preterm babies born with gestational age < 37 weeks with haemo-dynamically significant PDA and pharmacological closure was indicated. Patients who gave informed consent (inscribed informed consent was taken from the parent or guardian of all neonates before enrolling them into the study) were considered in the current study.

Exclusion criteria

1. Patients not willing to give consent
2. Patients with Septic shock, Renal failure(Urine output < 0.6 ml/kg/hr), Thrombocytopenia(<20,000), Intracranial Haemorrhage, Active NEC, Active bleeding

Methodology

The Study was a Hospital based Open label randomized control trial between January 2021 to December 2021 in KLE’s Dr Prabhakar Kore Hospital, Belagavi, Karnataka.

After obtaining approval and clearance from the institutional ethics committee (Annexure – 1), the patients fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent. (Annexure – 2)

All the neonates who were diagnosed clinically with PDA and confirmed by 2D-echo (which was done by same person to rule out selection bias) was enrolled randomly assigned into 2 groups in the ratio of 1:1. Each of the groups received treatment allotted to them as follows

i. Intravenous PARACETAMOL - Group A - 15 mg/kg every 6 hourly for 3 consecutive days)

ii. Oral IBUPROFEN - Group B - 10 mg/kg ibuprofen followed by 5 mg/kg/day for 2 days)

The patients had undergone repeated 2D ECHO to assess the closure of PDA after 3days. If the PDA was still persistent, a repeat dose of the same drug was given for another 3 days. Repeated echocardiographical examination was done within 24 hours of last dose.

History including birth weight, gestational age, and gender were collected. Clinical examination including complete haemogram, renal function test, and Liver function test were done before and after treatments. Data were collected and stored in Microsoft Excel.

Patients with septic shock, renal failure (Urine output < 0.6 ml/kg/hr), Thrombocytopenia (<20,000), Intracranial Hemorrhage, active NEC and active bleeding were excluded from the study.

Statistical analysis

Continuous variables were compared using independent T-test/ or a Kruskal-Wallis test, and categorical variables were compared using a $\chi 2$ test or fisher's exact test to test for differences across groups. Continuous variables are represented as mean ± SD (standard deviation) whereas categorical variable are presented as frequency and percentages (n(%)). Groups were made based on the treatment received. Post treatment ECHO findings like were compared between two groups. Pre and post treatment laboratory finding like Haemoglobin, TLC, Platelets, Urea, Creatinine, SGOT and SGPT were compared between two groups as well as with in groups using independent t-test and repeated measures t-test respectively. P value < 0.05 was considered statistically significant. R version 4.1.2 statistical software was used for the statistical analyses. Microsoft word and Excel was used to generate graphs, tables etc.

RESULTS

The study was carried out on preterm babies born with PDA in KLE's Dr Prabhakar Kore Hospital, Belagavi, Karnataka to compare the efficiency of oral Ibuprofen and intravenous Paracetamol in the closure of hsPDA. The study comprised 52 neonatal who met the inclusion and exclusion criteria**.** Out of 52 preterm babies, 26 each were randomly grouped as A and B. Group A patients were administered with intervenes paracetamol whereas group B patients with oral ibuprofen.

Table 2 show cases the mean values for age, gestational age, weight and APGAR (appearance, Pulse, grimance, Activity and respiration) score for 1minute as well as 5 minutes. The mean age with standard deviation of total 52 neonatal with PDA was calculated to be 6.92±6.88 days with minimum age of 2 days and maximum age of 30 days. Mean (along with SD) gestational age of study population was found to be 221.77±21.30 days. Average weight of 52 patients was recorded to be1510.29±473.61g. i- minute and 5- minute Apgar scores were 5.98 ±1.55 and 8.36±1.102 respectively.

Table 2: Demographic distribution of preterm babies born with PDA in the study

Parameter	Value, Mean ± SD
AGE (DAYS)	6.92±6.88
GESTATIONAL AGE (DAYS)	221.77±21.30
WEIGHT (Gram)	1510.29±473.61
1 MIN APGAR SCORE	5.98 ±1.55
5 MIN APGAR SCORE	8.36±1.102

Among 52 patients in our study, there were 22(43.14%) and 29(56.86%) patients were respectively female and male (Table 3). Distribution of patients based on gender is depicted in the following graph (Figure 7).

Table 3: Distribution of patients based on the gender

Gender	Number	Percentage
Female	22	43.14
Male	29	56.86

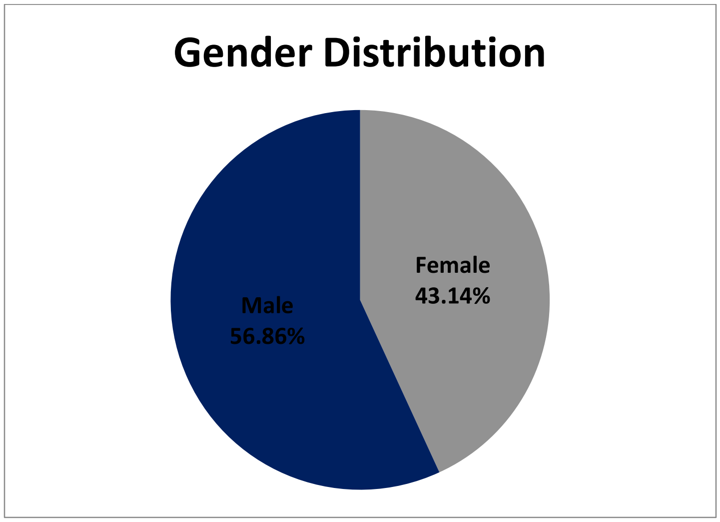

Figure 6: Distribution of patients based on gender

In the current study maximum patients of 29(55.77%) were from rural area where as 23(44.23%) neonatal were from urban area (Table 4).Graphical representation of Rural/Urban distribution of study population is shown in Figure 7.

Table 4: Rural/Urban distribution of study population

Rural/Urban	Number	Percentage
Rural	29	55.77
Urban	23	44.23

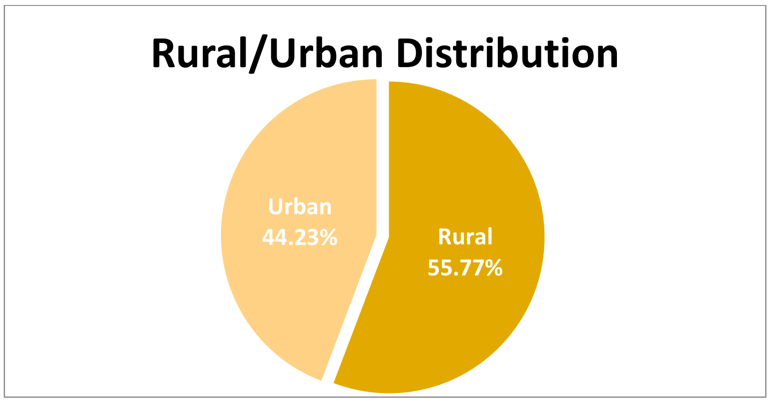

Figure 7: Pie chart showing Rural/Urban distribution of study population

Modes of delivery of newborns were broadly classified as lower segment cesarean sections (LSCS) and Normal vaginal delivery (NVD). In the current study, 28(53.85%) and 24(46.15%) patients were born by LSCS and NVD respectively (Table 5). Figure 8 shows distribution of patients with PDA based on mode of delivery.

Table 5: Distribution of patients with PDA based on mode of delivery (n=52)

Mode of delivery	Number	Percentage
lower segment cesarean sections (LSCS)	28	53.85
Normal vaginal delivery (NVD)	24	46.15

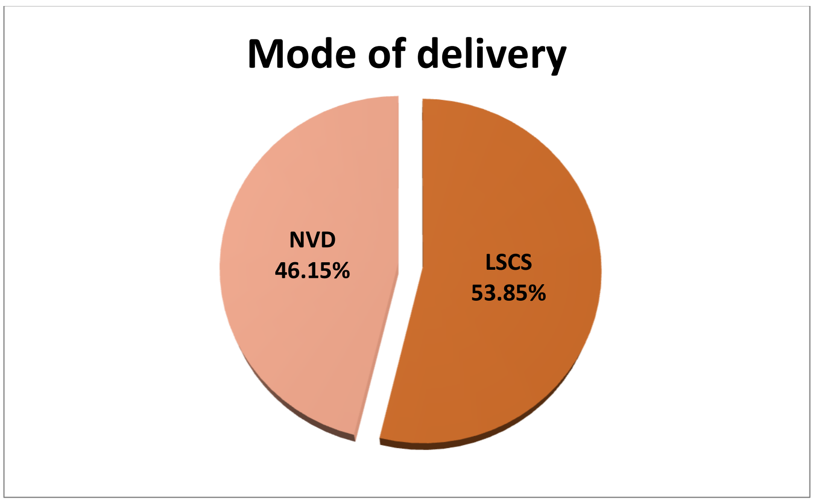

Figure 8: Distribution of patients based on mode of the delivery

In the current study, neonatal with PDA exhibited symptoms like Feeding Difficulty, sweating with crying/feeding, fast breathing, easy tiring and rapid heart rate (Table 6). Maximum of 42 (80.77%) patients had fast breathing followed by 37(71.15%) patients had rapid heart rate. 23(44.23%), 19(36.54%) and 25(48.08%) newborns showed symptoms of feeding difficulty, sweating with crying/feeding and easy tiring respectively. Percentage of patients showing different symptoms is graphically shown in Figure 9.

Table 6: Distribution of patients based on symptoms (n=52)

Symptoms	Present	Percentage
Feeding Difficulty	23	44.23
Sweating with crying/feeding	19	36.54
Fast breathing	42	80.77
Easy Tiring	25	48.08
Rapid Heart Rate	37	71.15

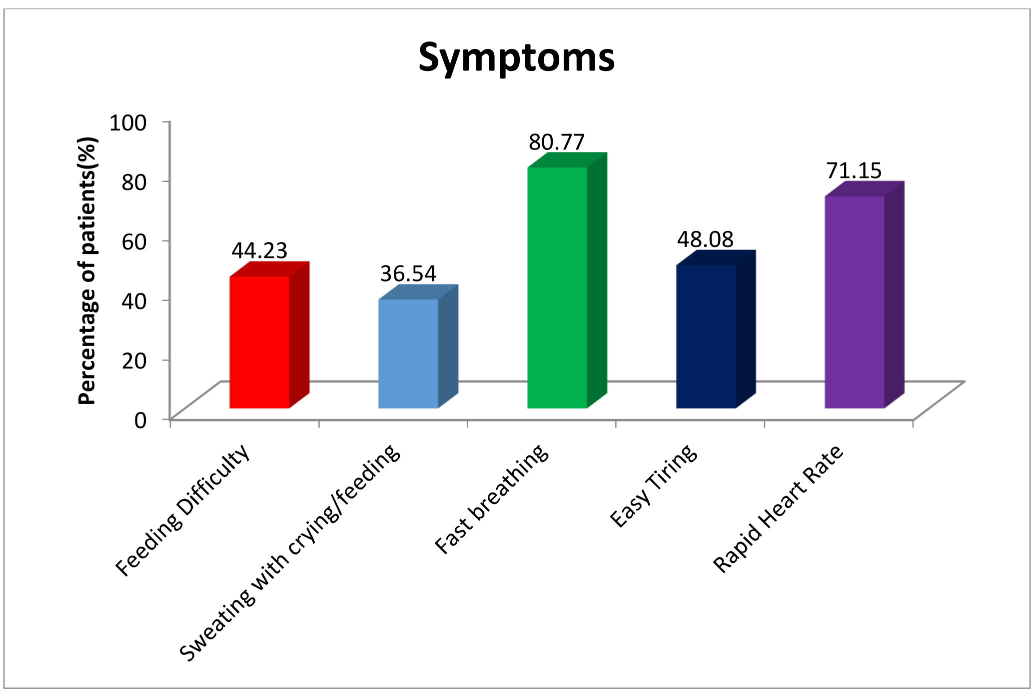

Figure 9: Graphical representation of patients' distribution based on the symptoms

Distribution of patients based on the clinical findings like bounding pulse, murmur tachycardia, hyperactive pericardium and oxygen desaturation is tabulated in Table 7. In most of the patients (44(84.62%)), murmur and oxygen desaturation was noticed. In 43(82.69%) and 38(73.08%) patients, bounding pulse and Tachycardia respectively was noticed. Hyperactive pericardium was found in only 20(38.46%) infants with PDA. Clinical findings frequency of PDA patients is shown in the bar graph below (Figure 10).

Table 7: Distribution of patients based on clinical findings (n=52)

Clinical findings	Present	Percentage
Bounding Pulse	43	82.69
Murmur	44	84.62
Tachycardia	38	73.08
Hyperactive Pericordium	20	38.46
Oxygen Desaturation	44	84.62

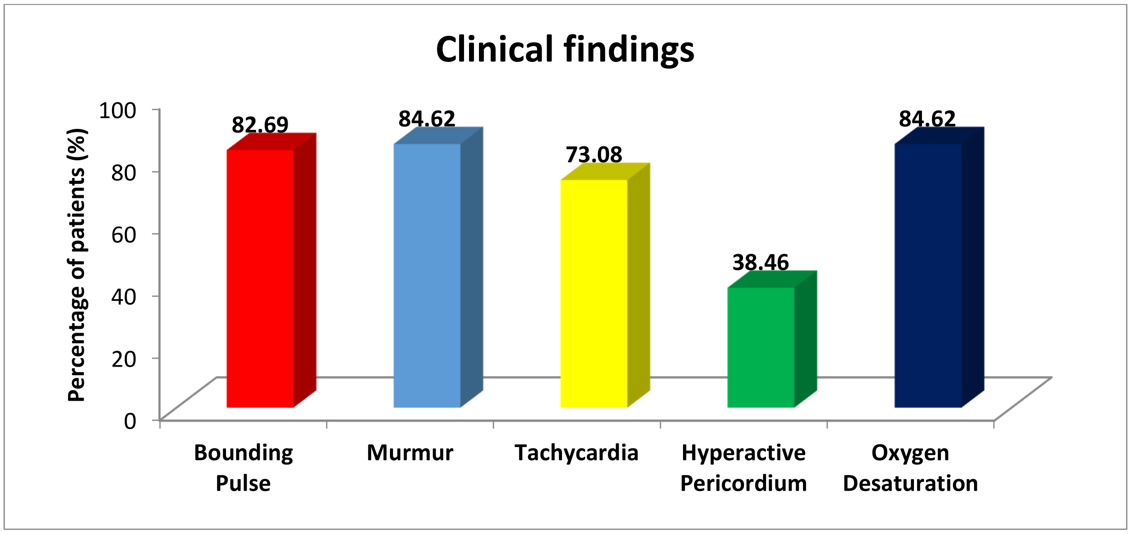

Figure 10: Bar graph representing the distribution of patients based on clinical findings (n=52)

After treatment, preterm Infants' Echocardiographic Evaluation of PDA was carried out to check the size of duct. Table 8 clearly shows that after the treatment of infants with Ibuprofen (n=26) and Paracetamol (n=26), maximum patients of 32(61.54%) had large ducts and only 20(38.46%) had moderate duct size. When compared between two treatment groups, chi- square test indicated that there was no statistically significant (p value =0.388) difference between the groups with 17(65.38%) and 15(57.69%) infants having large ducts respectively in Ibuprofen and Paracetamol groups. Figure 11 depicts the comparison between ibuprofen and paracetamol group for post treatment 1st 2D ECHO findings.

Table 8: Comparison between ibuprofen and paracetamol group for post treatment 1st 2D ECHO

POST TREATMENT 1st 2D ECHO	Total (N=52)	Treatment received		P value*
		Ibuprofen (n=26)	Paracetamol (n=26)	
Large, n (%)	32(61.54%)	17(65.38%)	15(57.69%)	0.388
Moderate, n (%)	20(38.46%)	9(34.62%)	11(42.31%)	
Total, n (%)	52(100%)	26(100%)	26(100%)	NA

*** Statistically significant if p value < 0.05 (for chi- square test)**

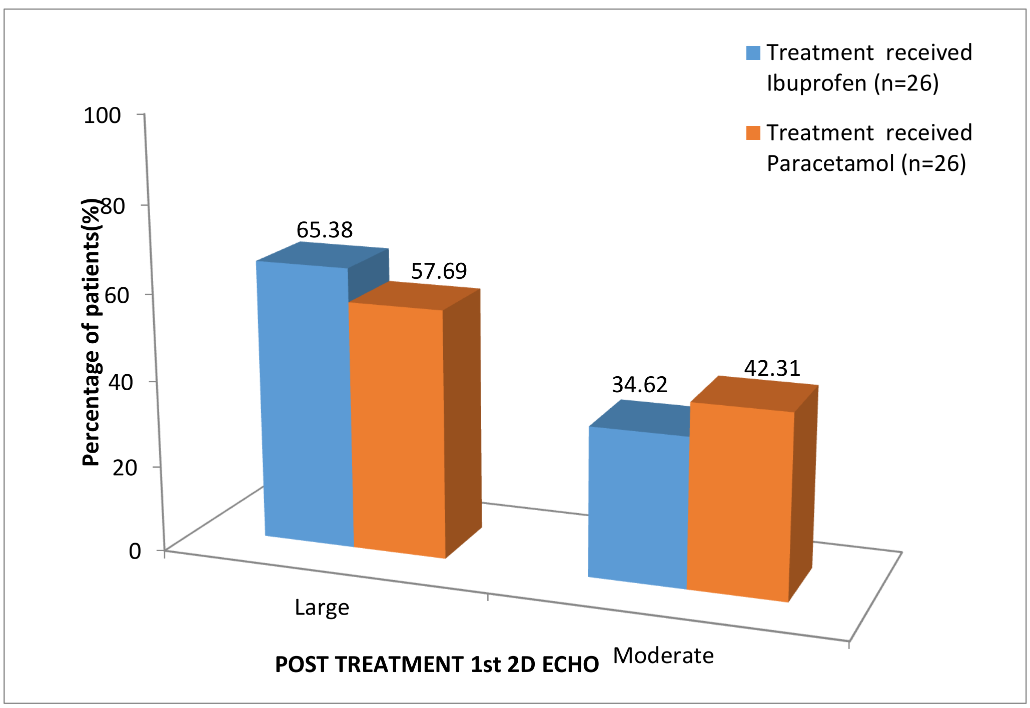

Figure 11: Graphical representation of post treatment 1st 2d ECHO-comparison between ibuprofen and Paracetamol group

After treatment, preterm Infants' ECHO Evaluation of PDA for second time was carried out to check the size of duct and closure of the duct. Table 9 clearly shows that after the treatment of infants with Ibuprofen (n=26) and Paracetamol (n=26), maximum patients of 22(42.31%) had ducts with reduced size followed by 21(40.39%) had closed ducts. When compared between two treatment groups, Fisher’s exact test indicated that there was statistically significant (p value =0.043) difference between the groups with 07(26.92%) and 14(53.85%) infants with closed ducts respectively in Ibuprofen and Paracetamol groups as well as 15(57.69%)

and 7(26.92%) infants with reduced size respectively in Ibuprofen and Paracetamol groups. It was also found that only one patient (3.85%) in paracetamol group had a complete closure of duct. Figure 12 depicts the comparison between ibuprofen and paracetamol group for post treatment 2nd 2D ECHO findings.

Table 9: Comparison between ibuprofen and paracetamol group for post treatment 2nd 2D ECHO

POST TREATMENT 2nd 2D ECHO	Total (N=52)	Treatment received		P value*
		Ibuprofen (n=26)	Paracetamol (n=26)	
Closed, n (%)	21(40.39%)	07(26.92%)	14(53.85%)	
Completely closed, n (%)	01(01.92%)	(0%)	01(03.85%)	
Large, n (%)	04(07.69%)	03(11.54%)	01(03.85%)	**0.043**
Moderate, n (%)	01(01.92%)	01(3.85%)	0(0%)	
Reduced size, n (%)	22(42.31%)	15(57.69%)	7(26.92%)	

*** Statistically significant if p value < 0.05 (for Fisher's exact test)**

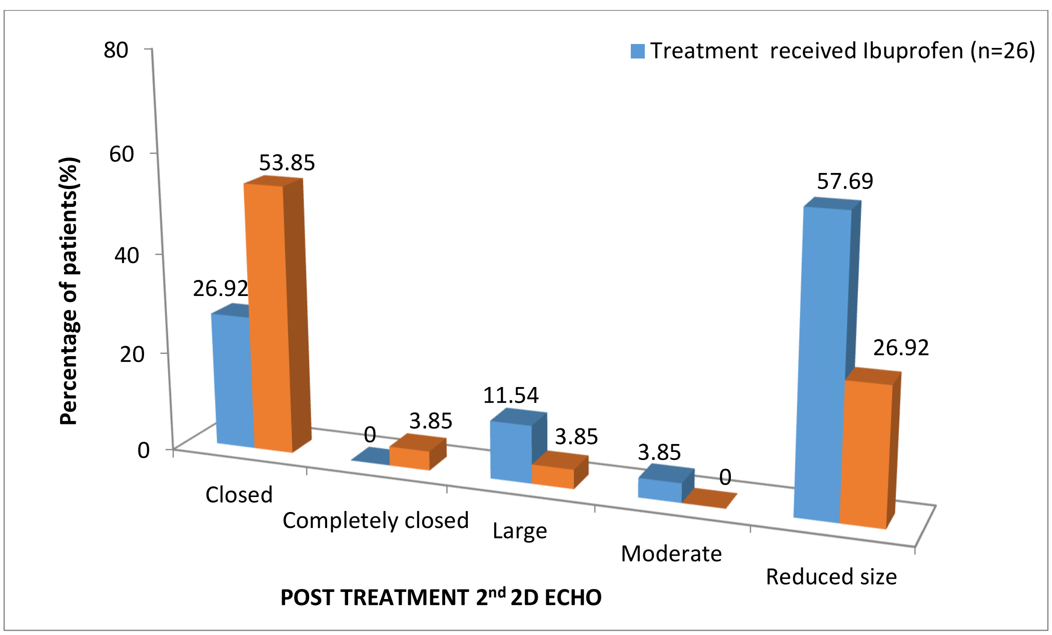

Figure 12: Graphical representation of post treatment 2nd 2D ECHO- comparison between ibuprofen and Paracetamol group

After first dose of treatment, infants with PDA were examined for completely closed ducts, Death, no reduction in Size of the duct, not closed, Reduction in size, and significant Reduction in size (Table 10). Overall, 21(40.39%), 3(05.77%), 4(07.69%), 1(01.92%), 2(03.85%) and 21(40.39%) infants with PDA, had completely closed ducts, died, no reduction in duct's size, not closed , reduction in size and significant reduction in size respectively. Comparison of outcomes after first dose of treatment with ibuprofen and paracetamol showed that there was statistically significant difference between two groups(p value =0.038). It was found that significantly higher infants had completely closed ducts in paracetamol group (14(53.85%)) than in Ibuprofen group 7(26.92%). It was found that significantly higher infants had significant Reduction in size of ducts in Ibuprofen group (14(53.85%)) than in paracetamol group 06(23.08%). There was a death of 3(11.54%) infants in paracetamol group whereas no death was recorded in Ibuprofen group. Comparison between ibuprofen and Paracetamol groups after 1st dose of treatment was graphically shown in Figure 13.

Table 10: Treatment effects comparison between ibuprofen and Paracetamol groups after 1st dose of treatment

Treatment effects after 1st dose	Total (N=52)	Treatment received		P value*
		Ibuprofen (n=26)	Paracetamol (n=26)	
Completely closed, n (%)	21(40.39%)	07(26.92%)	14(53.85%)	**0.038**
Death, n (%)	03(05.77%)	0(0%)	03(11.54%)	
No reduction in Size, n (%)	04(07.69%)	02(07.69%)	02(07.69%)	
Not closed, n (%)	01(01.92%)	01(03.85%)	0(0%)	
Reduction in size, n (%)	02(03.85%)	01(03.85%)	01(03.85%)	
Significant Reduction in size, n (%)	21(40.39%)	15(57.69%)	06(23.08%)	

*** Statistically significant if p value < 0.05 (for chi square test)**

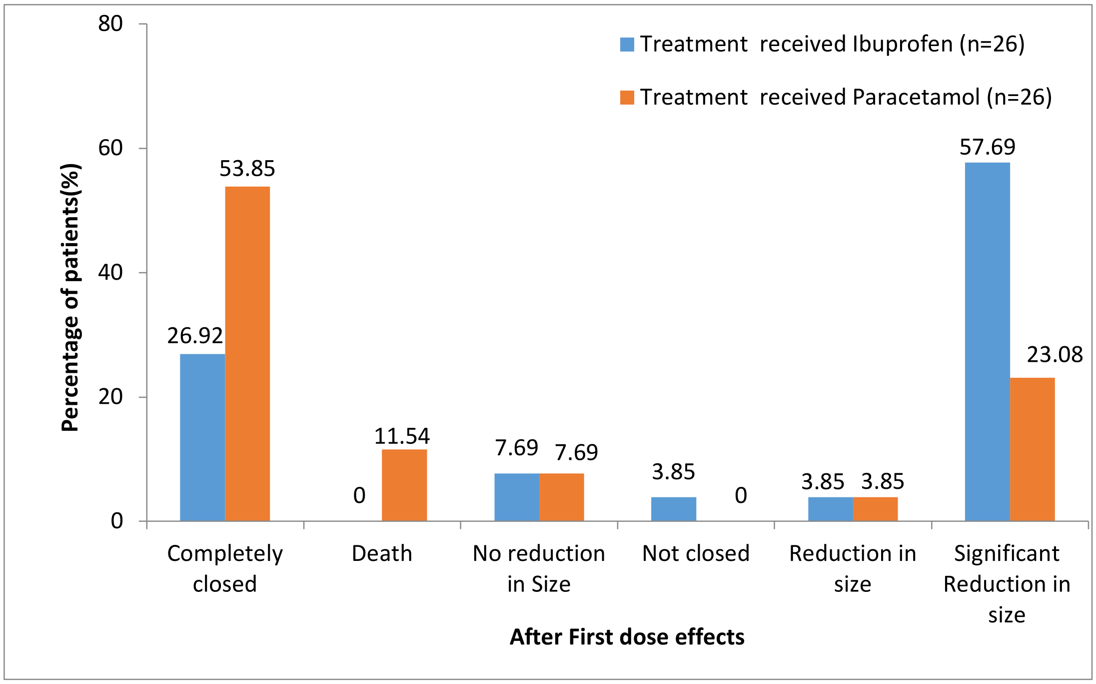

Figure 13: Treatment effects comparison between ibuprofen and Paracetamol groups after 1st dose of treatment

24 hours after second dose of treatment for persistent PDA, infants were examined for completely closed ducts, AMA, and not closed (Table 11). Out of 27 patients who received 2nd dose of drugs, 01(3.70%),

16(59.26%), and 10 (37.04%) infants with PDA, had AMA, Completely closed, and Not closed respectively. Comparison of outcomes after second dose of treatment with ibuprofen and paracetamol did not show statistically significant difference between two groups (p value =0.3739). There was no death was recorded in either of the group. Comparison between ibuprofen and Paracetamol groups after 2nd dose of treatment was graphically shown in Figure 14.

Table 11: Treatment effects comparison between ibuprofen and Paracetamol groups after 2nd dose of treatment

Treatment effects after 2nd dose	Total (N=27)	Treatment received		P value*
		Ibuprofen (n=16)	Paracetamol (n=11)	
AMA, n (%)	01(03.70%)	0(0%)	01(09.09%)	0.3739
Completely closed, n (%)	16(59.26%)	11(68.75%)	05(45.46%)	
Not closed, n (%)	10 (37.04%)	06(37.50%)	04(36.36%)	

* Statistically significant if p value < 0.05 (for chi-square)

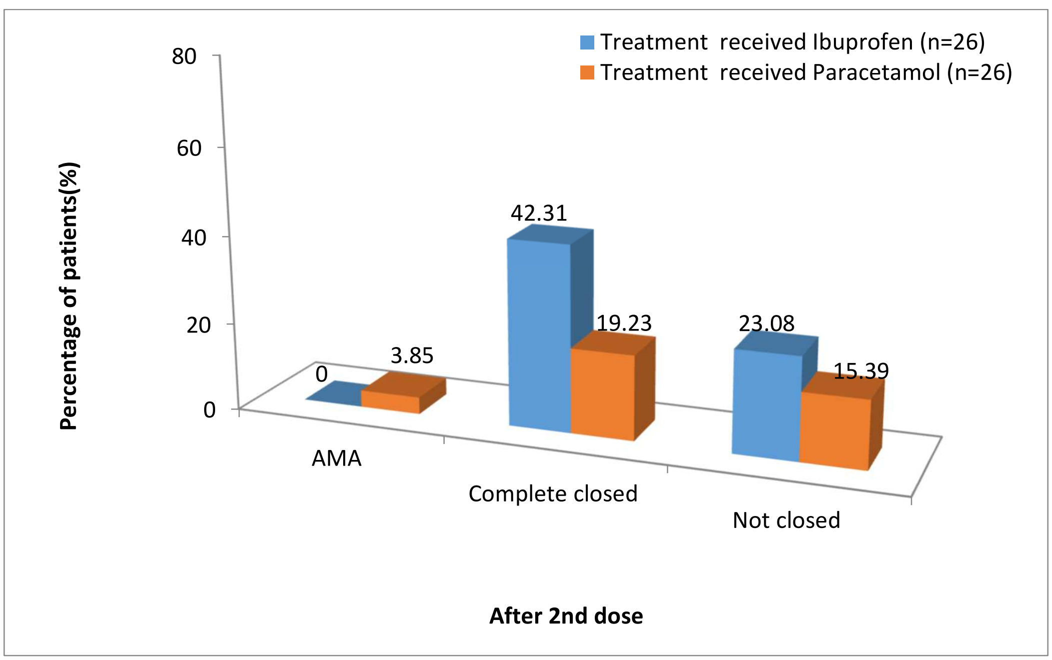

Figure 14: Treatment effects comparison between ibuprofen and Paracetamol groups after 2nd dose of treatment

Total mortality percentage in the study population after the treatment was calculated to be 7.69% (4 patients out of total 52). Figure 15 shows the distribution of 5 patients based on the mortality after treatment. Comparison between two groups (ibuprofen and Paracetamol groups) for the mortality by Fisher's exact test showed no statistically significant difference between groups. It was found that 1(03.85%) and 3(11.54%) infants with PDA had died after the first dose treatment of ibuprofen and Paracetamol respectively (P value = 0.6098). Distribution of patients based on the mortality with respect to different treatment is graphically shown in Figure 16.

Table 12: Comparison of mortality after treatment

Outcome	Total	Treatment Received		P value*
		Ibuprofen	Paracetamol	
Alive	48(92.31%)	25(96.15%)	23(88.46%)	0.6098
Death after first dose	04(07.69%)	01(03.85%)	03(11.54%)	

*Statistically significant if p value < 0.05 (for Fisher's exact test)

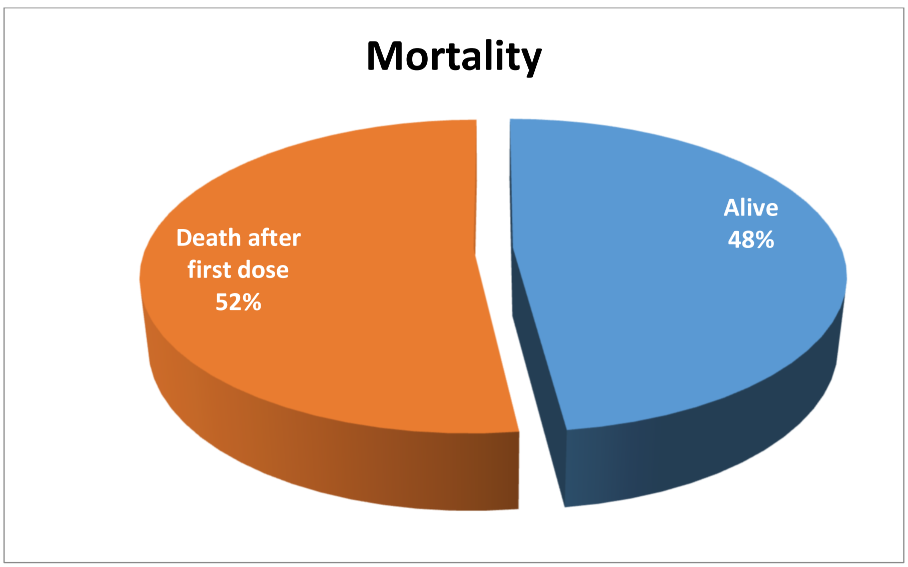

Figure 15: Distribution of PDA patients based on the mortality after the treatment

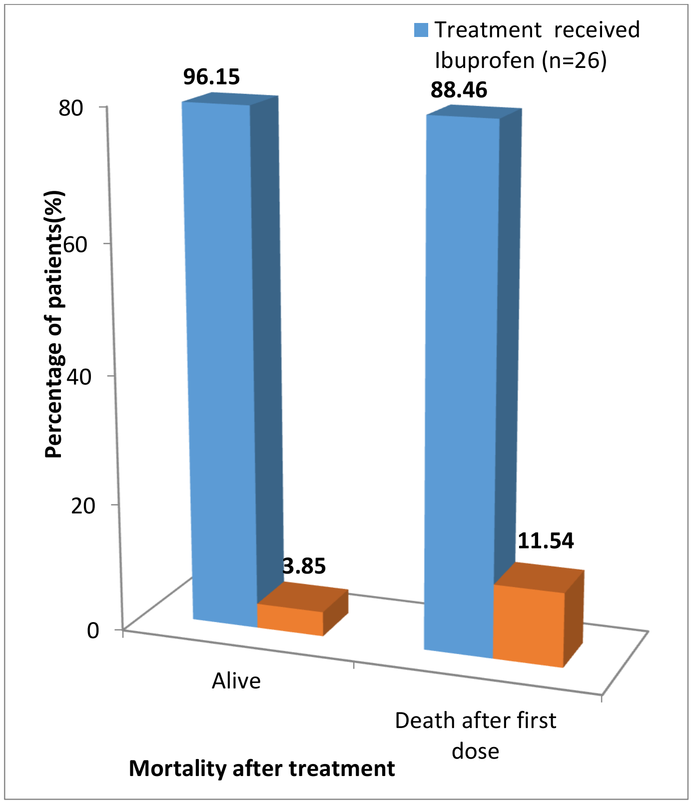

Figure 16: Distribution of patients based on the mortality with respect to different treatment

Comparison between 1st and 2nd EHCO findings after ibuprofen treatment is showcased in Table 13. In the first ECHO, 17(65.39%) and 9(34.61%) infants had large and moderate ducts respectively and none of the infant had reduced (size) or closed ducts. In the second echo ECHO, 7(26.92%), 3(11.54%), 1(38.46%) and 15(57.69%) infants had closed, large, moderate and reduced ducts respectively. Chi-square test carried out to compare the findings of first and second ECHO after the ibuprofen treatment revealed that there was statistically significant increase in the number of patients who had closed and reduced ducts and decrease in the number of patients who had large and moderate ducts(P value <0.0001). Comparison between 1st and 2nd EHCO findings after ibuprofen treatment is graphically represented in figure 17.

Table 13: IBUPROFEN – 1ST ECHO AND 2ND ECHO COMPARISON

Parameters	2 D ECHO		P value
	First	Second	
Closed	0(0%)	7(26.92%)	<0.001
Large	17(65.39%)	3(11.54%)	
Moderate	9(34.61%)	1(38.46%)	
Reduced	0(0%)	15(57.69%)	

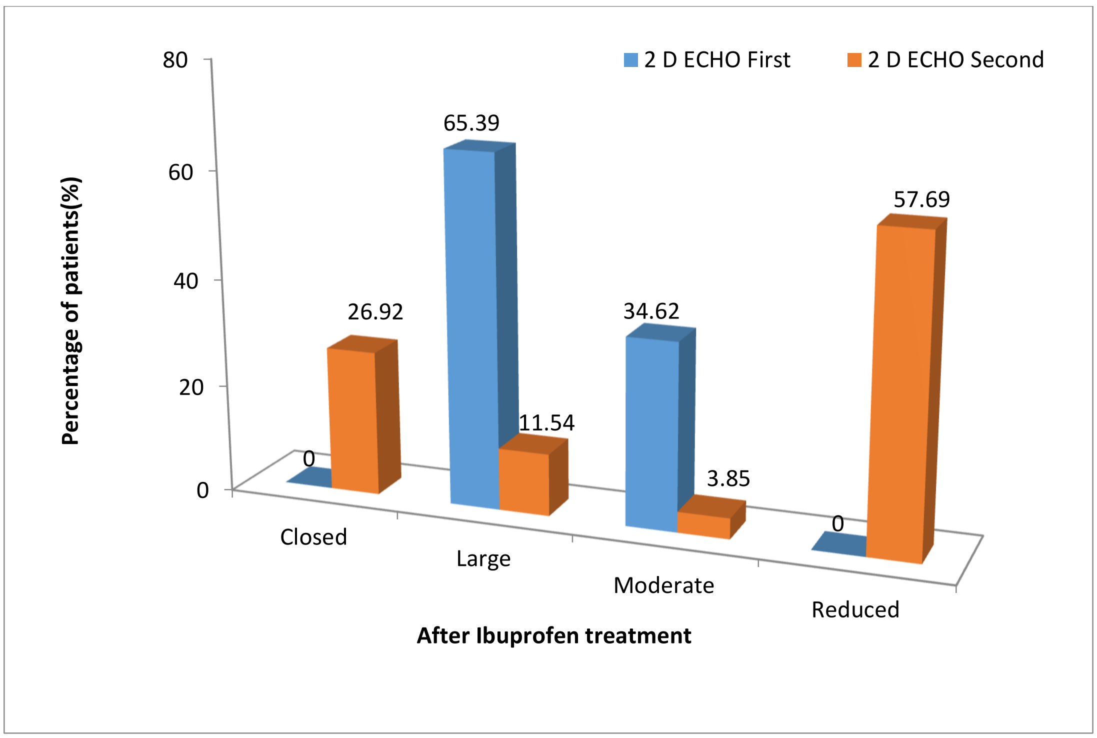

Figure 17: Graphical representation of 1st and 2nd ECHO findings after ibuprofen treatment

Comparison between 1st and 2nd EHCO findings after paracetamol treatment is showcased in Table 14. In the first ECHO, 13(50.00%) and 10(38.46%) infants had large and moderate ducts respectively and none of the infant had reduced (size) or closed ducts. In the second ECHO, 14(53.85%), 1(03.85%), 1(03.85%), 0(0%), and 07(26.92%) infants had closed, completely closed, large, moderate and reduced ducts respectively. Chi-square test carried out to compare the findings of first and second ECHO after the paracetamol treatment shown that there was statistically significant increase in the number of patients who had closed, completely closed and reduced ducts and decrease in the number of patients who had large and moderate ducts (P value <0.0001). Comparison between 1st and 2nd EHCO findings after paracetamol treatment is graphically represented in figure 18.

Table 14: PARACETOMOL – 1ST ECHO AND 2ND ECHO COMPARISON

Parameters	2D ECHO		P value
	First	Second	
Closed	0(0%)	14(53.85%)	<0.001
Completely closed, n (%)	0(0%)	01(03.85%)	
Large, n (%)	13(50.00%)	1(03.85%)	
Moderate, n (%)	10(38.46%)	0(0%)	
Reduced size, n (%)	0(0%)	07(26.92%)	

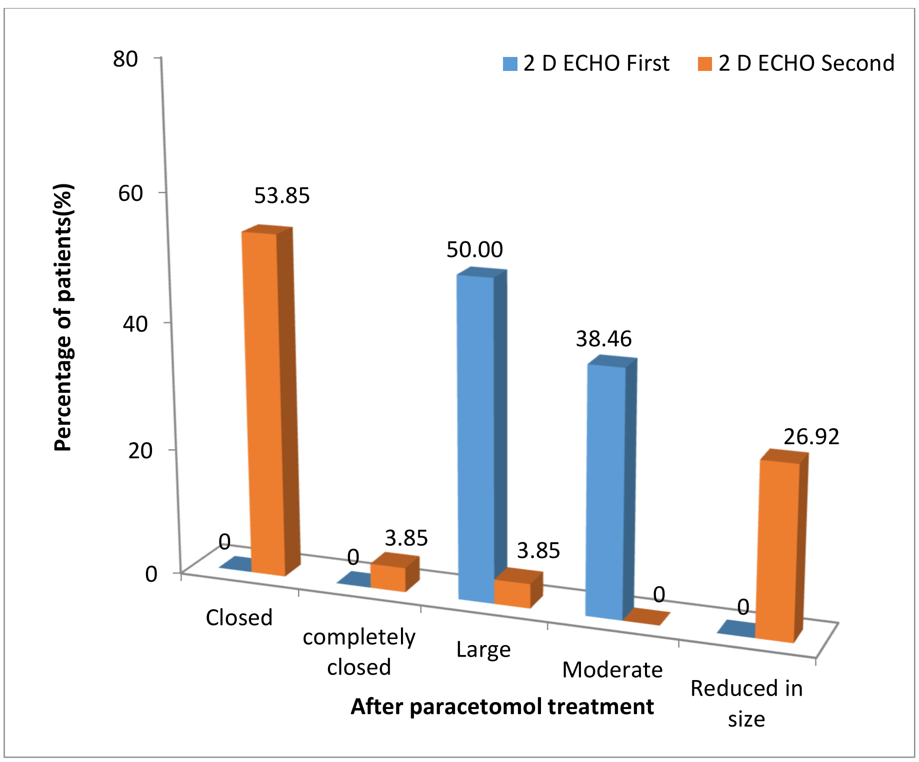

Figure 18: Graphical representation of 1st and 2nd ECHO findings after paracetamol treatment

Pre and post treatment comparison of laboratory parameters like Hemoglobin, TLC, Platelets, Urea, Creatinine, SGOT and SGPT was done for all the 52 infants (Table 15). It was found that there was significant difference in pre and post mean values of hemoglobin (15.97±2.75 Vs. 13.7±2.81), platelets count(177.37±75.94 Vs. 126.1±90.99), SGOT(49.35±123.57 Vs. 77.69±181.16) and SGPT (27.85±20.08 Vs. 39.35±31.12)(p value <0.05). Hemoglobin and platelets have higher pre-treatment mean values, whereas urea, SGOT and SGPT have higher post treatment mean values. For other parameters like TLC, urea and creatinine the difference between pre and post treatment records were statistically not significant (P value > 0.05).

Table 15: Comparison of pre and post treatment mean laboratory values

Parameters	Pretreatment	Post treatment	P value*
Haemoglobin (grams per decilitre)	15.97±2.75	13.7±2.81	<0.0001
Total Leucocyte Count (count/microliter)	10605.19±7150.03	10582.35±4457.46	0.8231
Platelets (count/microliter)	177.37±75.94	126.1±90.99	0.00008
Urea (mg/dL)	33.96±17.68	44.94±38.82	0.0764
Creatinine (mg/dL)	0.68±0.26	1.33±4.4	0. .3042
serum glutamic-oxaloacetic transaminase (SGOT) (U/L)	49.35±123.57	77.69±181.16	0.0037
Serum glutamic pyruvic transaminase (SGPT) (U/L)	27.85±20.08	39.35±31.12	0.0002

*statistically significant if p value <0.05 (for repeated measures of t-test)

Pre and post ibuprofen treatment comparison of laboratory parameters like Hemoglobin, TLC, Platelets, Urea, Creatinine, SGOT and SGPT was done for all the 26 infants using repeated measures of t- tests (Table 16). It was found that there was significant difference in pre and post mean values of hemoglobin (16.13±2.82 Vs. 14.11±2.51), platelets count (173.96±81.03Vs. 111.38±100.33), SGOT (33.81±32.32

Vs. 51.23±35.4) and SGPT (26.46±11.82 Vs. 37.92±16.46) (p value <0.05). Hemoglobin and platelets have higher pre-treatment mean values, whereas urea, SGOT and SGPT have higher post treatment mean values. For other parameters like TLC, urea and creatinine the difference between pre and post treatment records were statistically not significant (P value > 0.05).

Table 16: Comparison of Pre and post treatment laboratory values for ibuprofen treatment group

Parameters	Pretreatment	Post treatment	P value
Haemoglobin (grams per decilitre)	16.13±2.82	14.11±2.51	<0.001
Total Leucocyte Count (count/microliter)	11129.62±8609.76	10684.62±3912.31	0.585
Platelets (count/microliter)	173.96±81.03	111.38±100.33	0.002
Urea (mg/dL)	29.73±13.7	39.69±23.9	0.029
Creatinine (mg/dL)	0.66±0.26	1.94±6.14	0.226
serum glutamic-oxaloacetic transaminase (SGOT) (U/L)	33.81±32.32	51.23±35.4	<0.001
Serum glutamic pyruvic transaminase (SGPT) (U/L)	26.46±11.82	37.92±16.46	0.005

Pre and post paracetamol treatment comparison of laboratory parameters like Hemoglobin, TLC, Platelets, Urea, Creatinine, SGOT and SGPT was done for all the 26 infants using repeated measures of t- tests (Table 17). It was found that there was significant difference in pre and post mean values of hemoglobin (15.81±2.77 Vs. 13.27±3.08), platelets count (183.52±72.01Vs. 141.4±79.26), SGOT (66.2±175.47 Vs. 105.2±255.97) and SGPT (29.84±26.41Vs. 40.84±41.61) (p value <0.05). Hemoglobin and platelets have higher pre-treatment mean values, whereas urea, SGOT have higher post treatment mean values. For other parameters like TLC, urea, creatinine and SGPT the difference between pre and post treatment records were statistically not significant (P value > 0.05).

Table 17: comparison of Pre and post treatment laboratory values for Paracetamol treatment group

Parameters	Pretreatment	Post treatment	P value
Haemoglobin (grams per decilitre)	15.81±2.77	13.27±3.08	<0.001
Total Leucocyte Count (count/microliter)	10321.6±5408.6	10476±5042.47	0.747
Platelets (count/microliter)	183.52±72.01	141.4±79.26	0.008
Urea (mg/dL)	39.12±20.17	50.4±49.84	0.647
Creatinine (mg/dL)	0.7±0.27	0.7±0.54	0.404
serum glutamic-oxaloacetic transaminase (SGOT) (U/L)	66.2±175.47	105.2±255.97	0.003
Serum glutamic pyruvic transaminase (SGPT) (U/L)	29.84±26.41	40.84±41.61	0.057

Comparison between pretreatment laboratory values of ibuprofen and paracetamol groups were studied (Table 18). Similarly Comparison between post treatment laboratory values of ibuprofen and paracetamol groups were studied (Table 19). No statistical significance was noticed between laboratory values of two groups at pre-treatment and post treatment evaluation.

Table 18: comparison of Pre-treatment laboratory values between Ibuprofen and Paracetamol treatment group

Parameters	Pretreatment		P value
	Ibuprofen	Paracetamol	
Haemoglobin (grams per decilitre)	16.13±2.82	15.81±2.77	0.6722
Total Leucocyte Count (count/microliter)	11129.62±8609.76	10321.6±5408.6	0.6870
Platelets (count/microliter)	173.96±81.03	183.52±72.01	0.6549
Urea (mg/dL)	29.73±13.7	39.12±20.17	0.0551
Creatinine (mg/dL)	0.66±0.26	0.7±0.27	0.5888
serum glutamic-oxaloacetic transaminase (SGOT) (U/L)	33.81±32.32	66.2±175.47	0.3591
Serum glutamic pyruvic transaminase (SGPT) (U/L)	26.46±11.82	29.84±26.41	0.5541

Table 19: comparison of Post-treatment laboratory values between Ibuprofen and Paracetamol treatment group

Parameters	Post treatment		P value
	Ibuprofen	Paracetamol	
Haemoglobin (grams per decilitre)	14.11±2.51	13.27±3.08	0.2862
Total Leucocyte Count (count/microliter)	10684.62±3912.31	10476±5042.47	0.8687
Platelets (count/microliter)	111.38±100.33	141.4±79.26	0.2369
Urea (mg/dL)	39.69±23.9	50.4±49.84	0.3279
Creatinine (mg/dL)	1.94±6.14	0.70±0.54	0.3099
serum glutamic-oxaloacetic transaminase (SGOT) (U/L)	51.23±35.4	105.2±255.97	0.2920
Serum glutamic pyruvic transaminase (SGPT) (U/L)	37.92±16.46	40.84±41.61	0.7407

The overall outcome of preterm infants with PDA after the initial dose of medicine is tabulated in Table 20. It was found that 21(40.38%), 4 (7.69%), 4(7.69%), 1 (1.92%), 2(3.85%) and 20(38.46%) patients had completely closed, death , No reduction in the size of PDA, not closed, reduction in size and significant reduction in size respectively(Figure 19). Similarly overall outcome after the second dose of medicine is tabulated in table 21. Out of 56 patients, 21(40.38%), 16 (30.77%), 4(7.69%), 1(1.92%) and 10(19.23%) had Complete closed ducts after 1st dose, complete closed ducts after 2nd dose, death after 1st dose, AMA after 2nd dose and not closed after 2nd dose respectively(Figure 20)

Table 20: Outcome after 1st dose

Outcome after 1st dose	Number	Percentage
Completely closed	21	40.38
Death	4	7.69
No reduction in the size of PDA	4	7.69
Not closed	1	1.92
Reduction in size noted	2	3.85
Significant reduction in size	20	38.46

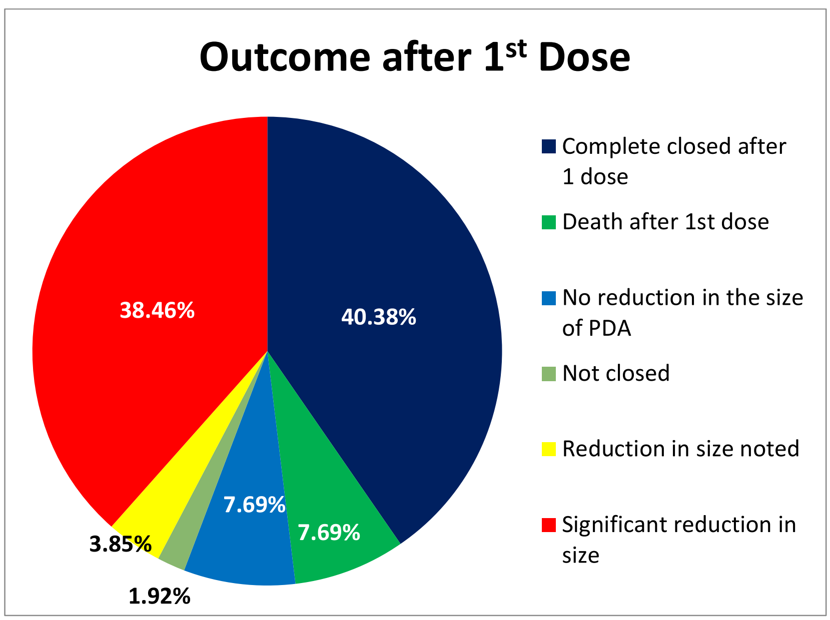

Figure 19: Pie chart depicting the outcome of PDA patients after 1st dose treatment

Table 21 Outcome after 2nd dose

Outcome after 2nd dose	Number	Percentage
Complete closed after 1st dose	21	40.38
Complete closed after 2nd dose	16	30.77
Death after 1st dose	4	7.69
AMA after 2nd dose	1	1.92
Not closed after 2nd dose	10	19.23

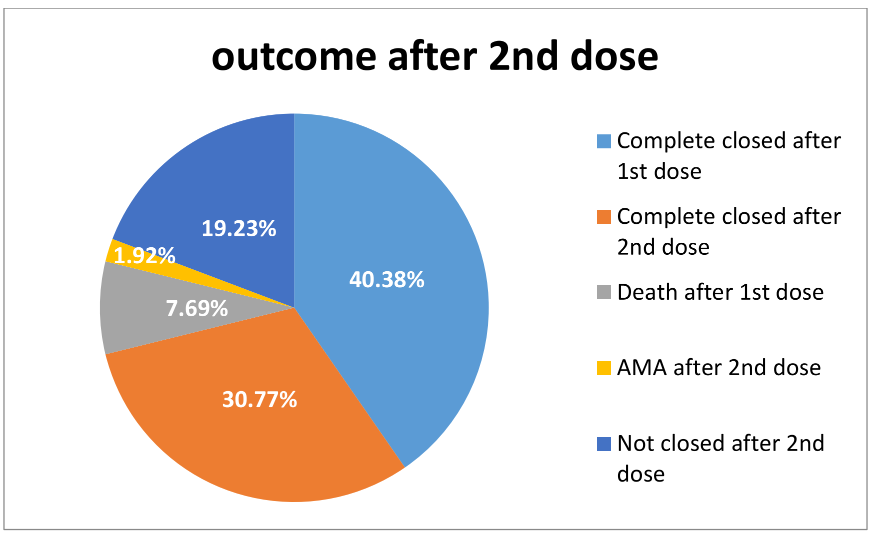

Figure 20: Pie chart depicting the outcome of PDA patients after 2nd dose treatment

DISCUSSION

Failure of the DA to close before the initial 72 hours of life is known as PDA. PDAs that are hemodynamically significant and linked to substantial morbidity and mortality, which can reach 30%. The use of NSAIDs for treating PDA may potentially complicate the course of treatment because these drugs interfere with blood coagulation, posing the risk of intraventricular haemorrhage in premature infants and leading to a prolonged course of recovery (66). A significant portion of PDA affects preterm newborns that are frequently treated in the ICU (67). There are a number of studies that claim that taking either oral/intervenous paracetamol or oral ibuprofen is safer medication for the treatment of PDA (66). Pharmacologic management of PDA is always with risk, and limiting treatment to neonates with hsPDA is the best strategy for balancing treatment benefits with the risks of potential adverse effects (68)There is dearth of studies that compare the safety of intravenous paracetamol and oral ibuprofen in Indian scenario for preterms with hemodynamically significant PDA. Therefore, in the current study, safety and efficacy of oral ibuprofen and intravenous paracetamol treatment in the closure of patent ductus arteriosus in preterm neonates was studied and compared. The objective of our study was to study the safety as well as efficacy of both these drugs which were administered by different routes.

Between January 2021 and January 2022, the hospital-based randomized control research was conducted. 52 neonates from the NICU of the Department of Pediatrics, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, who were diagnosed with hemodynamically significant hsPDA were included in the study who met the inclusion norms.

Based on a computer-based randomization system, these newborns were assigned to particular therapy groups. They were chosen at random to receive one of the two medications at the following doses: Ibuprofen (10mg/kg/dose) as a single oral dosage on day 1 followed by 5mg/kg/dose for the next two days, or paracetamol (15mg/kg/dose) administered intravenously four times a day for three days. After receiving treatment for three days in each group, a second ECHO test was administered. Results including being entirely closed, having a large size reduction, and remaining open were reported. If there was a considerable reduction in size but the wound didn't close, the same prescribed medication was given again at the same dose, days, and interval. Then, another scan was conducted, and the results were recorded as before.

In the current study, the mean age with standard deviation of all 52 neonates with PDA was 6.92±6.88 days, with a minimum of 2 days and a maximum of 30 days. The mean gestational age of the study population was 221.77±21.30 days. The average weight of the 52 patients was 1510.29±473.61g. Apgar scores at one and five minutes were 5.98 ±1.55 and 8.36±1.102, respectively. Premature neonates have a higher prevalence of patent ductus arteriosus (PDA) depending on gestational age and respiratory status. PDA incidence is inversely related to gestational age. It is still open at 4 days of age in 10% of neonates born at 30-37 weeks, 80% of those born between 25 and 28 weeks, and 90% of those born at 24 weeks (25). Prematurity clearly increases the incidence of PDA, and this is due to physiological factors associated with prematurity rather than an inherent ductal abnormality (28). Every third preterm infant with a birth weight (BW) of 501 to 1500 g (very low birth weight -VLBW) is expected to have a persistent PDA . The incidence depends on how small the infant is and the respiratory condition after birth. Furthermore, 55% of infants weighing 1000 g (extremely low birth weight, ELBW) have a symptomatic PDA that requires medical treatment (69). Lower Apgar scores and the need for resuscitation can be caused by the infant's immaturity or an acute obstetric condition such as asphyxia . It has been discovered that birth asphyxia and severe RDS were significant risk factors for the development of an early hemodynamically significant PDA in VLBW infants (70).

The number of males in the current study was 29 (55.77%) and the number of females was 22 (42.31%). indicating a slightly male predominance. A recent meta-analysis by Liu et al. evaluated several risk factors for developing PDA in preterm infants and discovered that the risk of developing PDA was slightly higher for boys than for girls (71). PDA was also found in a higher proportion of female infants than male infants (2:1), for unknown reasons. (72). The current study's male predominance contrasted with the findings of one of the largest and most comprehensive systematic reviews and meta-analyses, which found no gender difference in the risk of developing PDA among preterm infants (73). Because our study was limited by a small sample size and a single location of study, it may be insufficient to draw firm conclusions.

The study found that 29 (55.77%) were from rural areas and 23 (44.23%) were from urban areas. When we compared the mode of delivery, we found that 28 (53.85%) were delivered by LSCS and 24 (46.15%) were delivered by NVD.

According to our research, the most common symptom was fast breathing (80.77%), followed by rapid heart rate (71.15%), implying that the majority of them complained of fast breathing. Out of all clinical findings such as Bounding Pulse, Murmur, Tachycardia Hyperactive Precordium, and Oxygen Desaturation, the most common findings in our study were murmur and oxygen desaturation (84.62% each), followed by bounding pulse (82.69%).

The majority of babies (40.38%) showed complete closure after the first dose, followed by a significant reduction in size (38.46%). Four babies died after the first dose, despite the fact that a prior baby echo showed a significant reduction. After the second dose, 30.77% of the infants had complete closure. After the second dose, approximately 19.23% of the patients were still open. After receiving the first dose of treatment, 15 (57.69%) of the 26 patients in the ibuprofen group had significant reductions in the size of their PDA, while 7 (26.92%) had complete closure. In the paracetamol group, 14 (53.8%) of the 26 patients had complete closure and 7 (26.92%) had a significant reduction in the size of the PDA. After receiving the second dose of treatment, 11 (42.3%) of the 26 patients in the ibuprofen group had complete closure, while 6 (23.0%) remained unclosed. In the paracetamol group, 5 (19.2%) of the 26 wounds were completely closed, while 4 (15.3%) remained open. In our study, 19 patients (73.07%) had complete closure after paracetamol treatment, and 18 patients (69.23%) had complete closure after ibuprofen treatment.

Our study found that intravenous paracetamol and ibuprofen were equally effective for PDA closure; the closure rate of intravenous paracetamol was comparable to that of oral ibuprofen after the first and second courses of treatment, with comparable total ductal non-surgical closure between the two groups.

Several studies (2,46,53)confirmed the efficacy of paracetamol in very low birth weight neonates; six of them reported a rate of ductal closure of 71-100% (2,52,62). Concerning the safety of oral paracetamol, our findings were consistent with those of Oncel et al., Allegaert et al., El-Farrash et al., and Yurttutan et al., who reported no signs of hepatic or renal intolerance during or after paracetamol administration.

PDA closure studies comparing oral paracetamol vs. oral ibuprofen found that both paracetamol and ibuprofen were equally effective (2). In addition, Dang et al., published a randomised control trial comparing the efficacy of oral ibuprofen and oral paracetamol in the treatment of hsPDA and discovered that the ductus was closed in 65 infants (81.2%) of the paracetamol group compared to 63 (78.8%) of the ibuprofen group with no significant difference (p =0.693). Ductal closure occurred after the first course of treatment in 45 infants (56.3%) given oral paracetamol and 38 infants (47.5%) given oral ibuprofen (p=0.268). The ductus closed in another four patients from each group after continuing to receive the assigned drug treatment (p=0.62). Later, Oncel et al. conducted a randomised clinical trial and reported that, after the first course of treatment, the PDA was completely closed in 31/40 (77.5%) of patients assigned to the oral ibuprofen group and 29/40 (72.5%) of patients assigned to the oral paracetamol group (p=0.6).

The current study found that a second pharmacological course of ibuprofen was more effective than the first course of treatment in closing hsPDA in preterm infants. According to the study conducted by van der Lugt and Lopriore, repeated courses of ibuprofen are more effective than single courses, and a second dose can be considered if the first dose fails to close the PDA.

When we compared pre-treatment and post-treatment laboratory values in the overall study group, paracetamol and ibuprofen groups, there was a statistically significant difference in hemoglobin, platelets, SGPT and SGOT, urea (for paracetamol group there was no statistical significance was observed for urea and

SGPT) but no difference in TLC, and creatinine. Pre-treatment mean values for hemoglobin and platelets were higher, whereas post-treatment mean values for SGOT and SGPT (only in ibuprofen group).

Abd El-Rahman El-Mashad conducted a study. Concerning the hepatotoxicity of paracetamol in neonates, they discovered that there was no significant change in serum levels of SGPT or SGOT after treatment, including the paracetamol. This was consistent with the findings of Jacqz-Aigrain et al., who discovered that neonates are less susceptible to the hepatotoxic effects of paracetamol than older children. Both of the preceding studies contradicted our findings. In our study, there was an increase in SGOT after paracetamol and an increase in SGOT, SGPT, and urea with ibuprofen. However, Alan et al., reported elevated liver transaminases in two out of three preterm neonates treated for PDA, which is consistent with our findings.

In our study, we found a decrease in platelets and haemoglobin in both the ibuprofen and paracetamol groups, in contrast to a study conducted by Abd El-Rahman El-Mashad, who found a significant decrease in platelet level after ibuprofen treatment, but no thrombocytopenia after paracetamol treatment, which was consistent with studies conducted by Hammerman et al, Lee ch et al, and van Overmeire. The role of platelet function in preterm infant spontaneous PDA closure has been investigated (74). Lower mature platelet counts are an independent predictor of hsPDA .

In the current study, the study population's total mortality rate after treatment was calculated to be 7.69%. Comparison between two group (ibuprofen and Paracetamol) revealed no statistically significant difference in mortality. It was discovered that 1 (03.85%) and 3 (11.54%) infants with PDA died after receiving the first dose of ibuprofen and Paracetamol, respectively (P value = 0.6098).

The findings of our study support paracetamol's efficacy in ductal closure same as ibuprofen, with intermittent low and transient elevations of liver enzymes being reported as a side effect. Our study indicated that paracetamol may has higher renal safety as compared to ibuprofen which is in the line with findings of Yang et al., who demonstrated a significantly lower reduction in PGE2 urinary excretion and a minor incidence of oliguria when comparing two groups of infants treated with paracetamol versus ibuprofen.

The current study was limited in that no placebo control group was included, which would have made estimating the spontaneous PDA closure rate more meaningful. Using a placebo in such preterms with hsPDA, on the other hand, would have been unethical. Due to the different number of paracetamol and ibuprofen daily doses, the study also lacked a double-blind design.

CONCLUSION

Hemodynamically significant PDA is one of the most common heart conditions seen in preterm neonates, and 2D ECHO is a very useful scan for diagnosing PDA. Early detection of signs and close monitoring of babies aid in the early diagnosis of PDA. Fast breathing was the most common symptom (80.77%), followed by rapid heart rate (71.15%). Murmur and oxygen desaturation were the most common findings (84.62% each), followed by bounding pulse (82.69%). Early diagnosis results in earlier administration of these medications.

We concluded from this study that both drugs are equally effective in closing the hemodynamically significant PDA. However, when compared to Oral Ibuprofen, the closure rate of PDA with intravenous paracetamol was higher after the first course of the drug. In addition, paracetamol has fewer side effects than ibuprofen.

Because we compared both routes of drug administration, clinicians can select drugs based on the needs of the baby. In relatively stable neonates, the oral route of drug administration can be used, whereas when the neonate is sick and has NBM, paediatricians can choose the intravenous route of administration. Thus, the use of any of the drugs is effective in the closure of hsPDA, reducing the need for the baby to be subjected to unnecessary surgical procedures.

The current study's findings support the use of IV paracetamol as a first-line drug for the treatment of hsPDA. However, according to the most recent guidelines and a Cochrane review, conservative management with fluid restriction and wait and watch is still preferred before beginning pharmacological closure.

SUMMARY

In the current study “Comparison of efficacy and safety of oral ibuprofen versus intravenous paracetamol in the closure of patent ductus arteriosus in preterm neonates”, total 52 preterm neonates were included. All neonates who were clinically diagnosed with PDA and confirmed by 2D-echo (which was done by the same person to eliminate selection bias) were randomly assigned to one of two groups in a 1:1 ratio.

- Each of the groups received the treatment that was assigned to them (Paracetamol and ibuprofen).

- The mean age with standard deviation of all 52 neonates with PDA in the current study was 6.92±6.88 days, with a minimum of 2 days and a maximum of 30 days. The study population' s mean gestational age was 221.77±21.30 days. The 52 patients weighed an average of 1510.29±473.61g. At 1 minute and 5 minutes, the Apgar scores were 5.98 ±1.55 and 8.36±1.102, respectively. In the current study, there were 29 males (55.77%) and 22 females (42.31%).

- According to the study, 29 (55.77%) were from rural areas, while 23 (44.23%) were from urban areas. When we compared the modes of delivery, we discovered that LSCS delivered 28 (53.85%) and NVD delivered 24 (46.15%). Fast breathing was the most common symptom (80.77%), followed by rapid heart rate (71.15%), implying that the majority of them complained of fast breathing.

- Murmur and oxygen desaturation were the most common clinical findings in the study (84.62% each), followed by bounding pulse (82.69%). After the first dose, the majority of babies (40.38%) showed complete closure, followed by a significant reduction in size (38.46%). Despite a prior baby echo showing a significant reduction, four babies died after the first dose. 30.77% of the infants had complete closure after the second dose.

- Approximately 19.23% of the patients were still open after the second dose. 15 (57.69%) of the 26 patients in the ibuprofen group had significant reductions in the size of their PDA after receiving the first dose of treatment, while 7 (26.92%) had complete closure. 14 (53.8%) of the 26 patients in the paracetamol group had complete closure, and 7 (26.92%) had a significant reduction in the size of the PDA. After the second dose of ibuprofen, 11 (42.3%) of the 26 patients in the ibuprofen group had complete closure, while 6 (23.0%) remained open. 5 (19.2%) of the 26 wounds in the paracetamol group were completely closed, while 4 (15.3%) remained open.

- In our study, 19 patients (73.07%) experienced complete closure following paracetamol treatment, and 18 patients (69.23%) experienced complete closure following ibuprofen treatment.

- A comparison of pre-treatment and post-treatment laboratory values in the overall study group, paracetamol, and ibuprofen groups revealed a statistically significant difference in haemoglobin, platelets, SGPT and SGOT, urea (no statistical significance was observed for urea and SGPT in the paracetamol group), but no difference in TLC and creatinine.

- Pre-treatment mean haemoglobin and platelet values were higher, whereas post-treatment mean SGOT and SGPT values were lower (only in ibuprofen group).The total mortality rate after 1st dose of treatment for the study population was calculated to be 7.69%. (4 patients out of a total of 52).

- For mortality, the difference was statistically insignificant between the two groups (ibuprofen and Paracetamol). It was discovered that 1 (03.85%) and 3 (11.54%) infants with PDA died after receiving the initial dose of the drugs ibuprofen and Paracetamol, respectively (P value = 0.6098).

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ANNEXURE I – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH

‘‘COMPARISON OF EFFICACY AND SAFETY OF ORAL IBUPROFEN VERSUS INTRAVENOUS PARACETAMOL IN THE CLOSURE OF PATENT DUCTUS ARTERIOSUS IN PRETERM NEONATES, A ONE YEAR RANDOMISED CONTROL TRIAL.’’

Investigator: REG NO. BM120017

Guide: DR_________________

ASSOCIATE PROFESSOR

DEPARTMENT OF PEDIATRICS,

KLE ACADEMY OF HIGHER EDUCATION & RESEARCH,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELGAUM -590010.

You are hereby requested to involve your child in the above said research to be

conducted at

KLE’S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from

July 2020

to December 2020 by me.

Introduction

PURPOSE OF THE STUDY

To compare the efficacy of oral Ibuprofen and IV Paracetamol in the closure of PDA.

To determine the safety and side effects of both ibuprofen and paracetamol.

Voluntary participation

Your child's participation in this study is your voluntary decision. Whether to participate or not to participate will not affect your current or future relationship with the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

You are free to discontinue the participation in the study at any time for any reasons and you will not be paid any reimbursement for participation in the research.

Risk and benefits

There are no major risks involved, other than discomfort and pain caused during collection of biological sample.

Privacy and Confidentiality

The only people who will know that you are a research participant are member of the research team. No information about you or provided by you, during research will be disclosed to others without your written consent. When the results of the research are published or discussed in the conferences, no information will be disclosed that would reveal your identity. Any information obtained in connections with this study and that can be identified with you remain confidential and will be disclosed only with your permission.

Queries

If you have any queries you may contact

REG NO. BM120017

Post Graduate Student

Department of Pediatrics

JNMC, Belagavi-590010

DR.________________

ASSOCIATE PROFESSOR

DEPARTMENT OF PEDIATRICS,

KLE ACADEMY OF HIGHER EDUCATION & RESEARCH,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELGAUM -590010.

If you have any questions about your rights or research participation you may contact

Dr. Harsha Hegde

Chairperson , JNMC,IEC

& Scientist D,

ICMR,National Institute of Transfusion Medicine

Belgavi

Phone No.9480422500

You will be given a copy of this form for your information and to keep for your records.

STATEMENT OF CONSENT

I hereby voluntarily agree for my and my childs participation in this study. I understand that even if I choose to allow my child to take part in this study I have the liberty to withdraw at any time. My signature below indicates that I have read or have been told about this entire consent form including the risks and benefits and have had all my questions answered. I will be given a copy of this consent form.

Signature of the authorized representative/ parent: _______________

Date: _____________

Name: ____

Relation to the Subject: __________________________________

Signature of the participant: _______________

Date: _____________

Name: ____

Signature of the witness: ____________________________

Date: _____________

Name: ____

Signature of investigator: ____________________________

Date: _____________

Name: ____

ANNEXURE II – PROFORMA

SERIAL NUMBER- RANDOMISATION NUMBER-

DATE OF ADMISSION.-

NAME-

AGE-

SEX-

ADDRESS-

INFORMANT-

DATE OF BIRTH-

GESTATIONAL AGE-

WEIGHT-

MODE OF DELIVERY-

APGAR SCORE-

1 MIN-

5 MIN-

PRETERM BIRTH-

RUBELLA INFECTION-

SYMPTOMS	PRESENT	ABSENT
FEEDING DIFFICULTY		
SWEATING WITH CRYING/FEEDING		
FAST BREATHING		
EASY TIRING		
RAPID HEART RATE		

CLINICAL EXAMINATION	PRESENT	ABSENT
BOUNDING PULSE(easily palpable dorsalis pedis)		
MURMUR(systolic/continous)		
PERSISTENT TACHYCARDIA		
HYPERACTIVE PRECORDIUM(visible pulsations in >2 ribs)		
NEED FOR OXYGEN SUPPORT		

ON 2D ECHO				
INTERNAL DIAMETER(PDA SIZE)				
FLOW(L->R/R->L/BIDIRECTIONAL)				
LEFT ATRIAL DILATATION(LA/LV SIZE)				
PAH AND PASH				

DATE OF DIAGNOSIS-	
REPORT-	

TREATMENT RECEIVED-

ROUTE OF ADMINISTRATION-

INVESTIGATIONS	PRE-TREATMENT	POST TREATMENT
HAEMOGLOBIN		
PLATELET		
TOTAL COUNTS		
UREA		
CREATININE		
SGOT		
SGPT		

REPEAT 2 DECHO DATE-

INFERENCE-

REPEAT 2 DECHO DATE-

INFERENCE-

REMARKS:-

ANNEXURE III – PROFORMA

KEY TO MASTER CHART

Gender	Male-1 Female-2
Mode of delivery	NVD-1 LSCS-2
PRETERM BIRTH	YES-1 NO-2
WEIGHT	≤1000-1 1001-1500-2 1501-2500-3
RUBELLA INFECTION	YES-1 NO-2
Place	Rural-1 Urban-2
Informant	Mother-1 Father-2
Gestational age	≤32 weeks-1 32-35 weeks-2 ≥35 weeks-3
Symptoms	Present-3 Absent-4

SIGNS	Present-3 Absent-4
2DECHO	Normal-1 Mild-2 Moderate-3 Severe-4 Large-5
Flow	L-R -1 R-L -2
Results-	Complete closed after 1 dose of treatment Significant reduction in the size-2 Complete closed after 2 dose of treatment-3 No reduction in the size of PDA-4 Not closed-5 Death after 1st dose-6 Could not be done-7 Reduction in size noted-8
Treatment	Paracetamol-1 Ibuprofen-2
Route of administration	oral-1 Intravenous-2

SL 2	AGE	SEX	DOB	ADDRESS	RURAL/URBAN	PH 2	INFORMANT	GESTATIONAL AGE	WEIGHT	MODE OF DELIVERY	APGAR		PRETERM BIRTH	RUBELLA INFECTION	SYMPTOMS					CLINICAL EXAMINATION					ON 2 D ECHO					
											1 MIN	5 MIN			FEEDING DIFFICULTY	SWEATING WITH CRYING/FEEDIN	FAST BREATHING	EASY TIRING	RAPID HEART RATE	BOUNDING PULSE	MURMUR	TACHYCARDIA	HYPERACTIVE PRECORDIUM	OXYGEN	INTERNAL DIAMATER	FLOW	LA DILATATION	LV DILATATION	PAH	PASP
1	3 DAYS	1	11-02-2021	ANGOL	1	9108929958	1	2	3	2	7	9	1	2	3	4	3	3	4	3	3	4	4	3	5	1	2	2	3	3
2	30 DAYS	1	11-01-2021	KHANAPUR	2	819766590	2	1	2	1	7	9	1	2	3	4	3	4	4	4	3	4	4	3	3	1	2	2	4	4
3	6 DAYS	1	13-02-2021	NEGINHAL	1	7866547876	1	2	2	1	7	9	1	2	4	4	3	4	3	3	3	3	4	3	3	1	3	3	2	2
4	5 DAYS	1	14-02-2021	HUBLI	2	8722748045	2	1	1	1	2	6	1	2	4	4	4	4	4	3	3	3	3	3	5	1	4	4	4	4
5	11 DAYS	2	11-03-2021	KURGOD	1	9878765447	1	1	1	2	6	8	1	2	3	4	3	4	3	3	3	3	4	3	5	1	3	3	4	4
6	7 DAYS	2	12-03-2021	ATHANI	1	9956347812	2	3	3	2	7	9	1	2	3	3	4	3	4	3	3	3	4	3	3	1	3	3	3	3
7	9 DAYS	2	15-03-2021	BELGAUM	2	9980765676	2	1	1	1	6	9	1	2	4	4	3	3	4	3	3	3	3	3	3	1	3	3	2	2
8	2 DAYS	1	19-03-2021	UMARANI	1	8971709717	2	2	3	2	6	9	1	2	3	3	3	4	3	3	3	3	4	4	3	1	4	4	3	3
9	7 DAYS	2	23-03-2021	KITTUR	1	9535371274	2	2	3	1	N/C	N/C	1	2	3	4	3	3	4	3	3	3	4	4	5	1	3	3	4	4
10	2 DAYS	2	29-03-2021	GOKAK	1	8050451576	2	1	2	2	N/C	N/C	1	2	4	3	3	3	3	3	3	3	3	3	5	1	4	4	3	3
11	2 DAYS	1	10-04-2021	HAJGOLI	1	8879678567	2	1	2	2	7	9	1	2	3	4	4	4	3	3	3	4	4	3	3	1	2	2	2	2
12	11 DAYS	1	13-04-2021	MACCHE	2	7886957689	2	1	2	1	8	9	1	2	4	4	3	3	4	3	3	3	3	3	5	1	1	1	2	2
13	13 DAYS	1	19-04-2021	BELGAUM	2	9449260689	1	1	3	2	6	7	1	2	3	4	3	3	3	3	3	3	4	3	5	1	3	3	4	4
14	5 DAYS	2	24-04-2021	BELGAUM	2	9964043205	2	2	3	2	6	8	1	2	4	3	3	4	3	3	3	3	4	3	5	1	3	3		
15	4 DAYS	1	29-04-2021	KANABARGI	2	9844860039	1	1	2	2	4	7	1	2	4	3	3	4	3	3	3	3	3	3	3	1	1	1	3	3
16	5 DAYS	1	13-06-2021	MUMBAI	2	9619442843	1	2	3	1	8	9	1	2	4	3	4	3	3	4	3	4	3	3	3	1	3	3	3	3
17	4 DAYS	2	19-06-2021	KADABAGTTI	1	9983454567	1	3	3	1	6	9	1	2	4	4	3	4	3	4	3	3	4	3	5	1	3	3	3	3
18	3 DAYS	1	20-06-2021	BAILHONGAL	2	8277713899	1	2	3	2	6	9	1	2	4	4	3	3	3	3	3	3	4	4	5	1	1	1	3	3
19	30 DAYS	2	10-06-2021	BELGAUM	2	8245571389	2	1	3	2	N/C	N/C	1	2	3	4	4	4	4	3	3	4	4	3	3	1	1	1	4	4
20	30 DAYS	2	28-06-2021	MUGALI	1	9778654634	1	1	1	1	2	5	1	2	4	4	3	4	3	3	3	3	4	3	5	1	4	4	4	4
21	3 DAYS	1	18-09-2021	HUKKERI	1	8897658768	1	1	2	1	5	7	1	2	4	4	3	4	3	3	4	3	4	3	5	1	3	3	4	4
22	2 DAYS	2	25-09-2021	MURGODAVAR	1	6366601046	1	1	2	2	5	7	1	2	4	4	3	4	3	3	3	3	4	3	5	1	1	1	4	4
23	6 DAYS	1	21-07-2021	MACCHE	2	7349627457	1	1	2	1	7	9	1	2	4	4	3	4	3	3	3	3	4	3	5	1	1	1	3	3
24	5 DAYS	1	02-04-2022	CHOKKANAHALLI	1	9740526941	1	1	1	1	5	7	1	2	4	4	3	4	3	3	3	3	4	3	3	1	2	2	3	3
25	5 DAYS	2	07-07-2022	THAMBA	1	9686157296	2	1	2	1	7	9	1	2	3	4	3	3	4	3	4	4	3	4	5	1	3	3	3	3
26	10 DAYS	1	01-11-2021	CHANCHAD	1	9972693588	2	1	2	2	7	10	1	2	4	3	3	4	3	3	3	3	3	3	5	1	3	3	1	1
27	2 DAYS	2	30-11-2021	CHIKKODI	1	9967454536	2	3	3	1	N/C	N/C	1	2	4	4	3	3	3	3	3	3	3	3	5	1	4	4	4	4
28	12 DAYS	1	20-10-2022	ATHANI	2	8970705580	2	3	3	2	N/C	N/C	1	2	3	3	3	3	3	3	3	3	4	3	5	1	4	4	4	4
29	15 DAYS	1	29-01-2022	KANGRAL	1	9980013997	1	1	2	2	N/C	N/C	1	2	3	3	3	3	3	3	3	3	3	3	5	1	3	3	4	4
30	4 DAYS	1	02-02-2022	CHIKKODI	2	9008328629	2	1	2	1	6	9	1	2	4	4	3	4	3	3	3	3	4	3	5	1	3	3	3	3
31	4 DAYS	2	04-02-2022	GOKAK	1	7829522365	1	1	2	2	7	9	1	2	3	4	3	4	3	3	3	3	3	4	3	1	2	2	3	3
32	19 DAYS	1	17-02-2022	GOKAK	2	7649356676	2	1	2	1	7	9	1	2	4	4	4	4	3	3	3	4	4	3	5	1	3	3	4	4
33	4 DAYS	2	21-02-2022	KAKTI	1	8793367165	1	1	2	1	6	8	1	2	3	3	3	3	3	3	3	3	3	3	5	1	4	4	4	4
34	2 DAYS	1	03-03-2022	NANAWADI	2	9972139997	1	2	3	2	6	8	1	2	4	4	3	4	3	3	4	3	4	3	3	1	2	2	3	3
35	6 DAYS	1	10-03-2022	GOKAK	2	9948673546	2	3	3	2	N/C	N/C	1	2	4	3	3	3	3	3	3	3	4	3	5	1	3	3	4	4
36	5 DAYS	2	17-03-2022	BAILHONGAL	2	9945999348	1	1	1	2	2	6	1	2	3	3	3	4	3	3	4	3	4	3	5	1	3	3	4	4
37	5 DAYS	2	30-03-2022	HATTI	1	7022242959	1	1	2	1	7	9	1	2	3	4	3	4	3	3	3	3	3	3	5	1	4	4	4	4
38	2 DAYS	1	27-04-2022	BAILHONGAL	2	9902749067	1	1	2	2	5	7	1	2	3	4	3	3	3	3	3	3	4	3	5	1	4	4	4	4
39	2 DAYS	1	05-05-2022	KINAYE	1	9686518695	2	1	3	2	7	10	1	2	4	4	3	4	3	3	3	3	4	4	3	1	3	3	3	3
40	2 DAYS	2	05-05-2022	KINAYE	1	9686518695	2	1	2	2	6	9	1	2	4	3	4	3	4	3	4	3	4	3	3	1	3	3	3	3
41	3 DAYS	1	10-05-2022	BAILHONGAL	2	9770887432	1	2	2	2	2	7	1	2	4	4	3	4	3	3	3	4	4	3	5	1	1	1	3	3
42	2 DAYS	1	29-05-2022	GHATAPRABHA	2	9445312678	1	3	3	1	7	9	1	2	4	3	3	3	3	3	3	3	4	3	5	1	3	3	4	4
43	3 DAYS	2	09-06-2022	BELGAUM	2	9923674561	1	3	3	2	7	9	1	2	4	3	3	3	4	4	3	4	3	3	5	1	3	3	3	1
44	2 DAYS	1	10-05-2022	INDI	1	7856995381	1	2	3	2	6	8	1	2	3	3	4	4	3	3	4	4	3	3	3	1	3	3	4	4
45	4 DAYS	2	07-04-2022	HAGEDAL	1	9743874661	1	1	2	1	7	9	1	2	3	4	3	3	3	4	3	3	3	4	3	1	3	3	3	3
46	3 DAYS	1	08-03-2022	SAVDATTI	1	7892845043	1	1	3	1	5	9	1	2	4	3	3	4	3	3	4	4	3	3	5	1	3	1	1	1
47	7 DAYS	2	12-01-2022	GANGAVATHI	1	9986214680	1	1	1	2	N/C	N/C	1	2	4	4	3	3	4	4	3	4	3	4	5	1	4	3	3	3
48	12 DAYS	2	24-03-2022	SULAGA	1	9535562038	1	1	2	2	8	8	1	2	3	4	4	3	4	3	3	3	4	3	3	1	4	4	4	4
49	5 DAYS	1	01-06-2022	KOPPAL	2	9448110480	1	1	2	2	7	9	1	2	4	3	4	3	3	4	3	4	4	3	3	1	3	3	3	3
50	4 DAYS	2	12-04-2022	HORTI	1	8804567165	2	1	2	1	5	9	1	2	3	4	3	4	3	4	3	4	3	3	5	1	4	4	4	4
51	8 DAYS	1	29-07-2022	DODDWAD	1	9935674682	2	3	3	1	7	9	1	2	3	3	3	3	4	3	3	3	3	3	3	1	3	3	1	1
52	3 DAYS	2	31-07-2022	KHANAPUR	1	9978132656	2	3	3	1	6	9	1	2	3	4	3	3	4	4	4	3	4	3	3	1	3	3	1	1

2ND 2 DECHO						TREATMENT RECEIVED	ROUTE ON ADMINISTRATION	INVESTIGATIONS BEFORE TREATMENT							INVESTIGATIONS AFTER TREATMENT			CLOSED AFTER 1ST DOSE OF TREATMENT	CLOSED AFTER 2ND DOSE OF TREATMENT	DEATH	AMA
INTERNAL DIAMATER	FLOW	LA DILATATION	LV DILATATION	PAH	PASP			HB	TLC	PLATELETS	UREA	CREAT	SGOT	SGPT	HB	TLC	SGPT				
COMPLETE CLOSED	1	1	1	2	2	1	2	18.6		152K	47	0.77	32	24	13.1		72	1			
CLOSED	1	1	1	1	1	1	2	14.9	24,400	193K	42	0.9	24	17	12	10,200	27	1			
REDUCED SIZE	1	1	1	M	M	1	2	15.4	10,200	296K	26	1.02	32	17	8.8	8,000	14	2	5		
REDUCED SIZE	1	4	4	4	4	2	1	17.3	9600	155K	56	0.92	17	22	13.1	13,000	32			6	
						1	2	15.8	4060	112K	15	0.5	32	14				7		6	
CLOSED	1	1	1	1	1	1	2	16.4	22000	117K	28	0.67	30	16	16.3	17,000	65	1			
CLOSED	1	1	1	1	1	1	2	16.4	3180	105K	55	1	50	46	16.4	5,600	46	1			
CLOSED	1	1	1	2	2	2	1	15.4		173K	25	0.56	46	22	15.3	7300	44	1			
3	1	2	2	3	3	2	1	13.2	14,900	104K	60	0.91	24	22	12.7	10,000	38	2			AMA AFTER 2ND DOSE
						1	2	17.5	4,300	188K	27	0.81	36	32	16.4	7,400	17	7		6	
CLOSED	1	1	1	1	1	2	1	19.1	9,070	112K	30	0.32	24	17	17.2	10,600	26	1			
REDUCED SIZE	1	1	1	2	2	1	2	15.4	8,000	277K	79	0.72	17	21	13.9	14,600	31	2	3		
CLOSED	1	1	1	2	2	2	1	14.4	9700	324K	24	0.61	17	24	11.2	7200	30	1			
CLOSED	1	1	1	2	2	1	2	17.7	9000	230K	13	0.6	906	143	13.1	10,000	212	2	3		
5	1	2	2	4	4	2	1	16.2	5400	251K	18	0.59	15	21	11.7	7000	80	5	5		
REDUCED SIZE	1	2	2	1	1	2	1	13.6	7000	238K	15	0.13	12	15	10,000	23,000	43	2	3		
CLOSED	1	2	2	2	2	1	2	19.2	12,790	148K	38	0.56	22	7	10.2	7,400	14	1			
REDUCED SIZE	1	1	2	1	1	1	2	7.9	14,200	214K	10	0.31	18	26	6.4	21,000	43	2	3		
REDUCED SIZE	1	1	1	2	2	2	1	15.7	9700	204K	10	0.68	44	38	13.3	11,100	46	2	3		
5	1	1	1	2	2	2	1	11	3500	80K	30	0.72	148	40	13.9	14,600	54	4	5		
CLOSED	1	2	2	1	2	1	2	19	6900	295K	26	0.91	72	64	14.3	6,100	70	1			
REDUCED SIZE	1	1	1	2	2	2	1	16.8	8000	225K	44	1.02	82	44	15.6	10,800	34	4	3		
CLOSED	1	1	1	2	2	2	1	16.9	3600	52K	27	0.87	114	56	15.5	7,300	48	1			
CLOSED	1	1	1	1	1	1	2	19.6	14,600	238K	64	0.83	18	24	15.2	17,200	30	1			
REDUCED SIZE	1	1	1	1	1	2	1	16.4	12000	112K	45	0.82	23	42	17.4	16,000	23	2	5		
5	1	3	3	1	1	1	2	11.9	3000	27K	72	0.26	50	18	12.9	2,240	63	4	5		
REDUCED SIZE	1	2	2	2	2	2	1	20.4	48500	95K	42	0.79	28	36	19.3	9,300	39	8	3		
REDUCED SIZE	1	1	1	2	3	1	2	12.5	15,700	132K	61	1.07	24	30	8.4	8,700	14	8	5		
REDUCED SIZE	1	2	2	2	2	2	1	12.3	8900	146K	12	0.46	37	10	11.4	9,700	16	2	5		
CLOSED	1	1	1	2	2	2	1	14.2	23000	74K	36	0.7	20	24	13.4	12,000	20	1			
CLOSED	1	1	1	1	1	1	2	15.8	8170	253K	23	0.76	18	14	15.2	11,800	10	1			
REDUCED SIZE	1	2	2	3	3	1	2	16.1	6700	130K	53	1.05	45	14	11	13,400	12	2	3		
REDUCED SIZE	1	1	3	3	3	2	1	15.4	7200	172K	35	0.67	26	24	10.8	14,000	63	2	3		
CLOSED	1	2	2	1	1	1	2	17.6	5600	291K	12	0.86	34	24	18.6	5,500	26	1			
5	1	3	3	3	3	2	1	16.7	7800	45K	18	0.55	17	18	12.9	8,000	44	2	5		
REDUCED SIZE	1	2	2	1	1	2	1	16	13100	286K	53	1.07	16	24	12	14,300	30	2	3		
CLOSED	1	2	2	2	2	2	1	9.2	13300	314K	15	0.37	26	12	10.2	11,000	46	1			
REDUCED SIZE	1	1	1	1	1	2	1	20.1	9700	199K	28	1.12	24	17	17.7	2,500	22	2	3		
CLOSED	1	1	1	1	1	1	2	19.5	10000	193K	20	0.75	12	20	16.7	5,600	31	1			
REDUCED SIZE	1	1	1	1	1	2	1	20.1	13,000	120K	23	0.45	16	24	16.4	6,800	17	2	3		
CLOSED	1	1	1	1	1	1	2	14	6200	69K	35	1.09	39	17	10.4	11,000	10	1			
REDUCED SIZE	1	1	1	2	2	1	2	11.6	9200	215K	40	0.45	17	27	11.2	7,060	17	4	3		
CLOSED	1	1	1	1	1	2	1	19.4	10,600	295K	24	1.02	26	14	14.6	8,900	12	1			
REDUCED SIZE	1	1	3	3	3	2	1	17.6	12000	132K	12	0.33	27	48	16.4	13,000	52	2	3		
CLOSED	1	1	1	1	1	1	2	16.3	7000	123K	77	0.76	25	22	14.3	7,400	18	1			
CLOSED	1	1	1	1	1	1	2	13.8	13,000	226K	46	0.34	42	44	16.3	12,000	77	1			
REDUCED SIZE	1	3	3	3	3	1	2	16.3	6200	156K	25	0.16	32	25	14	8,900	54	8	5		
REDUCED SIZE	1	1	1	1	1	2	1	19.4	9200	162K	32	0.44	17	20	16.2	10,400	36	8	3		
								15.3	16,000	203K	23	0.45	32	22	10.2	13,000	24	7		6	
REDUCED SIZE	1	3	3	3	3	2	1	15.4	7000	231K	32	0.42	18	24	13.3	8400	65	2	5		
REDUCED SIZE	1	1	1	1	1	2	1	17.3	4500	222K	27	0.67	15	30	15.4	11600	26	2	3		
CLOSED	1	1	1	1	1	1	2	16.5	8300	117K	36	0.45	28	32	16.4	7800	24	1			