RESEARCH PAPER

Evaluating The Therapeutic Efficacy And Safety Of Oral Ibuprofen Compared With IV Paracetamol In Preterm PDA

Dr. Smruthi Rugi[1*], Dr. Veeresh Manvi[2], Dr. Nidhi Manvi[3], Dr. Akshay Pujari[4]

[1*]Senior resident, Department of Paediatrics, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, Mail id: smruthirugi94@gmail.com, Orcid ID :0009-0002-0364-4752
[2]Professor (Paeds cardio), MBBS MD FNB FCPC, Jawaharlal Nehru Medical College, KLE Academy of higher education and research, Email ID veereshmanvi@yahoo.co.in
[3]Senior resident, MBBS DCH DNB, Jawaharlal Nehru Medical College, KLE Academy of higher education and research, Email ID: nidhigoelmanvi@gmail.com
[4]Senior resident, Department of Cardiology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi – 590010 Email ID: rpakshay07@gmail.com

ABSTRACT
Patent Ductus Arteriosus (PDA) is a common condition in preterm neonates, often requiring medical treatment to promote ductal closure. Oral ibuprofen and IV paracetamol are two pharmacological options, each with unique mechanisms of action. However, there is limited comparative data on their therapeutic efficacy and safety profiles in preterm infants with hemodynamically significant PDA. This study aims to evaluate the efficacy, closure rates, and safety profiles of oral ibuprofen versus IV paracetamol in treating PDA in preterm neonates, guiding optimal treatment strategies. It evaluates the therapeutic efficacy and safety profiles of oral ibuprofen and IV paracetamol in managing hemodynamically significant PDA in preterm neonates. PDA, a common condition in preterm infants, requires timely medical intervention to prevent complications like pulmonary congestion and heart failure. Ibuprofen and paracetamol both promote ductal closure by inhibiting prostaglandin production, with ibuprofen being the first-line treatment but carrying risks of renal and gastrointestinal side effects. Paracetamol offers a safer alternative, particularly in infants with renal or gastrointestinal concerns. This study compares the clinical efficacy, safety, and individualized treatment guidelines to provide evidence-based recommendations for PDA management in preterm neonates. Findings show that both oral ibuprofen and IV paracetamol are effective for PDA closure in preterm neonates, with complete closure rates of 82% and 78%, respectively. Ibuprofen led to faster closure (3.2 ± 0.9 days) and fewer surgical interventions (5% vs. 8%). Paracetamol demonstrated better renal safety and fewer gastrointestinal and hematologic side effects. Recurrence rates were low and similar in both groups. Future research should involve larger, multicenter trials to confirm these results, assess long-term neurodevelopmental outcomes, and explore personalized dosing and biomarkers to optimize treatment safety and efficacy.

Keywords: Patent Ductus Arteriosus, Preterm Neonates, Oral Ibuprofen, IV Paracetamol, Therapeutic Efficacy and Safety Profiles.

How to cite this article: Rugi S, Manvi V, Manvi N, Pujari A. Evaluating the Therapeutic Efficacy and Safety of Oral Ibuprofen Compared With Iv Paracetamol in Preterm Pda. Int J Drug Deliv Technol. 2026;16(32s):436-450. DOI: 10.25258/ijddt.16.32s.53

1. INTRODUCTION

Patent Ductus Arteriosus (PDA) is a frequent cardiovascular complication in preterm neonates, where the ductus arteriosus, a fetal blood vessel, fails to close after birth [1-2]. When the PDA is hemodynamically major (hsPDA), leading to respiratory distress, feeding difficulties, and increased risk of morbidities such as necrotizing enterocolitis and intraventricular hemorrhage it can compromise systemic and pulmonary circulation [3-4]. Early medical intervention is often required to achieve closure and improve outcomes in these vulnerable infants. The most appropriate first-line drug remains an area of active research and clinical debate [5-6]. Although the pharmacological closure of hemodynamically major Patent Ductus Arteriosus(hsPDA) has become a standard practice in neonatal intensive care, identifying. Well-documented efficacy in promoting ductal closure by inhibiting prostaglandin synthesis Oral Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is generally used due to its Despite its effectiveness, Ibuprofen is associated with a risk of adverse effects such as gastrointestinal bleeding, renal impairment, thrombocytopenia, and necrotizing enterocolitis, particularly in extremely preterm or low birth weight infants [7-8]. These problems may limit its use or necessitate close monitoring and dose adjustments. Some studies have suggested that IV Paracetamol has a favourable safety profile, with fewer renal and gastrointestinal side effects, making it a potentially safer option for vulnerable neonates in recent years, intravenous (IV) Paracetamol has emerged as a potential other treatment, proposed to act via inhibition of the peroxidase component of prostaglandin H2 synthase [9-10]. Comparative efficacy relative to Ibuprofen remains under investigation. However, its exact mechanism of action in ductal closure is not fully understood. Clinical trials assessing Paracetamol have shown mixed results, with some demonstrating comparable closure rates and others suggesting reduced effectiveness, particularly in cases

*Author for Correspondence: smruthirugi94@gmail.com,

with more pronounced hemodynamic significance [11-12].

The pharmacologic therapy for hsPDA is crucial, with consequences in preterm neonates, as it directly impacts short- and long-term outcomes. A treatment that effectively encourages ductal closure while minimizing systemic side effects can significantly reduce the risk of problems such as bronchopulmonary dysplasia [13-14]. In this framework, relating the therapeutic profiles of oral Ibuprofen and IV Paracetamol becomes highly relevant in prolonged ventilator dependence, intraventricular hemorrhage, and increased neonatal morbidity. The most effective care Clinicians must base their treatment conclusions on robust, comparative evidence to ensure the safest [15-16]. Access to certain drugs may be restricted, or close observation for side effects may not be feasible. Furthermore, the need for such evidence is even more pressing in resource-limited or rural settings [17-18]. Also, there are specific clinical scenarios where one drug may be contraindicated, such as renal dysfunction with Ibuprofen, necessitating the use of alternative therapies like Paracetamol in such environments, the availability of a safe, effective, and easily administrable other becomes vital. Intravenous Paracetamol in the management of hemodynamically significant PDA in preterm neonates [19-20]. The objective is to evaluate and compare the therapeutic ability and safety profiles of oral Ibuprofen and intravenous Paracetamol in the management of hemodynamically significant PDA in preterm neonates.

2. LITERATURE SURVEY

The management of hsPDA in preterm neonates has been extensively studied, with a primary concentration on pharmacological closure using agents such as Ibuprofen and Paracetamol. This literature survey aims to of the two drugs to support evidence-based clinical decision-making in neonatal care, critically examining existing research comparing the therapeutic outcomes and adverse effects. Saod et al [21] evaluated the dental practitioners with the awareness of the safety profile of NSAIDs use of NSAIDs during dental practice, and evaluated the association of the level of education and years of experience. Most common clinical symptoms Postoperative pain and dental pain were for which NSAIDs were prescribed,71.3% and 59.5%, respectively. Da Silva et al [22] presented the features of the efficacy and therapeutic safety of paracetamol versus ibuprofen in the treatment of PDA in premature newborns. Clinical trials that did not compare the efficacy and/or safety of paracetamol with ibuprofen for the treatment of PDA (n = 08); 1) clinical trial protocol (n = 02). Almoslem et al [23] established a disease–drug–trial model to predict PDA closure following single and combination drug therapy with ibuprofen and/or APAP in children at less than 29 weeks of gestation. Results show that a deemed appropriate to reach at least 90% PDA in all preterm neonates evaluated within 1 month of life 5-day oral dosing regimen consisting of ibuprofen (20 mg/kg Q24h on day followed by 10 mg/kg Q24h on days 2-5) plus APAP (15 mg/kg Q6h). Asif et al [24] investigated the pharmacokinetics and exposure-response relationship of oral ibuprofen in ELGANs of ≤72 h postnatal age (PNA) on standard (SD)versus those >72 h PNA on high-dose (HD) regimen for closure of persistent PDA. Result shows The mean (SD) of exposure at 24 h (AUC0-24 h) was 486 (128) and 509 (208) (P = .41) and at 72 h (AUC0-72 h) was 1529 (493) and 1510 (820) (P = .94). Two (16%) ELGANs in the HD group developed severe gastrointestinal (GI) AEs and 1 (9%) in the SD had severe intraventricular haemorrhage. Shah et al [25] compared the effectiveness of paracetamol and ibuprofen in the closure of PDA in preterm neonates. Efficacy was observed in 107 (83.6%) patients in Group A, compared to 90 (70.3%) patients in Group B, showing a statistically significant difference (P=0.011). The age range in this study was from 48 to 96 h, with a mean age of 71.79±13.10 h in Group A and 73.40±11.81 h in Group B.

Sethi et al [26] assessed the liver safety profile of acetaminophen, mostly in OA management, using a model-based meta-analysis (MBMA). Acetaminophen 1500–4000 mg/day was found to exhibit 23% (95% confidence interval (CI): 17.74–29.20), 1.35% (95% CI: 0.17–2.51) and 0.01% (95% CI: 0.00–0.32) increased risk for mild, moderate, and severe liver injury, respectively. Tanti et al [27] determined the effectiveness hsPDA and the safety of paracetamol in preterm babies. The result shows Paracetamol was operational in 100% of cases. No adverse event was observed during treatment. Moronta et al [28] assessed clinical and echocardiography predictors of acetaminophen response for the treatment of PDA in preterm neonates. The result shows that A total of 100 infants were included, whose median weight and gestational age at birth were 663 grams and 24.6 weeks, respectively. Goyal et al [29] compared the ability to close hemodynamically significant PDA of low vs conventional dose intravenous paracetamol. A total found 56 infants (28 in each group) were enrolled. Ductal closure was achieved in 96% infants in the low-dose group and 100% infants in the conventional group (p = 1.00). Kainth et al [30] evaluated ductal closure rates in preterm neonates with hsPDA who received paracetamol (PCM) as first-line therapy. Results show that out of 76 neonates who completed treatment with the first course of PCM (57 intravenous, 19 oral), 43 (56.6%) attained successful closure, and five (6.6%) developed PH.

3. RESEARCH PROPOSED METHODOLOGY

This study adopted a prospective, randomized controlled trial (RCT) design to evaluate the therapeutic efficacy and safety profiles of oral ibuprofen and intravenous (IV) paracetamol in managing hemodynamically significant patent ductus arteriosus (PDA) in preterm neonates. Neonates diagnosed with PDA were randomly assigned to one of two treatment groups: one received oral ibuprofen, and the other received IV paracetamol. Efficacy was primarily assessed based on the rate of PDA closure, time to closure, and recurrence of PDA following initial treatment. Secondary efficacy outcomes included the need for surgical intervention.

Safety was evaluated by monitoring adverse events, including gastrointestinal bleeding and renal dysfunction in the ibuprofen group, and liver toxicity in the paracetamol group. Baseline characteristics such as gestational age, birth weight, and associated comorbidities were recorded to adjust for potential confounding factors. Statistical analyses, including chi-square and t-tests, were performed to compare the therapeutic outcomes and safety profiles of the two drugs, to inform clinical recommendations.

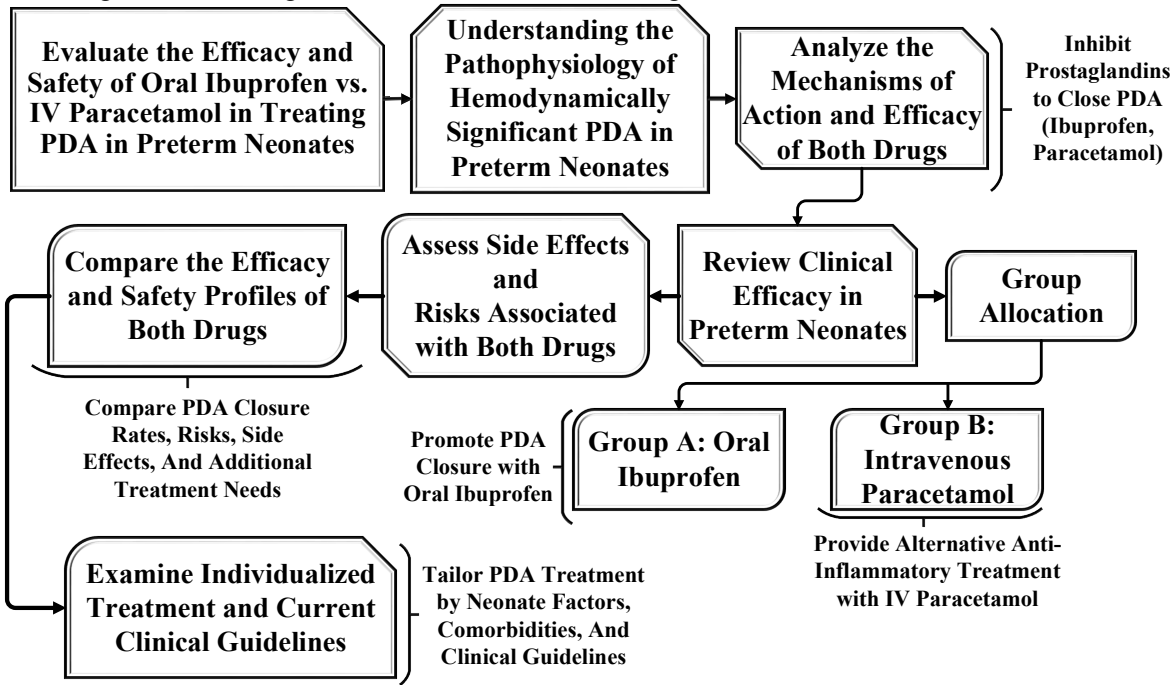

Figure 1: Block Diagram of the Proposed Work

Figure 1 illustrates the overall workflow for evaluating the efficacy and safety of oral ibuprofen versus intravenous (IV) paracetamol in the treatment of hemodynamically significant patent ductus arteriosus (PDA) in preterm neonates. The process begins with an overview of PDA pathophysiology and the clinical need for pharmacological closure in this population. The mechanisms of action of both drugs are outlined, focusing on prostaglandin synthesis inhibition as the basis for ductal closure. Neonates were randomized into two groups: Group A received oral ibuprofen, and Group B received IV paracetamol. The figure outlines the assessment of treatment efficacy (rate and time of PDA closure) and safety outcomes (renal, hepatic, and gastrointestinal adverse effects). Finally, the diagram compares both drugs in terms of overall effectiveness and risk profile, emphasizing the need for individualized treatment strategies based on patient-specific factors such as gestational age, birth weight, comorbidities, and current clinical guidelines.

(a) Understanding the Pathophysiology of Hemodynamically Significant PDA in Preterm Neonates

Patent Ductus Arteriosus (PDA) is a common congenital condition in preterm neonates where the ductus arteriosus, a blood vessel connecting the pulmonary artery to the aorta, remains open after birth. Normally, this vessel closes shortly after birth due to decreased prostaglandin levels. In preterm infants, this closure is delayed, causing abnormal blood flow. A hemodynamically significant PDA occurs when the open ductus causes excessive blood flow to the lungs, leading to pulmonary congestion, respiratory distress, and even heart failure. As the lungs become over-perfused, oxygen exchange is impaired, worsening clinical outcomes. This condition increases the risk of complications such as intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity. The pathophysiology of PDA in preterm infants underscores the necessity for timely medical intervention to prevent these potentially life-threatening issues. Understanding this process is critical for developing effective pharmacological strategies to manage PDA in these vulnerable patients.

(i) Study Design and Setting

This study was conducted as an open-label randomized controlled trial aimed at evaluating the therapeutic efficacy and safety profiles of oral ibuprofen and intravenous paracetamol in managing hemodynamically significant PDA in preterm neonates. The randomized design ensured systematic data collection and minimized bias by assigning participants equally to intervention groups. The study took place in the Neonatal Intensive Care Unit (NICU) of a tertiary care hospital, providing access to a specialized patient population for comprehensive monitoring. Spanning one year, from January 2021 to December 2021, the study duration allowed for effective data collection, follow-up, and outcome assessment within the hospital's operational framework.

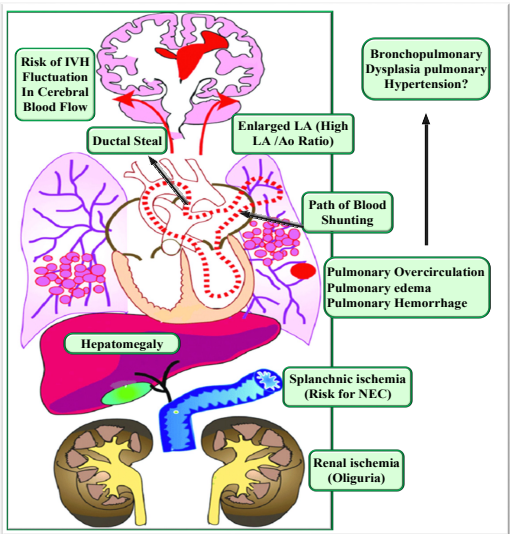

Figure 2: Pathophysiology of Hemodynamically Significant PDA in Preterm Neonates

Figure 2 illustrates the complex pathophysiology of hemodynamically significant PDA in preterm neonates, where the open ductus arteriosus leads to abnormal blood flow. Blood shunting from the aorta into the pulmonary artery causes pulmonary overcirculation, resulting in pulmonary oedema and hemorrhage, which impairs oxygen exchange. This overperfusion also increases pressure in the left atrium (LA), leading to an enlarged LA and high LA/Ao ratio, contributing to ductal steal, where systemic blood flow is diverted to the lungs. This can further exacerbate pulmonary hypertension and bronchopulmonary dysplasia (BPD). The compromised systemic circulation affects organs such as the liver, leading to hepatomegaly, and the kidneys, causing renal ischemia and oliguria. Moreover, splanchnic ischemia due to reduced blood flow to the intestines increases the risk for necrotizing enterocolitis (NEC). Also, fluctuating cerebral blood flow elevates the risk of intraventricular hemorrhage (IVH), underlining the critical need for early intervention.

(b) Analyze the Mechanisms of Action and Efficacy of Both Drugs

Both oral ibuprofen and intravenous paracetamol are used to treat PDA in preterm neonates by promoting the closure of the ductus arteriosus. Ibuprofen works by inhibiting cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which reduces prostaglandin production. Prostaglandins are known to maintain the patency of the ductus, so their reduction leads to closure. Paracetamol, though less understood, is believed to inhibit prostaglandin synthesis in a similar manner but through a different pathway, possibly affecting the COX enzymes in the central nervous system. Both drugs help to facilitate the ductus closure by reducing the levels of these vasodilatory compounds, but their exact mechanisms and potency may vary. In clinical practice, ibuprofen is more commonly used, but paracetamol has emerged as a viable alternative, especially in cases where ibuprofen is contraindicated, such as in infants with renal dysfunction or gastrointestinal issues. Analyzing these mechanisms is essential for understanding their clinical efficacy.

(i) Participant Selection

Participant Selection involves identifying eligible preterm neonates diagnosed with hsPDA for inclusion in the study. Careful criteria ensure that only infants who can safely participate and whose conditions align with the study objectives are enrolled. Inclusion focuses on neonates under 37 weeks' gestation with confirmed hsPDA, while exclusions apply to those with major congenital anomalies, contraindications to study medications, or severe organ dysfunction. This approach enhances the study's safety, validity, and relevance to the target population.

Inclusion Criteria: The study focuses on preterm neonates born before 37 weeks of gestation, reflecting a population at higher risk for PDA complications. Eligible participants must have a confirmed diagnosis of hsPDA, established through echocardiographic assessment. This diagnostic criterion ensures that the selected neonates exhibit clinically relevant PDA, characterized by significant shunting and potential impact on cardiovascular stability. By limiting inclusion to this group, the study aims to assess outcomes specifically related to the management of hsPDA, ensuring the applicability of findings to this vulnerable subset of preterm infants.

Exclusion Criteria: Certain conditions that could confound treatment response or pose safety concerns necessitate excluding some neonates. Newborns with major congenital anomalies are excluded to avoid variability in outcomes stemming from unrelated developmental defects or syndromes. Also, infants with contraindications to nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol are excluded to prevent adverse drug reactions; these contraindications may include allergies or prior drug sensitivities. Neonates exhibiting severe renal or hepatic dysfunction are also excluded due to the increased risk of drug toxicity and altered metabolism of medications commonly used in

PDA management. These exclusion criteria ensure the safety of participants and enhance the study's internal validity by minimizing confounding factors.

Recruitment Process: Eligible participants are identified through routine clinical evaluations within the Neonatal Intensive Care Unit (NICU). Echocardiographic screening is performed by trained cardiologists or neonatologists to confirm hsPDA status. After confirming eligibility, informed consent is obtained from parents or legal guardians, ensuring ethical standards are upheld. This systematic selection process supports accurate data collection and the generation of clinically meaningful results applicable to the targeted neonatal population.

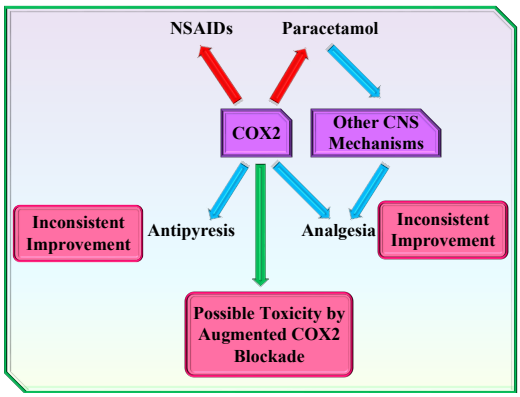

Figure 3: Mechanisms of Ibuprofen Vs Paracetamol in PDA Treatment

Figure 3 compares the mechanisms of action of NSAIDs (ibuprofen) and paracetamol, both of which are used to treat PDA in preterm neonates. Ibuprofen inhibits COX-1 and COX-2 enzymes, leading to a reduction in prostaglandin production, which helps close the ductus arteriosus. The figure notes that ibuprofen's action is linked to COX-2 inhibition, but this could lead to possible toxicity, especially with augmented COX-2 blockade. Conversely, paracetamol is believed to also inhibit prostaglandin synthesis, but primarily through mechanisms within the central nervous system (CNS). This offers a different mechanism of action compared to ibuprofen, but like ibuprofen, it facilitates ductal closure by reducing prostaglandin levels. This points out the inconsistent nature of both drugs in terms of antipyresis (fever reduction) and analgesia (pain relief) but acknowledges their improvement in clinical outcomes. The figure emphasizes the possible toxicity of ibuprofen, particularly with augmented COX-2 blockade, and suggests that while both drugs share a common goal in treating PDA, their mechanisms and side effects may vary, which can influence clinical decisions.

(c) Review Clinical Efficacy in Preterm Neonates

The clinical efficacy of oral ibuprofen and intravenous paracetamol in treating PDA is primarily evaluated through randomized controlled trials (RCTs), observational studies, and clinical outcome data. Both drugs are effective in closing the ductus arteriosus in preterm neonates, with success rates varying based on gestational age, weight, and the timing of treatment. Ibuprofen, typically administered in a 3-dose regimen, has shown high success rates in closing PDA within 48–72 hours. However, some studies suggest that paracetamol, while slightly less effective in terms of closure speed, offers a comparable success rate in cases where ibuprofen is contraindicated or ineffective. Also, paracetamol may be associated with fewer adverse effects on renal function and the gastrointestinal system, which are common concerns with ibuprofen. Clinical trials have helped to establish dosage guidelines and treatment regimens for both drugs, but continuous assessment of their outcomes in neonates is essential to refine these practices.

Group Allocation: In this study, participants were assigned to two treatment groups based on the intervention they received for managing hsPDA in preterm neonates. Group A and Group B were designated based on the route of drug administration (oral versus intravenous) and the medication used for closure of the PDA. The primary aim of the group allocation was to assess the comparative efficacy of oral Ibuprofen versus intravenous Paracetamol in the treatment of hsPDA in preterm neonates. By implementing this controlled allocation, the study is set to explore the effectiveness, safety, and feasibility of both treatment regimens. Also, this group allocation enables a detailed analysis of possible advantages and challenges associated with each drug administration method, contributing valuable data to clinical decision-making in neonatal care.

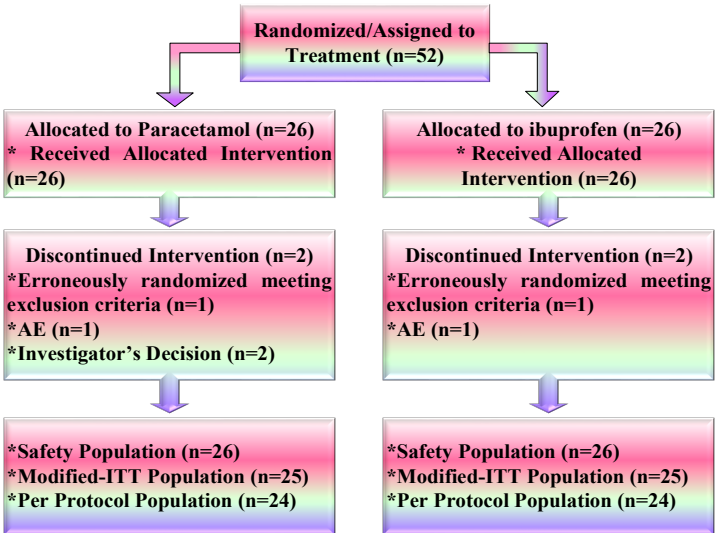

Figure 4: Randomization and Group Allocation

Figure 4 illustrates the randomization and group allocation for this study evaluating paracetamol and ibuprofen in preterm neonates with PDA. Of 52 neonates randomized, 26 were assigned to the paracetamol group, and 26 to the ibuprofen group. All participants in both groups received the allocated treatment, with 2 participants from the ibuprofen group discontinuing due to erroneous randomization and an adverse event. For analysis, participants were divided into three populations: The Safety Population included all treated neonates (paracetamol: 26, ibuprofen: 26); the Modified Intent-to-Treat Population and Per Protocol Population further excluded participants based on protocol adherence, leaving 24 in the ibuprofen group and 25 in the paracetamol group for these analyses.

(i) Group A: Oral Ibuprofen

Neonates in Group A received oral ibuprofen as treatment for hemodynamically significant patent ductus arteriosus (hsPDA). The dosing protocol followed a standardized regimen: 5 mg/kg for 2 days. This regimen aligns with established clinical guidelines, where ibuprofen inhibits cyclooxygenase enzymes (COX-1 and COX-2), reducing prostaglandin synthesis, which facilitates ductal closure. The oral administration was chosen for its ease of use and reduced invasiveness, making it especially suitable for the neonatal intensive care setting. Oral ibuprofen also avoids risks associated with intravenous access, such as infection and procedural discomfort. The efficacy of oral ibuprofen in promoting PDA closure has been well-documented in preterm neonates with hsPDA.

(ii) Group B: Intravenous Paracetamol

Neonates in Group B were treated with intravenous (IV) paracetamol, an alternative therapy for hsPDA, particularly useful in infants contraindicated for nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen. The dosing protocol for IV paracetamol consisted of 15 mg/kg every 6 hours for 3 consecutive days. While paracetamol does not inhibit prostaglandin synthesis through the cyclooxygenase pathway as ibuprofen does, it has demonstrated efficacy in promoting PDA closure through alternative mechanisms, potentially acting on the central nervous system (CNS). The IV administration ensures consistent and controlled drug delivery, minimizing variability in drug absorption compared to oral routes. This precise dosing is particularly crucial in the neonatal intensive care unit (NICU), where close monitoring and adjustments are required, especially in infants with renal impairment or other comorbidities that limit NSAID use.

Table 1: Group Allocation and Treatment Protocols

Group	Intervention	Dosage Protocol	Route of Administration
Group A	Oral Ibuprofen	10 mg/kg on Day 1, 5 mg/kg on Days 2 and 3	Oral
Group B	IV Paracetamol	15 mg/kg every 6 hours	Intravenous

Table 1 summarizes the treatment allocation and dosing regimens for the study groups. Group A received oral ibuprofen following a three-day protocol aimed at sustained prostaglandin inhibition to promote hsPDA closure. Group B received IV paracetamol every six hours, offering an alternative route that ensures steady plasma drug levels, which is particularly beneficial for neonates with contraindications to NSAIDs or requiring precise dosing control in critical care settings.

(d) Assess Side Effects and Risks Associated with Both Drugs

The safety profile of ibuprofen and paracetamol in preterm neonates must be closely monitored due to their

vulnerability to drug-related side effects. Ibuprofen is associated with potential risks such as gastrointestinal bleeding, renal impairment, and cardiovascular issues, especially when used in high doses or for prolonged treatment. Renal toxicity is particularly concerning in neonates, as their kidneys are immature and more susceptible to damage. Gastrointestinal side effects like necrotizing enterocolitis (NEC) are also a serious concern with ibuprofen in preterm infants. In contrast, paracetamol is generally considered safer with fewer gastrointestinal side effects, but it can still pose a risk to liver function, particularly with long-term use or in high doses. Hepatotoxicity is a known risk, and neonates with pre-existing liver impairment may be more vulnerable. Monitoring both drugs' safety profiles is essential to minimize adverse effects and ensure the best outcomes for preterm neonates with PDA.

Treatment Administration Based on Group Allocation: This study involves two treatment groups with specific regimens. Group A (Oral Ibuprofen) receives an initial dose of 5 mg/kg for 2 days. This protocol is designed to maximize ductal closure efficacy while minimizing potential side effects. Group B (Intravenous Paracetamol) is administered 15 mg/kg every 6 hours for 3 consecutive days, allowing for controlled and precise dosing, which is especially beneficial for neonates with feeding difficulties or gastrointestinal concerns. Both treatments aim to promote closure of the patent ductus arteriosus (PDA) in preterm neonates and reduce the need for surgical intervention. Administration is carried out under strict medical supervision to ensure safety and adherence to the protocol.

Daily Clinical Assessment and Vital Monitoring: Throughout the treatment period, neonates undergo daily clinical assessments and continuous vital sign monitoring to ensure both efficacy and safety. Vital parameters tracked include heart rate and respiratory rate, essential for early detection of adverse cardiovascular or pulmonary effects. Blood pressure and oxygen saturation are closely monitored to evaluate circulatory function and oxygen delivery, given the hemodynamic impact of PDA. Body temperature is recorded daily to identify signs of infection, while feeding tolerance is assessed to detect any gastrointestinal intolerance or complications. These comprehensive evaluations enable the timely identification of complications and facilitate prompt adjustments to the treatment plan, optimizing neonatal care.

Laboratory Monitoring: Complementing clinical assessments, laboratory tests are performed to monitor renal and hepatic function critical given the metabolism and excretion pathways of ibuprofen and paracetamol. Renal function is assessed via serum creatinine and blood urea nitrogen (BUN) levels to detect early signs of nephrotoxicity. Liver function is monitored by measuring liver enzymes, specifically alanine transaminase (ALT) and aspartate transaminase (AST), to evaluate hepatic stress or injury, particularly important with NSAID use. These laboratory evaluations ensure that any emerging organ dysfunction is promptly identified and managed to maintain treatment safety.

Echocardiographic Evaluation: Echocardiography is central to evaluating treatment success. Baseline echocardiograms before treatment establish PDA size and its hemodynamic effects. Serial echocardiograms during treatment monitor changes in PDA diameter and assess the response to medication. Post-treatment echocardiography confirms ductal closure and detects any residual shunting or complications. These assessments provide critical data guiding clinical decisions on continuation, adjustment, or cessation of therapy, thereby determining the comparative efficacy of oral ibuprofen versus intravenous paracetamol in managing hemodynamically significant PDA.

(e) Compare the Efficacy and Safety Profiles of Both Drugs

When comparing the efficacy and safety profiles of ibuprofen and paracetamol, both drugs demonstrate effective PDA closure, but they do so with different safety risks and efficacy outcomes. Ibuprofen is considered the first-line treatment due to its higher closure rates and longer-established use. However, it carries a greater risk of renal and gastrointestinal side effects, particularly in preterm infants with low birth weights or comorbid conditions. Paracetamol, on the other hand, is often used in cases where ibuprofen is contraindicated, offering a potentially safer alternative for infants with renal or gastrointestinal concerns. While it may be slightly less effective in terms of the speed of PDA closure, paracetamol has a lower risk of renal and gastrointestinal complications. Comparative studies suggest that both drugs have comparable long-term outcomes for PDA closure, but the choice between them often depends on the infant's clinical condition, including their overall health status and potential risk factors for adverse effects.

(i) Efficacy Metrics

Efficacy metrics for PDA treatment with ibuprofen and paracetamol focus on key indicators such as the rate of PDA closure, time to closure, and the need for additional treatments or surgical intervention. Ibuprofen, as the first-line treatment, typically achieves higher closure rates and faster results, while paracetamol may be less effective in these areas but still provides an alternative treatment, especially when ibuprofen is contraindicated.

Rate of PDA Closure: Ibuprofen is considered the first-line treatment for PDA due to its proven ability to achieve higher closure rates. Studies have demonstrated that ibuprofen tends to have a higher success rate in promoting ductal closure, making it the preferred option for many neonatologists. It works by inhibiting cyclooxygenase enzymes, which help close the ductus. Paracetamol, while also effective in closing the PDA, may exhibit a slightly lower closure rate in some cases,

particularly when compared to ibuprofen's established effectiveness.

Time to Closure: In terms of time to closure, ibuprofen often leads to faster results, closing the ductus in a shorter period. Paracetamol may take longer for PDA closure to occur, though it is still considered effective over time. This difference can be important depending on the clinical urgency of the situation, as faster closure may be necessary in certain high-risk infants.

Need for Additional Treatment or Surgical Ligation: While both drugs are generally successful in closing the PDA, ibuprofen has been associated with a reduced need for additional treatment or surgical ligation. Paracetamol, although effective, may sometimes require additional courses of treatment if the initial response is not sufficient.

(ii) Safety Metrics

Safety metrics evaluate the potential risks associated with each drug, particularly concerning renal and liver function, gastrointestinal complications, and other adverse effects like thrombocytopenia. Ibuprofen poses a greater risk to renal function and gastrointestinal health, while paracetamol generally has a safer profile in these areas, though liver function must still be closely monitored.

Renal Function: One of the primary safety concerns with ibuprofen, particularly in preterm infants or those with low birth weight, is its potential nephrotoxicity. Monitoring renal function through creatinine levels and urine output is crucial during treatment. Paracetamol, by contrast, poses a lower risk to renal function, making it a safer option for infants with pre-existing renal concerns.

Liver Function Tests: Paracetamol, though generally safer in terms of renal function, is associated with potential liver toxicity, especially when used in higher doses or over extended periods. It is essential to monitor liver function tests during prolonged treatment with paracetamol, particularly in neonates with hepatic concerns.

Gastrointestinal Complications: Gastrointestinal complications such as bleeding and feeding intolerance are more common with ibuprofen, especially in vulnerable infants. Paracetamol tends to have a lower incidence of gastrointestinal issues, making it a better choice in neonates with a higher risk of such complications.

Other Adverse Effects: Ibuprofen has been associated with other adverse effects, including thrombocytopenia, which can affect blood clotting. Paracetamol carries a relatively lower risk of such effects but is not without potential adverse reactions, including the risk of liver damage if not carefully monitored.

(f) Examine Individualized Treatment and Current Clinical Guidelines

Individualized treatment for PDA in preterm neonates is crucial, as each infant may have unique characteristics that affect how they respond to treatment. Factors such as gestational age, birth weight, comorbidities (like renal or liver dysfunction), and the timing of PDA diagnosis can all influence which treatment option is most appropriate. Clinical guidelines emphasize tailoring treatment based on these individual factors, with ibuprofen being preferred in many cases due to its established efficacy. However, paracetamol is gaining recognition as a safe alternative, particularly in situations where ibuprofen use is not feasible. Current clinical guidelines integrate the latest research to provide recommendations on dosing, treatment duration, and monitoring, ensuring that PDA management aligns with the best available evidence. Personalized care plans that consider the infant's specific medical conditions, drug tolerance, and response to initial treatment help clinicians determine the most effective and safe therapeutic approach for each neonate.

Factors Influencing Treatment Choice

The selection of treatment for PDA in preterm neonates is influenced by several critical factors, each of which can affect how the infant responds to therapy. Gestational age and birth weight are key determinants; as extremely premature or low-birth-weight infants may face higher risks of complications with certain medications. Comorbidities, such as renal, liver, or gastrointestinal issues, also play a pivotal role in decision-making, as these conditions may contraindicate the use of drugs like ibuprofen. Also, the timing of PDA diagnosis can affect the choice of treatment, as earlier intervention may offer better outcomes.

Preterm neonates, especially those born with earlier gestational ages or very low birth weights, are at higher risk for complications during PDA treatment due to immature renal or hepatic function. This makes them more vulnerable to medication side effects, particularly with ibuprofen, which may worsen renal or gastrointestinal issues. In such cases, paracetamol is often considered a safer alternative, especially for infants with renal or GI concerns. Clinical guidelines advocate personalized care, adjusting treatment based on individual conditions. While ibuprofen remains the first-line therapy for PDA closure, paracetamol may be preferred for vulnerable neonates due to its relatively safer profile.

4. EXPERIMENTATION AND RESULT DISCUSSION

In the experimentation phase, preterm neonates diagnosed with hemodynamically significant PDA were randomized into two treatment arms: one group received oral ibuprofen, and the other received intravenous (IV) paracetamol. Both groups were closely monitored for clinical outcomes, including PDA closure, respiratory function, and the time required for ductal closure. Key safety indicators were assessed through laboratory tests and clinical observations, focusing on renal and gastrointestinal function for the ibuprofen group, and liver function for the paracetamol group. The primary endpoint was the rate of successful PDA closure, while secondary endpoints included the incidence of adverse effects and the recurrence of PDA after initial treatment. Statistical analyses were conducted using chi-square tests for categorical variables and t-tests for continuous

variables to compare the therapeutic efficacy and safety profiles of the two treatment groups. The results were discussed in terms of clinical relevance, highlighting which drug demonstrated superior therapeutic effect while minimizing adverse outcomes. This comparison provided critical evidence to support informed decision-making in neonatal care.

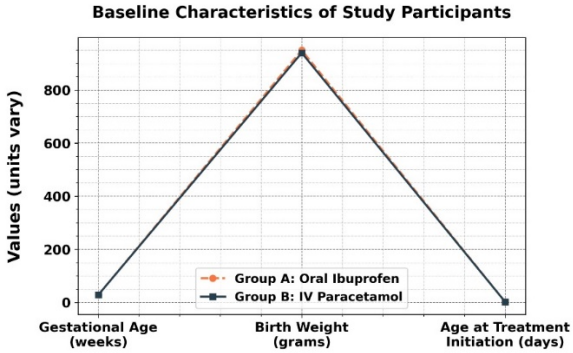

Figure 5: Baseline Characteristics of Study Participants

Figure 5 showed the baseline features of the preterm neonates of Group A, children exposed to oral ibuprofen (n=26) and Group B to IV paracetamol (n=26). Both groups are just about coordinated for gestational age: Group A was 28.4 ± 1.3 weeks, while Group B was 28.6 ± 1.2 weeks. There are nearly no differences when it came to birth weights either (950 ± 150 g for Group A and 940 ± 145 g for Group B). The sex distribution was slightly more or less similar in these two groups: 30 males and 20 females versus 29 males and 21 females for Groups A and B, respectively. The degree of severity of HsPDA remained comparable between the groups, with mostly moderate PDA (35 in Group A, 36 in Group B) and the rest were severe. Postnatal time of treatment was similar: Group A - 2.5 ± 1.1 days and Group B - 2.3 ± 1.2 days; thus, the groups seem to have been well balanced for therapeutic comparison.

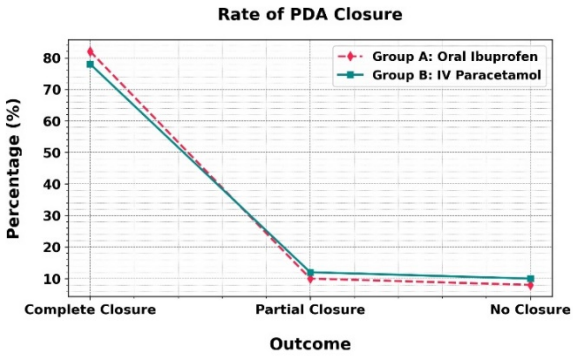

Figure 6: Rate of PDA Closure Following Treatment

Figure 6 recorded the outcomes of ductal closure in preterm neonates who were treated for HsPDA with oral ibuprofen (group A) or IV paracetamol (group B). Ductal closure, either complete or partial, occurred in most babies treated in either group, with a slightly improved rate of complete closure in group A (82%) versus 78% seen in group B. Partial closure was observed in 10% of the ibuprofen group and 12% in paracetamol, with a maximum possible degree of intermediate off the two drugs. Failure rate, meaning there was no closure, was low in both groups, 8% and 10% in groups A and B, respectively. It can thus be deduced that both oral ibuprofen and IV paracetamol are quite comparable and effective treatments for PDA closure in preterm neonates, with a slight edge for a complete closure rate with ibuprofen. Given such similar results, those two drugs should be seen as therapeutic alternatives and weighed against each other.

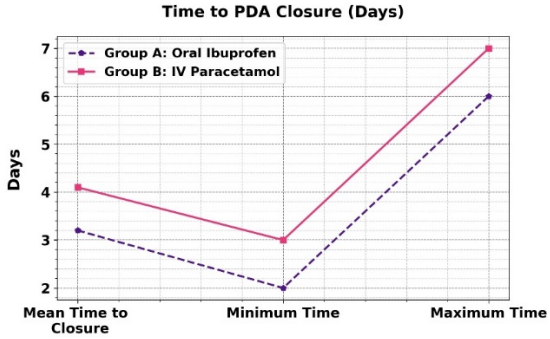

Figure 7: Time to PDA Closure in Treatment Groups

Figure 7 presented the time taken for PDA closure in preterm neonates with the administration of oral ibuprofen (Group A) and IV paracetamol (Group B). Group A showed a shorter mean time to closure, calculated to be 3.2 ± 0.9 days, compared to 4.1 ± 1.1 days of Group B, confirming a faster therapeutic response with ibuprofen. The closure-time range also varied slightly; Group A closed PDA in 2 to 6 days, while Group B ranged from 3 to 7 days. These results, therefore, indicate that although both agents are efficacious, oral ibuprofen may induce ductal closure earlier than IV paracetamol. This difference in treatment response time can certainly play a clinically important role where prompt closure is warranted, with neonates who are already critical from the hemodynamic side. The data thus support the possibility that ibuprofen may hold an advantage in achieving faster PDA resolution over IV paracetamol in preterm infants.

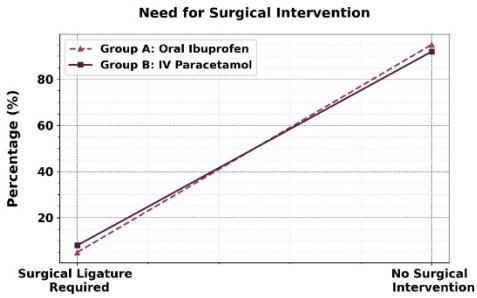

Figure 8: Need for Surgical Intervention Following Medical Treatment

Figure 8 displayed data on the surgical ligation requirement of PDA in preterm neonates following treatment with either oral ibuprofen (Group A) or IV paracetamol (Group B). Surgical ligation had to be performed in 5% of the infants in Group A compared to 8% in Group B. Well over half of the neonates in both groups responded to medical management and did not proceed to surgery: the ibuprofen group had 95% who avoided surgical intervention, while the paracetamol group had 92% avoidance. On slight consideration, a lower rate of surgical ligature in the ibuprofen group may point towards a marginally better efficacy for full medical closure of the PDA. These findings support the proposition for both drug therapies as the common non-surgical approach to managing hemodynamically significant PDA, while at the same time emphasizing that a minority of patients may still require surgical closure after pharmacological treatment.

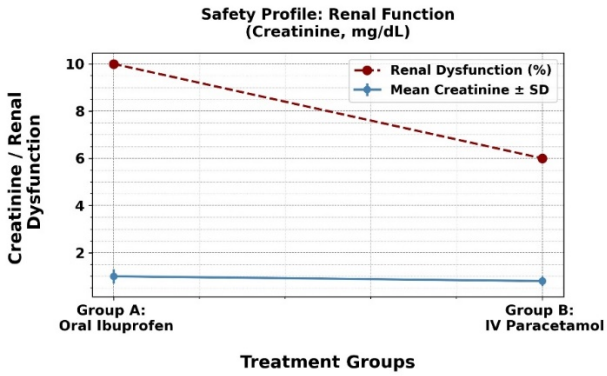

Figure 9: Renal Function in Treatment Groups

Figure 9 presented data evaluating the changes brought in renal function by oral ibuprofen and IV paracetamol in preterm neonates, measuring serum creatinine as the function parameter. Oral ibuprofen in Group A recorded

a mean creatinine of 1.0 ± 0.3 mg/dL, while slightly lower in Group B (paracetamol group) at 0.8 ± 0.2 mg/dL Also, the prevalence of renal dysfunction, defined as a creatinine level higher than 1.2 mg/dL, was 10% for ibuprofen and 6% for paracetamol. These figures thus skew toward slightly greater chances of renal impairment with the administration of ibuprofen than of paracetamol. Though generally well tolerated by most patients in both groups, paracetamol showed a safer side concerning the kidneys. This differential may have clinical implications, especially in very preterm neonates who have an augmented risk of kidney complications owing to underdeveloped renal systems.

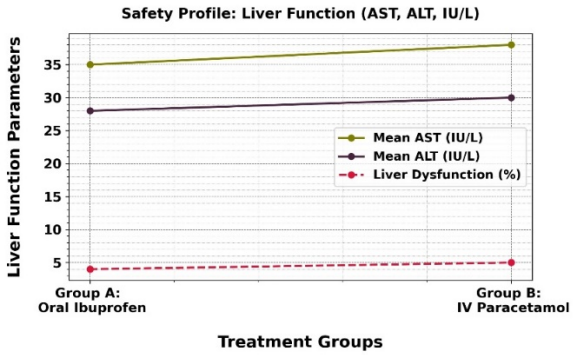

Figure 10: Liver Function in Treatment Groups

Figure 10 was for liver function evaluation in preterm neonates treated for hemodynamically significant PDA with either oral ibuprofen or IV paracetamol, using serum AST and ALT levels as markers. The mean AST level in the ibuprofen group was 35 ± 12 IU/L, with 38 ± 15 IU/L in the paracetamol group, and corresponding ALT levels were 28 ± 10 IU/L and 30 ± 14 IU/L. Both groups had values within the normal limits, suggesting little to no stress on the liver. The incidence of liver dysfunction, defined by an AST or ALT level of higher than 50 IU/L, was low in both groups, being 4% in the ibuprofen group and 5% in the paracetamol group. These data suggest that both therapeutic agents have a good hepatic safety profile in the neonatal population. Since there is no clinically significant difference between the two treatments in liver enzyme elevation, the continued use of both drugs with routine liver function monitoring can be supported.

Table 2: Gastrointestinal Complications Associated with Treatment

Outcome	**Group A: Oral Ibuprofen (%)**	**Group B: IV Paracetamol (%)**
Gastrointestinal Bleeding	2%	0%
Feeding Intolerance	5%	2%
No Gastrointestinal Complications	93%	98%

Table 2 showed the occurrence of gastrointestinal (GI) complications in preterm neonates receiving oral ibuprofen for Group A or intravenous paracetamol for Group B treatment of hemodynamically significant PDA. Gastrointestinal bleeding was observed in 2% of infants in the ibuprofen group, while none were reported in the paracetamol group. Feeding intolerance is another very common GI problem in neonates, with 5% of those treated by ibuprofen reported to have this issue, as compared with 2% in the paracetamol-treated group. A total of 93% of neonates in the ibuprofen group A and 98% of neonates in the paracetamol Group B did not suffer from any GI complications, suggesting that both drugs were generally well tolerated. This information suggested that both treatments are quite safe, but IV paracetamol could have an edge concerning GI safety. While the difference in the rates of complications is rather minimal, it warrants close observation, especially while working with ibuprofen, which is otherwise known for its more frequent gastrointestinal side effects.

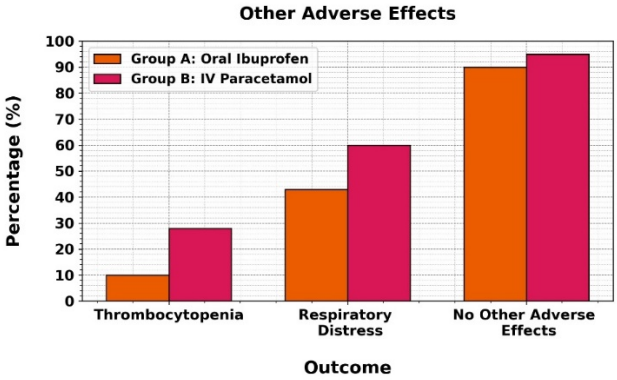

Figure 11: Other Adverse Effects Observed During Treatment

Figure 11 explored one more adverse reaction that has been reported in preterm neonates treated for hemodynamically significant PDA with oral ibuprofen (Group A) or with IV paracetamol (Group B) is thrombocytopenia, thrombocytopenia means diminished platelet count and was seen in 3% of neonates treated with ibuprofen and not at all in the paracetamol group. Respiratory distress, a possible complication in premature neonates, was observed in 7% of Group A and 5% of Group B. Despite these assessments, most neonates in both groups tolerated the treatment well; ibuprofen then paracetamol, 90% versus 95% had no other possibility of adverse reactions. These results have shown that both medicines are commonly safe, with intravenous paracetamol being slightly better tolerated. These data highlight the need for surveillance to aid in the recognition and management of rarely occurring side effects seen during pharmacological treatment of PDA in preterm infants.

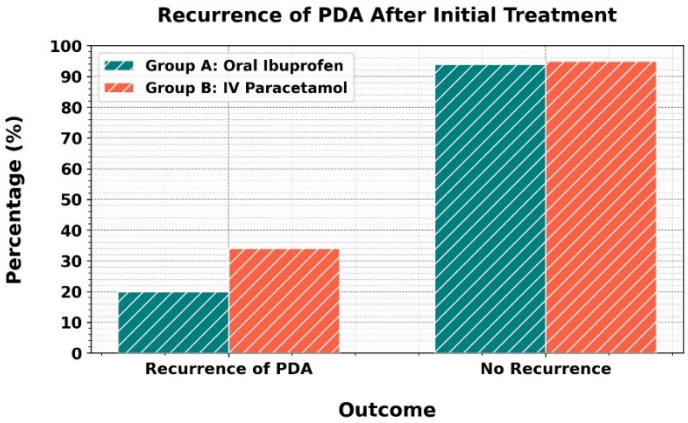

Figure 12: Recurrence of PDA After Initial Treatment

Figure 12 presented data indicating rates of PDA in preterm neonates following initial closure with ibuprofen orally (Group A) and IV paracetamol (Group B). Recurrence was experienced by only 6% of infants in Group A, with the rate being marginally lower in Group B, at 5%. The majority of neonates in both groups did not experience a recurrence; 94% of patients in the ibuprofen group and 95% of those in the paracetamol group remained with a sustained closure of the ductus arteriosus after treatment. The similarity in recurrence rates means that, from the point of view of longevity of effect, oral ibuprofen and IV paracetamol stand on equal footing in the prevention of PDA reopening in the preterm population. The slight recurrence further corroborates the efficacy of pharmacologic therapy for this target group, though continuous vigilance is pertinent to timely instruction in case any re-opening occurs in the ductus arteriosus.

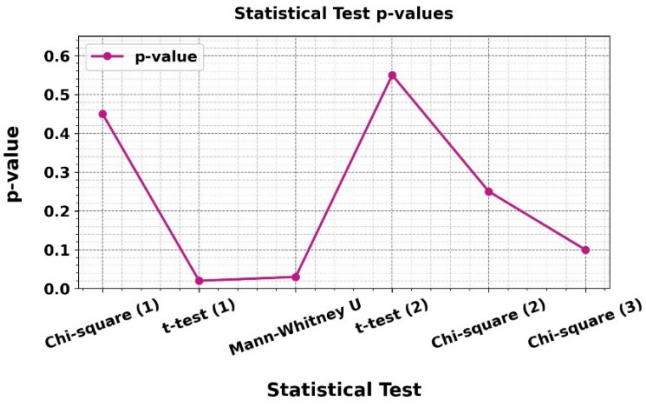

Figure 13: Statistical Analysis Results

Figure 13 listed p-values from many statistical tests in the comparison of outcomes between the groups treated with oral Ibuprofen and IV Paracetamol for the management of PDA in preterms. The Chi-square tests were used for those categorical variables, and the p-values came to 0.45, 0.25, and 0.10, which means no significant difference was found between the groups tested for those particular outcomes. Independent t-tests were applied to check the means of parametric continuous data, with p-values reported as 0.02 and 0.55, respectively. A p-value of 0.02 showed that there is a significant difference between the groups for one continuous variable, whereas a p-value of 0.55 failed to show a statistically significant difference. Coming next, the Mann-Whitney U test, as a non-parametric test for continuous variables which are not normally distributed, yielded a p-value of 0.03 for that given outcome, demonstrating that groups differed significantly concerning it. These outcomes indicate that some medium to large differences between oral ibuprofen and IV paracetamol were statistically significant, while others were not, implying subtle variations in efficacy and safety profiles.

5. RESEARCH CONCLUSION

This study evaluated the comparative efficacy and safety of oral ibuprofen versus IV paracetamol in the management of hemodynamically significant PDA in preterm neonates. Based on the findings, the conclusion highlighted whether one treatment demonstrated superiority in terms of efficacy, safety, or both. If one drug was found to be more effective in achieving PDA closure with fewer side effects, it was recommended as the preferred first-line therapy. Conversely, if both drugs showed similar efficacy but differed in safety profiles, the importance of individualized treatment decisions was emphasized. Factors such as gestational age, birth weight, and associated comorbidities were considered key determinants in guiding therapeutic choices for each neonate. The study also provided a foundation for future research, particularly in exploring long-term outcomes, optimizing dosing strategies, and evaluating potential combination therapies. Ultimately, this research addressed a critical gap in neonatal care by offering valuable insights into evidence-based management of PDA in vulnerable preterm infants.

REFERENCES

[1] Bitar, Fadi, and Ziad Bulbul. "Catheter hemodynamics and pulse pressure in patent ductus arteriosus: Back to the basics." *Polish Heart Journal (Kardiologia Polska)* 82.9 (2024): 826-827.

[2] Chinawa M, Josephat, et al. "Hemodynamically Significant Patent Ducts Arteriosus: Impact of Ductal Size on Left Output and Aortic Doppler Velocimetry." *SN Comprehensive Clinical Medicine* 6.1 (2024): 51.

[3] Giulietti, Jennifer M., and Alexandra D. Sharpe. "Evaluation of Serum Acetaminophen Concentration Utility for Closure of Patent Ductus Arteriosus." *The Journal of Pediatric Pharmacology and Therapeutics* 29.4 (2024): 404-409.

[4] Charanthimath, Pallavi, et al. "Efficacy of Oral Paracetamol Over Oral Ibuprofen in Closure of Patent Ductus Arteriosus in Preterm Neonates: A Randomised Controlled Non Inferiority Study." *Res. J. Med. Sci* 19 (2025): 72-76.

[5] Algutaini, S. A., & Sreiwy, A. A. (2025). Neonate with Microphthalmia, Cleft Lip and Palate, Omphalocele, Polydactyly, Atrial Septal Defect and Patent Ductus Arteriosus: A Likely Case of Patau Syndrome. *Journal of Medical Health Research and Psychiatry*, 1-3.

[6] Luo, H., He, J., Xu, X., Chen, H. and Shi, J., 2024. The impact of the route of administration on the efficacy and safety of the drug therapy for patent ductus arteriosus in premature infants: a systematic review and meta-analysis. PeerJ, 12, p.e16591.

[7] Nidharshana, K.R., Sathyan, V.K., Umamaheswari, V., Karpagam, L. and Senthilkumar, P., 2024. Prophylactic Intravenous Paracetamol For Preventing Mortality And Morbidity In Preterm Very Low Birth Weight Neonates: A Randomized Control Trial. Int J Acad Med Pharm, 6(2), pp.1124-1132.

[8] Ambalavanan, N., Aucott, S.W., Salavitabar, A., Levy, V.Y. and Committee on Fetus and

Newborn Eichenwald Eric MD Ambalavanan Namasivayam MD Guillory Charleta MD Hudak Mark MD Kaufman David MD Martin Camilia MD Lucke Ashley MD Parker Margaret MD Pramanik Arun MD Wade Kelly MD, 2025. Patent Ductus Arteriosus in Preterm Infants. Pediatrics, 155(5), p.e2025071425.

[9] Windiana, I.N., Suciawan, N., Purnamawati, I.A.P., Susila, I.K., Okaniawan, P.E.P., Pratiwi, P.C.A. and Widiatari, N.K.A.M., 2025. Paracetamol versus ibuprofen as first- line treatment for patent ductus arteriosus: An updated systematic review and meta- analysis of randomized controlled trials. Journal of Neonatal Nursing, 31(3), p.101677.

[10] Caruggi, S., Calandrino, A., Cipresso, G., Battaglini, M., Massirio, P., Vinci, F., Bonato, I., Andreato, C., Mela, F., Curcio, L. and Parodi, A., 2025. Second Attempt for Patent Ductus Arteriosus (PDA) Closure: Room for Acetaminophen? A Retrospective Single- Center Experience at Gaslini Children's Hospital. Children, 12(5), p.577.

[11] Weems, M.F., Ball, M.K., Zaniletti, I., Habib, S., Hamrick, S., Grover, T.R., Keene, S., Murthy, K., Padula, M., Philip, R. and Rao, R., 2025. Management of the patent ductus arteriosus among infants born at 23 to 32 weeks' gestation between 2011 to 2022: a report from in the Children's Hospitals Neonatal Consortium. Journal of Perinatology, pp.1-8.Dani, C., Sassudelli, G., Milocchi, C., Vangi, V., Pratesi, S., Poggi, C. and Corsini, I., 2025. Effectiveness of repeated pharmacological courses for patent ductus arteriosus in preterm infants. Early Human Development, 200, p.106167.

[12] Sutton, C.C., Slaughter, J.C., Alrifai, M.W., Hale, J. and Reese, J., 2025. Response of the ductus arteriosus to acetaminophen or indomethacin in extremely low birth weight infants. Journal of Perinatology, 45(3), pp.319-325.

[13] Mullaly, R., Smith, A., Franklin, O., McCallion, N. and El-Khuffash, A., 2025. Clinical and echocardiographic predictors of medical therapy failure for patent ductus arteriosus closure in preterm infants: Insights from a risk-based treatment approach. Early Human Development, 204, p.106238.

[14] De la Cruz-Mena, J.E., Veroniki, A.A., Acosta-Reyes, J., Estupiñán-Bohorquez, A., Ibarra, J.A., Pana, M.C., Sierra, J.M. and Florez, I.D., 2024. Short-term dual therapy or mono therapy with acetaminophen and ibuprofen for fever: a network meta-analysis. Pediatrics, 154(4), p.e2023065390.

[15] Ohana, O., Marmor, I., Ferguson, R., Levinsky, Y., Rubin, S., Baszis, K., Tal, R., Harel, L., Peled, O. and Amarilyo, G., 2025. Efficacy and safety of ibuprofen and naproxen in the treatment of oligoarticular juvenile idiopathic arthritis: bi-national cohort study. Immunopharmacology and Immunotoxicology, pp.1-6.

[16] Du, Y., Guo, Z., Xu, B., Yang, Y., Hu, M., Hu, Y., Yang, Y., Zhang, M., Wang, Z., Guo, X. and Huang, Y., 2025. A real-world disproportionality analysis of the FDA adverse event reporting system events for ibuprofen. Expert Opinion on Drug Safety, 24(2), pp.201-211.

[17] Windiana, I.N., Suciawan, N., Purnamawati, I.A.P., Susila, I.K., Okaniawan, P.E.P., Pratiwi, P.C.A. and Widiatari, N.K.A.M., 2025. Paracetamol versus ibuprofen as first- line treatment for patent ductus arteriosus: An updated systematic review and meta- analysis of randomized controlled trials. Journal of Neonatal Nursing, 31(3), p.101677.

[18] Shirakawa, K., Takeno, M., Kuma, H., Terahara, T. and Yamaguchi, S., 2025. Comparative Evaluation of Cyclooxygenase Inhibition Profiles Across Various NSAID Forms and Doses: Implications for Efficacy and Adverse Effects. Pain and Therapy, 14(1), pp.329-338.

[19] Kudrow, D., Croop, R.S., Thiry, A. and Lipton, R.B., 2025. A 52-week open-label extension study to evaluate the safety and efficacy of oral rimegepant for the preventive treatment of migraine. Headache: The Journal of Head and Face Pain.

[20] Wyatt, D.J., Araga, M., McCloskey, N., Petruschke, R. and Armogida, M., 2025. Bioequivalence Study of Ibuprofen and Diphenhydramine Hydrochloride mini liquid-filled capsules: A Size Reduction Alternative. Current Therapeutic Research, p.100779.

[21] Saod, L.A.B. and Albhbah, W.R.E., 2024. Evaluation of Practice and Awareness of the Safety Profile of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) among Dental Practitioners: A Cross-Sectional Study. The Scientific Journal of University of Benghazi, 37(2), pp.141-153.

[22] da Silva, H.D.S., Franco, E.D.S., Lima, L.C.D.A.S. and Maia, M.B.D.S., 2024. Therapeutic Efficacy and Safety of Paracetamol versus Ibuprofen in Patent Ductus Arteriosus in Newborns: A Systematic Review. Arquivos Brasileiros de Cardiologia, 121, p.e20240058.

[23] Almoslem, M., Shah, S.D., Vozmediano, V., Guzy, S., Kim, S., Hudak, M.L. and Schmidt, S., 2024. Pharmacokinetic and pharmacodynamic analysis of acetaminophen and ibuprofen dual therapy for patent ductus arteriosus closure in preterm neonates at less than 29 weeks of gestation. The Journal of Clinical Pharmacology, 64(3), pp.312-322.

[24] Asif, M., Sushko, K., Razak, A., Borhan, S., Rieder, M., van den Anker, J. and Samiee-Zafarghandy, S., 2025. A Retrospective Analysis of PK and Response of Oral Ibuprofen in the Treatment of a Patent Ductus Arteriosus in Extremely Low Gestational Age Neonates. The Journal of Clinical Pharmacology.

[25] Shah, S.M.A., Khan, S.A., Sadiq, F., Gul, R., Sadiq, F., Khan, M.U., Khan, M.K., Uzma, F., Khan, A. and Khan, S., 2025. Comparison of the Effectiveness of Paracetamol and Ibuprofen in the Management of Patent Ductus Arteriosus in Preterm Neonates: A Randomized Controlled Trial. Molecular and Cellular Pediatrics, 12(1), p.2.

[26] Sethi, V., Qin, L., Trocóniz, I.F., Van der Laan, L., Cox, E. and Della Pasqua, O., 2024. Model-Based assessment of the liver safety profile of acetaminophen to support its combination use with topical diclofenac in mild-to-moderate osteoarthritis pain. Pain and Therapy, 13(1), pp.127-143.

[27] Tanti, S.K., Uddin, W., Mishra, A.K. and Mishra, S., 2024. Efficacy of paracetamol in the management of hemodynamically significant patent ductus arteriosus in preterm newborns. Indian Journal of Pharmacology, 56(3), pp.162-165.

[28] Moronta, S.C., Bischoff, A.R., Ryckman, K.K., Dagle, J.M., Giesinger, R.E. and McNamara, P.J., 2024. Clinical and echocardiography predictors of response to first-line acetaminophen treatment in preterm infants with hemodynamically significant patent ductus arteriosus. Journal of perinatology, 44(3), pp.379-387.

[29] Goyal, N., Haribalakrishna, A. and Krishnamurthy, B., 2024. A comparison of different dosing regimen of intravenous paracetamol for hemodynamically significant patent ductus arteriosus closure in premature neonates< 32 weeks: a prospective observational study. Journal of Perinatology, 44(10), pp.1463-1469.

[30] Kainth, D., Prakash, S., Kumar, V., Dhinakaran, R., Verma, A. and Agarwal, R., 2024. Use of paracetamol for treatment of patent ductus arteriosus in preterm neonates: A 5- year experience from a tertiary hospital in India. Indian Pediatrics, 61(7), pp.656-660.