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Paracetamol Versus Ibuprofen in the Management of Patent Ductus Arteriosus in Preterm Infants in Dubai Hospital- A Retrospective study

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Abstract

Introduction & Background: *Patent ductus arteriosus (PDA) is one of most common complications in preterm infants. Although ibuprofen represents the first choice for the closure of PDA, this treatment can cause severe gastrointestinal and adverse renal effects and worsen platelet function. Paracetamol has been proposed as an effective and safer alternative to ibuprofen for closing hemodynamically significant patent ductus arteriosus (hsPDA) in recent years.*

Objectives: *To compare the efficacy and safety of paracetamol versus ibuprofen for pharmacological closure of hsPDA in premature infants.*

Methods: *In this observational, retrospective cohort study, with the help of both manual and electronic medical records, we identified 162 infants born at ≤ 35 weeks' gestation, diagnosed with PDA during admission to our neonatal intensive care unit in Dubai Hospital between August 2014 and August 2019. Out of these, we included 55 infants who were born at ≤ 35 weeks' gestation, had hsPDA-related clinical and echocardiographic findings, and received paracetamol or ibuprofen as first line therapy for hsPDA closure.*

Results*: Out of the 55 infants, 32 (58.1%) received paracetamol and 23 (41.8%) received ibuprofen as first line therapy. The demographic characteristics and echocardiographic features between the two groups were similar. The most common clinical findings for the diagnosis of PDA was the presence of systolic murmur (94.5%) and signs of pulmonary overperfusion (32.7%). The primary closure rate after single course of paracetamol was higher compared to those treated with ibuprofen (59.4% vs. 39.1%; respectively, P = 0.176) and the closure rate after repeated courses of paracetamol was found to be lower compared to that of ibuprofen (40.0% vs. 62.5%; P = 0.637). The secondary closure rate of paracetamol after failing treatment with single/repeat course of ibuprofen was higher compared to those in whom ibuprofen was given after failing treatment with paracetamol (87.5% vs. 75.0%; P = 0.584). However, the difference between the closure rates was statistically insignificant. The rates of adverse effects such as bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis feeding intolerance, acute kidney injury, elevated liver enzymes and platelet dysfunction was similar in both groups. Out of the 32 infants treated with paracetamol, only 1 had elevated liver enzymes after the treatment.*

Conclusion & recommendations: *Our results indicate that oral paracetamol was as effective as oral ibuprofen in the medical treatment of PDA. In addition, both drugs were considered well-tolerated in terms of effects on kidney, liver, and intestinal functions. Our study recommends that oral paracetamol can be used effectively and safely as the first-line treatment of PDA.*

List of abbreviations

ALT: Alanine aminotransferase AST: Aspartate aminotransferase BPD: Bronchopulmonary dysplasia BW: Birth weight

CI: Confidence intervals DA: Ductus arteriosus GA: Gestational age

hsPDA: Hemodynamically significant patent ductus arteriosus

ICD: International Classification of Diseases

IV: Intravenous

IVH: Intraventricular hemorrhage

LA:AO: Left atrium: Aortic root diameter ratio

NEC: Necrotizing enterocolitis

NICU: Neonatal Intensive Care Unit

NSAIDs: Non-steroidal anti-inflammatory drugs

OR: Odds ratio

PDA: Patent ductus arteriosus RCT: Randomized controlled trial ROP: Retinopathy of prematurity

Introduction

The ductus arteriosus is an essential vascular shunt during fetal life that connects the pulmonary artery with the aorta. (1,2) Under physiological conditions, the ductus arteriosus closes spontaneously a few hours after birth, leading to the complete independence of the systemic and pulmonary circulations. (1) In most full-term infants, the ductus arteriosus closes spontaneously during the first three days of life, but in preterm neonates it often fails to close. (3) The risk of PDA increases with decreasing

gestational age (GA) and birth weight (BW).(1,4) The incidence of patent ductus arteriosus in preterm neonates with gestational age less than 28 weeks is about 60-70% and 10 to 20% in those greater than 32 weeks of gestation. (1,2,4)

When the ductus remains open, a portion of the circulating blood volume is redirected from the systemic to the pulmonary circulation. Depending on the size of the ductus, the diverted flow may cause pulmonary overflow and impaired end-organ perfusion. This hemodynamic situation is known as hemodynamically significant patent ductus arteriosus (hsPDA).(1) The left to right shunt through the PDA is associated with several comorbidities, such as necrotizing enterocolitis, intraventricular hemorrhage, pulmonary edema/hemorrhage, chronic lung disease, and retinopathy of prematurity. (1,2,4,5,6,7) To prevent such complications, the practice of PDA closure is common and it is performed at first pharmacologically, but, in case of drugs failure or contraindication, with surgical ligation. (1,2, 4, 5,6,7,8)

Despite years of researches and clinical experience on PDA management, unresolved questions about the treatment and heterogeneity of clinical practices in different centers still remain, in particular regarding timing and modality of intervention. Nowadays, the most reasonable strategy seems to be reserving the treatment only to hemodynamically significant PDA with clinical and echocardiographic findings that provide evidence of left ventricular overload and pulmonary overcirculation.(2) The first-line therapy is medical, and NSAIDs (indomethacin and ibuprofen) have been the standard medical therapy for PDA closure.(1,2,3,4) Both are successful in promoting ductal closure in 70–80 % of cases. However, these drugs can cause severe adverse effects, inducing the development of gastrointestinal perforations, acute renal failure, and bleeding disorders (1,2,3,4,5,6,7)

Administration of oral or intravenous paracetamol (acetaminophen) has recently gained attention, appearing as effective as traditional nonsteroidal anti-inflammatory drugs (NSAIDs) in PDA closure, with lower toxicity.(1,2,3,4,5,6,7) In 2011, Hammerman et al. reported the first case series of use of paracetamol as treatment of hsPDA in five neonates who had either failed or had contraindications to ibuprofen therapy preterm infants. Rate of ductus closure was 100%, with no adverse events reported.(9) In subsequent years, additional case series and clinical trials evaluating this new treatment option have been published. A clinical trial comparing oral paracetamol with oral ibuprofen in 80 preterm neonates concluded that oral paracetamol was not superior to oral ibuprofen(10), whereas another trial with 160 preterm neonates reported that oral paracetamol was not inferior to oral ibuprofen in closure of PDA(11). According to the literature reported to date, hypertransaminasemia was the only adverse effect observed and no treatment was required.

(12) However, more studies are needed to confirm if this therapy shows a real safety profile and to evaluate its long-term outcomes, before considering paracetamol as first-choice drug in PDA treatment.

According to the local clinical protocol in the NICU in Dubai Hospital, the first line therapy for the management of hemodynamically significant PDA are the NSAIDs- ibuprofen and indomethacin. Paracetamol is used in those who failed to respond to 1st course of Ibuprofen/Indomethacin or in whom there were contradictions to the use of ibuprofen/indomethacin such as active bleeding, clinical or radiological evidence of NEC, platelets count <60,000/uL, impaired renal function and disturbed coagulation profile.

Thus, the aim of our study is to assess the efficacy and safety of paracetamol in comparison to ibuprofen for the treatment of hemodynamically significant PDA in preterm infants and to provide evidence in terms of efficacy and safety profile, that will supplement the studies that support the use of paracetamol for the first line management of hemodynamically significant PDA. Furthermore, our study can be utilized in updating the local hospital protocol for management of PDA, by using evidence-based recommendations that favor the use of paracetamol as an alternative to NSAIDs for the first line management of hemodynamically significant PDA.

Methodology

i. Study design

This research study was an observational, retrospective cohort study.

ii. Study setting

The study was conducted in the tertiary neonatal care unit at Dubai Hospital, which is a government organization under Dubai Health Authority.

iii. Study period

The study included patients over a period of 5 years, between August 2014 to August 2019.

iv. Study population and selection of study sample

All patients admitted in Dubai Hospital have their ICD (International Classification of Diseases) coding recorded in the manual and electronic filing system (SAM and SALAMA). Thus, with the help of these systems and ICD coding, we identified all preterm newborn infants, nationals and non-

nationals, ≤ 35 weeks of gestation, diagnosed with PDA in the NICU, during the study period. From this list, we further extracted the patients according to our inclusion and exclusion criteria listed below, to get our study sample.

Inclusion criteria

- Birth weight <2000 grams
- Boys & girls
- Nationals/non-nationals
- Infants with hemodynamically significant PDA who have clinical and/or echocardiographic findings that provide evidence of pulmonary overcirculation and left- to-right shunting, left ventricular overload and systemic undercirculation.

*Clinical criteria- tachypnea, tachycardia, active precordium, systolic or continuous murmur, prominent left ventricular impulse, bounding pulses, widened pulse pressure, systemic hypotension, increased oxygen dependency or hypercapnia, cardiomegaly and increased pulmonary vascular markings on chest radiography.

*Echocardiographic criteria- demonstration of a ductal left-to-right shunt with transductal diameter of ≥1.5 mm and evidence of left atrial enlargement (Left atrium: Aortic root diameter ratio ≥1.4)

- Infants with hsPDA who received pharmacological treatment (paracetamol or ibuprofen) for closure of PDA (according to the local hospital protocol)

Exclusion criteria

- Newborn infants more than 35 weeks of gestational age
- Birth weight >2000 grams
- Antenatally or postnatally suspected or diagnosed structural heart disease
- Infants with major congenital malformations and chromosomal abnormalities
- Infants with asymptomatic PDA with transductal diameter <1.5cm
- Infants with coexisting congenital liver and renal disorders

Sample size and data collection

Total number of neonates diagnosed with PDA during admission to the NICU between August 2014 and August 2019 were 162. 107 (66%) neonates from this list were excluded based on our exclusion criteria and 55 (34%) were included in the study. The data collected for each of the 55 neonates with hsPDA included the demographic characteristics, clinical presentation, echocardiographic features, management of hsPDA and adverse effects of hsPDA and the medications (ibuprofen/paracetamol). The definition of the presenting variables is outlined in Table 1. Data was retrieved from the electronic patient record system where patients' demographic information, medical investigations, and discharge summaries are saved (SAM & SALAMA) and from the case records section in medical records department in Dubai hospital. All data were saved to password encrypted flash drives.

vi. Treatment protocol

According to the protocol for management of PDA in Dubai Hospital, patients diagnosed with hsPDA are initially managed conservatively with fluid restriction and diuretics. If there is no improvement in clinical condition and/or echocardiographic features of hsPDA within 5 – 7 days, pharmacological treatment with either ibuprofen or paracetamol will be given. In Dubai Hospital, the first line drug is oral/IV ibuprofen. The dosing of ibuprofen for PDA closure is an initial dose of 10 mg/kg followed by two additional doses of 5 mg/kg given at 24 hours intervals. The contraindications for the use of ibuprofen are: active bleeding (intracranial, gastrointestinal), thrombocytopenia <60,000//mm3, NEC and impaired renal function (serum creatinine > 1.5 mg/dL, urine output < 1 mL/kg/h). Paracetamol is mainly used in patients who have contraindications to the use of ibuprofen or who have failed to respond to one or two courses of ibuprofen. It is administered at a dose of 15 mg/kg every 6 hourly over a three- to five-day period. Echocardiography is repeated after 24 hours from the last dose of the drug and subsequently at weekly intervals, to monitor for ductal closure/constriction. Infants in both groups who failed the primary closure and had a persistent hsPDA after the first course of treatment received a repeat course of the same drug. Further second line pharmacological treatment and the need for surgical closure were decided on the basis of case-by-case and local hospital protocol.

vii. Study outcomes

The primary outcome is the primary closure rate of both drugs after the first course of treatment, which is the main measure for comparison of efficacy between the two drugs. The secondary outcomes listed in Table 2. below, are also compared between the two drugs to further assess the efficacy and safety profile of the two drugs.

Patient characteristics:

Gender (male and female)

Gestational age: 1) less than 28 weeks 2) 28 to 31 weeks 3) 32 to 35 weeks

Birth weight: 1) less than 1000 grams 2) 1000 to 1500 grams 2) 1500 to 2000 grams

Length of hospital stay (in days)

Age of PDA diagnosis (in days)

Duration of any respiratory support and need for supplemental oxygen (in days)

All-cause mortality within the hospital

Clinical presentation of hsPDA:

signs of significant left→right shunt: systolic murmur, hyperdynamic pulsatile precordium, bounding peripheral pulses and wide pulse pressure (>25 mm Hg), abnormal weight gain, increase in liver size

signs of systemic underperfusion: poor peripheral pulse volume, prolonged capillary refill time, decreased urine output and hypotension

signs of pulmonary overperfusion: tachypnea, respiratory distress, new onset or increase in ventilatory requirements that primarily involve Positive End Expiratory Pressure (PEEP) Peak Inspiratory Pressure (PIP) and Fraction of Inspired Oxygen (FiO2), respiratory acidosis, pulmonary crepitations and pulmonary oedema

Echocardiographic features of hsPDA:

PDA size : 1) Moderate (1.5 to 3 mm) 2) Large (>3mm)

LA/AO ratio≥1.4

Presence of dilated left side of heart (defined as dilated left atrium and/or left ventricle)

Presence of pulmonary hypertension (defined as mean pulmonary artery systolic

pressure(mPAP) > 20 mmHg, according to 6th World Symposium on Pulmonary Hypertension)

Presence of heart failure (defined as left ventricular systolic dysfunction with ejection fraction (EF) <55%, according to the American Heart Academy guidelines)

Management of hsPDA:

Diuretic use (furosemide, spironolactone or hydrochlorothiazide)

First line treatment (paracetamol or ibuprofen)

Second line treatment (paracetamol or ibuprofen)

Surgical ligation

Adverse effects of:

hsPDA: intraventricular hemorrhage (Papile classification), periventricular leukomalacia (presence of cystic areas detected by brain ultrasound at 40-week post-conception birth), necrotizing enterocolitis (Bell's criteria), feed intolerance (inability to digest enteral feedings associated with increased gastric residuals, abdominal distension and/or emesis), bronchopulmonary dysplasia (oxygen requirement at 36 weeks of post-menstrual age) and retinopathy of prematurity (International Classification of ROP) and renal failure (serum creatinine > 1.5 mg/dL and urine output < 1 mL/kg/h in 24 hours)

Medications (paracetamol/ibuprofen): azotaemia (serum creatinine > 1.5 mg/dL), oliguria (urine output < 1 mL/kg/h in 24 hours), hepatitis with deranged liver transaminases (normal range: ALT 6–50 U/L; AST 35–140 U/L), platelet dysfunction and bleeding tendency (platelet count < 50,000/mm3)

References: The definition of the variables was referred to Bardanzellu et al(2), Yang et al.(13), El-Mashad et al. (14), Ohlsson et al. (15), Huang et al. (16), and Das et al. (17)

Table 1. Definition of presenting variables

Primary Outcome
○ Primary closure* rate after the first course of treatment
Secondary Outcomes
○ Proportion of neonates that required repeat course and the corresponding closure rate
○ Proportion of neonates that required second line treatment and the secondary closure rate
○ Time to primary closure (number of days needed for closure/constriction of PDA from last dose ofdrug)
○ Time to definitive closure (number of days from diagnosis to complete closure of PDA)
○ Proportion of neonates where the PDA reopened after initial closure
○ Proportion of neonates who required surgical ligation for closure of PDA
○ Occurrence of adverse effects of PDA- congestive heart failure, pulmonary artery hypertension, intraventricular haemorrhage (any grade of severity), periventricular leucomalacia, necrotising enterocolitis (all stages), feed intolerance, bronchopulmonary dysplasia and retinopathy of prematurity and renal failure.
○ Occurrence of adverse effects of the medications**- azotaemia, oliguria, hepatitis with derangedliver transaminases, platelet dysfunction and bleeding tendency
References: Kumar et al. [18]
*For the purpose of this study, ductus will be considered to be closed when the diameter measures <1mm on echocardiography
** Adverse events were defined as those occurring during and up to 1 week after administration of thedrug treatment.

Table 2. Primary and secondary outcomes

viii. Statistical analysis

The collected data was coded and entered to the Statistical Package for Social Science (IB SPSS) version 23 for analysis. The variables listed in Table 1. and Table 2. were analyzed and compared between the two groups. The quantitative data was presented as mean and standard deviation when their distribution was parametric and as median and range when their distribution was nonparametric. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used to determine the type of distribution of the data (parametric or nonparametric). Qualitative variables were presented as number, percentages, or proportions. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P-value was considered significant if $P \leq 0.05$. The student's t-test was used to compare means of variables with parametric distribution and the Mann- Whitney U test was used to compare

medians of variables with nonparametric distribution. The chi-square test and Fisher's exact test was used to compare proportions. The confidence interval was set to 95% and P-value was considered significant if $P \leq 0.05$.

ix. Ethical compliance

The study was undertaken after receiving approval from the Dubai Scientific Research & Ethics Committee. Patient data was saved and handled confidentially. Personal information of the patients or their families was not disclosed to anyone.

Results

In our study, we included 55 (34%) out of 162 infants who received pharmacological treatment (paracetamol or ibuprofen) for closure of hemodynamically significant PDA. Out of these, 32 (58%) received paracetamol and 23 (42%) received ibuprofen as first line therapy.

i. Patient characteristics

The enrolled infants (n=55) had gestational age between 23 to 35 weeks with median of 26 weeks. 76.4% of the infants had gestational age less than 28 weeks, 20% were between 28 to 31 weeks and only 3.6% were between 32 to 35 weeks of gestation. Birth weight of the patients ranged between 450 grams to 1660 g with median of 810 grams. 78.2% weighed less than 1000 grams at birth, 18.2% weighed between 1000 and 1500 grams and 3.6% weighed between 1500 and 2000 grams. Among all patients, 60% were males and 40% were females. The age at diagnosis of PDA ranged between 1 to 30 days of life with median of 7 days. The duration of oxygen support required for the patients with PDA ranged between 16 to 240 days with median of 67 days. The length of hospital stay ranged between 30 to 275 days with median of 96 days. The all- cause mortality rate for the infants with hsPDA who were medically treated is 7.3% (n=4). Out of these 4 infants, 2 died due to septic shock and multi- organ failure, 1 died due to cardiogenic shock due to hsPDA and 1 died due to respiratory failure.

The characteristics of the patients between the paracetamol and ibuprofen treatment groups are compared in Table 3., below. Most of the patient characteristics between the two drugs were found to be similar as the P value for all the variables was >0.05 that means there is no statistically significant

difference. The duration of respiratory support required for the patients with PDA between the two drugs was found to be statistically different as the P value was less than 0.05.

Patient characteristics	**Paracetamol (n=32)**	**Ibuprofen (n=23)**	***P* value**
Gestational age (weeks), median (range)	25 (23 - 35)	26 (23 – 29)	0.371
Gestational age category, n (%) <28 weeks 28 – 31 weeks 32 – 35 weeks	27 (84.4) 3 (9.4) 2 (6.3)	15 (65.2) 8 (34.2) -	0.412
Birth weight (in grams), median (range)	800 (450 – 1660)	760 (530 -1000)	0.509
Birth weight category, n (%) <1000 grams 1000 – 1500 grams 1500 – 2000 grams	25 (78.1) 5 (15.6) 2 (6.3)	18 (78.3) 5 (21.7) -	0.425
Gender, n (%) Female Male	14 (43.8) 18 (56.3)	8 (34.8) 15 (65.2)	0.583
Age of PDA diagnosis (in days), median (range)	7 (1 – 30)	8 (2 – 21)	0.696
Duration of any respiratory support (in days), median (range)	67 (16 – 240)	41 (25 – 153)	0.038
Length of hospital stay (in days), median (range)	96 (30 – 275)	87 (30 – 153)	0.065
All-cause mortality, n (%)Yes No	3 (9.4%) 29 (90.6%)	1 (4.3%) 22 (95.7%)	0.628

Table 3. Patient characteristics between paracetamol and ibuprofen groups

Specifically, the comparison of gestational age and birth weight between the two drugs is represented in Figure 1. and Figure 2., respectively.

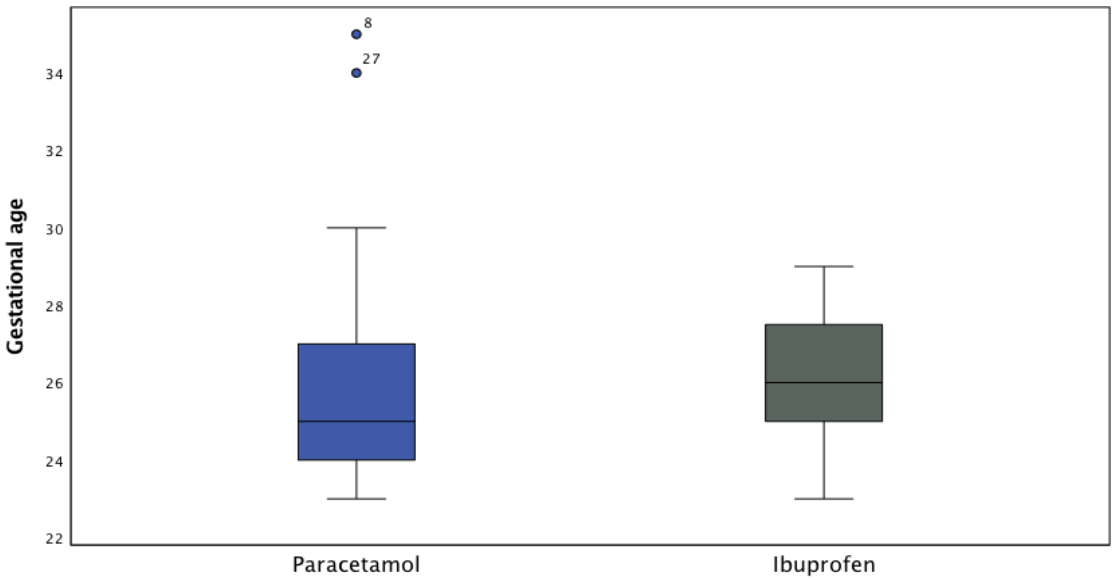

Figure 1. Comparison of gestational age (in weeks) between paracetamol and ibuprofen groups

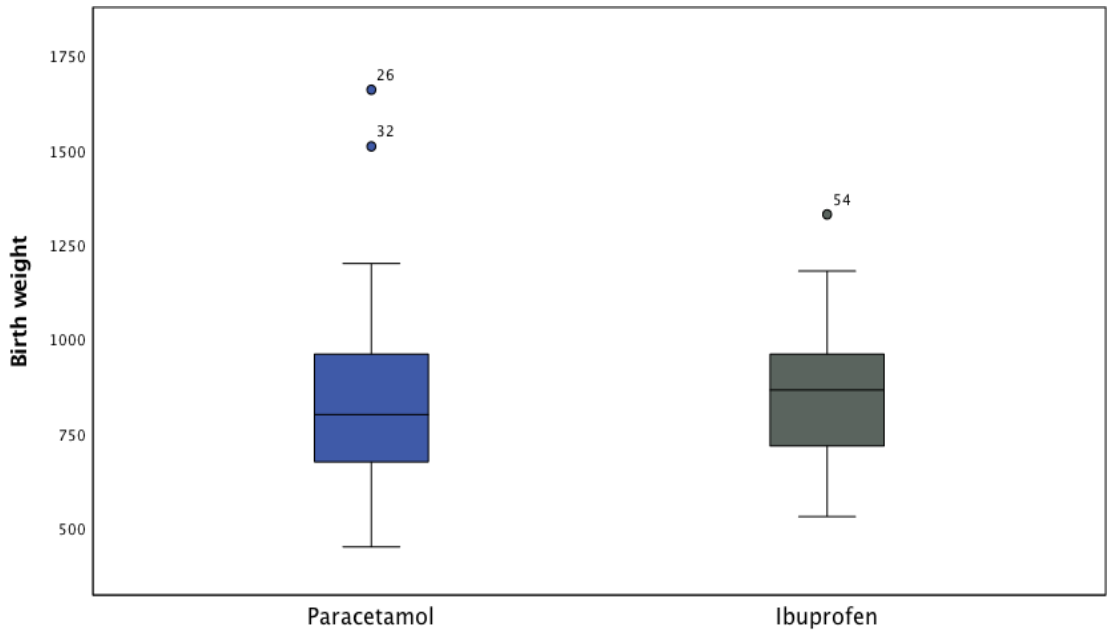

Figure 2. Comparison of birth weight (in grams) between paracetamol and ibuprofen groups

ii. Clinical presentation of hsPDA

The clinical findings of hsPDA are represented in Figure 3. The most common clinical finding in the enrolled infants was systolic murmur that was present in 94.5% (n=52) of the infants. 10.9% (n=6) of the infants presented with other signs of significant left to right shunt and volume overload such as hyperdynamic precordium, bounding peripheral pulses and liver enlargement. 32.7% (n=18) of the infants presented with signs of pulmonary overperfusion such as tachypnea, respiratory distress, increase in ventilatory requirements and pulmonary oedema. 7.3% (n=4) of the infants presented with signs of systemic under perfusion such as hypotension and prolonged capillary refill time.

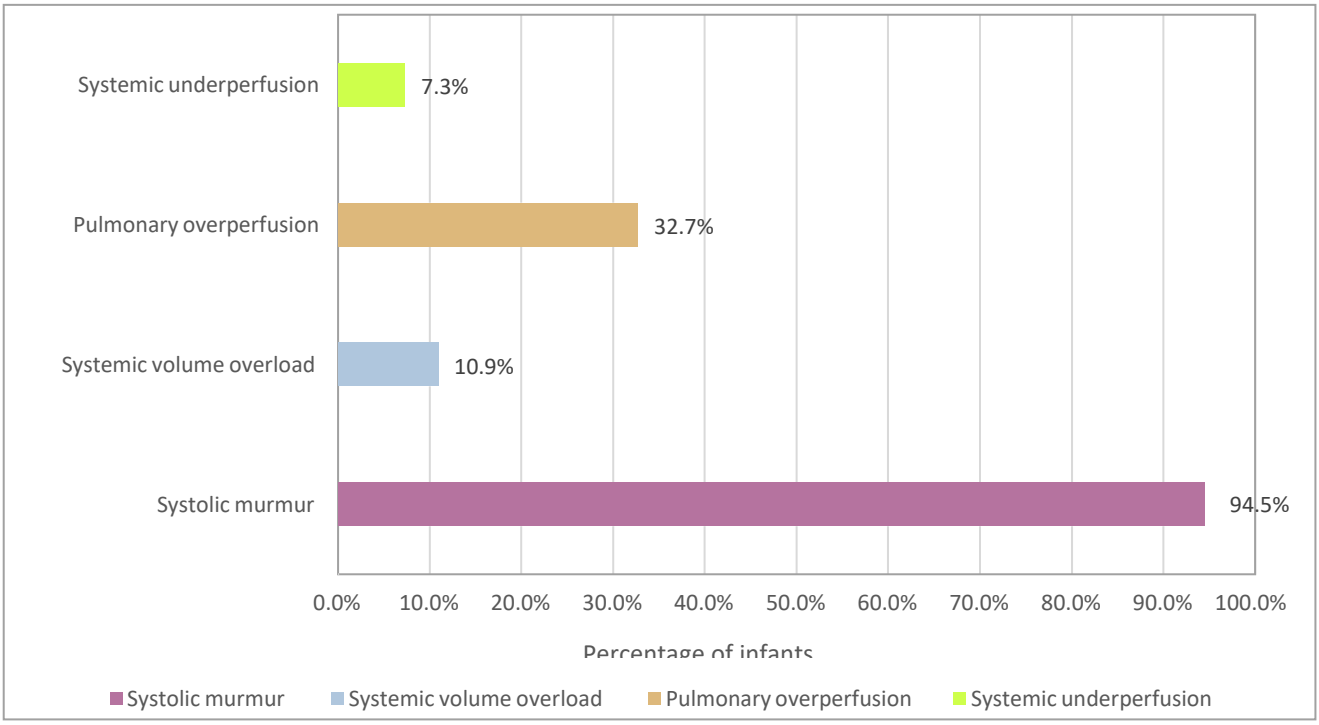

Figure 3. Clinical presentation of hsPDA

iii. Echocardiographic features of hsPDA

The mean size of hsPDA among the enrolled infants was 2.99±0.75 mm with a 95% CI of (2.79 – 3.19 mm). The size of the hsPDA was moderate (1.5 to 3 mm) in 65.5% (n=36) of infants and large (>3 mm) in 34.5% (n=19) of infants. The mean LA/AO ratio was 1.93±0.32 with a 95% CI of (1.85 – 2.01). The left side (left atrium and/or left ventricle) of the heart was dilated in 65.5% (n=36) of infants. 25.5% (n=14) of the infants had echocardiographic evidence of pulmonary hypertension and 18.2% (n=10) had heart failure. The comparison of the echocardiographic characteristics between the

paracetamol and ibuprofen treatment groups is shown in Table 4. The characteristics between the two groups were found to be comparable as demonstrated by P value > 0.05 for all the variables.

Echocardiographic characteristics	**Paracetamol (n= 32)**	**Ibuprofen (n=23)**	***P* value**
hsPDA size (mm), mean± SD	2.96±0.79 mm	3.03±0.71mm	0.760
hsPDA size category, n (%) moderate (1.5 to 3 mm) large (>3 mm)	 22 (68.8) 10 (31.3)	 14 (60.9) 9 (39.1)	}0.577
LA/AO ratio, mean± SD	1.94±0.32	1.75±0.23	0.858
Dilated left side of heart, n (%)	20 (62.5)	16 (69.6)	0.775
Pulmonary hypertension, n (%)	9 (28.1)	5 (21.7)	0.756
Heart failure, n (%)	6 (18.8)	4 (17.4)	1.000

Table 4. Echocardiographic characteristics between paracetamol and ibuprofen groups

In particular, the comparison of size of hsPDA and LA/AO ratio between the two drugs is represented in Figure 4. and Figure 5., respectively.

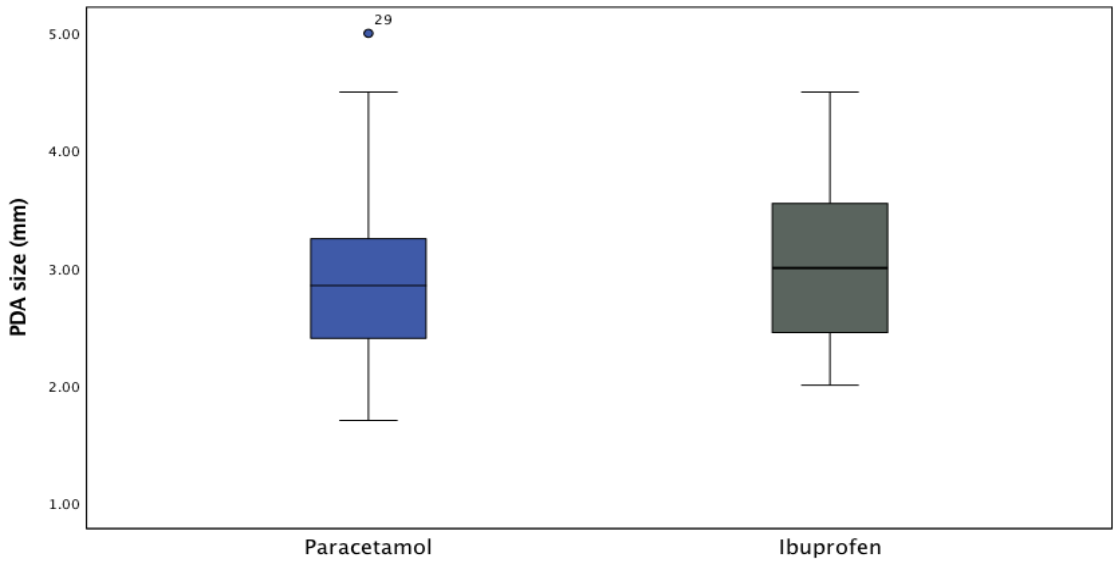

Figure 4. Comparison of PDA size between paracetamol and ibuprofen groups

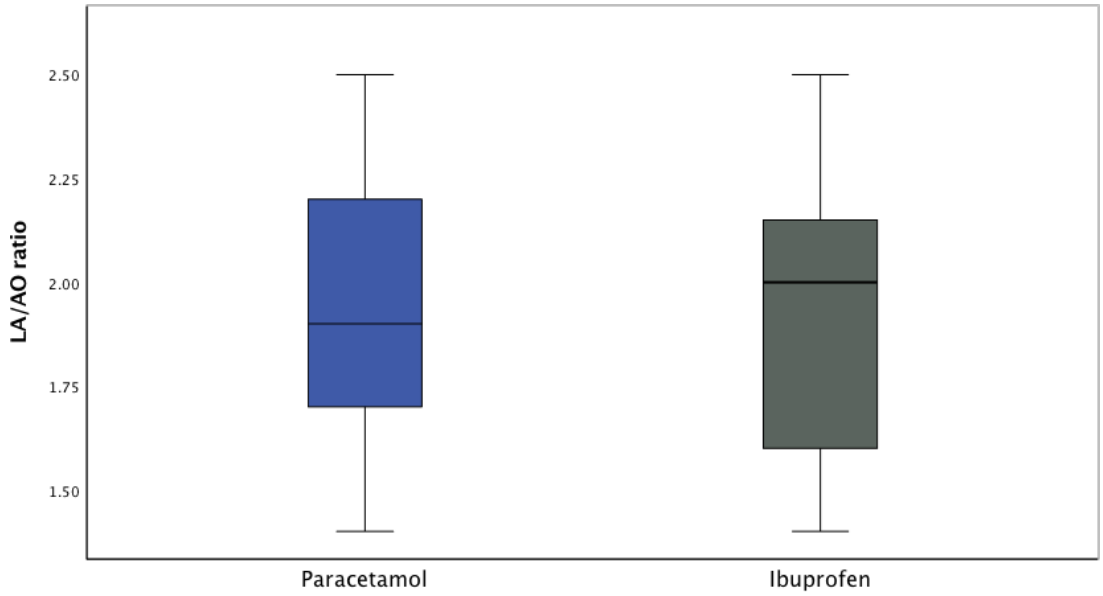

Figure 5. Comparison of LA/AO ratio between paracetamol and ibuprofen groups

iv. Management of hsPDA

a) Use of diuretics

Diuretics such as furosemide, spironolactone or hydrochlorothiazide were used in 42 (76.3%) of the 55 included infants.

b) First line management

Among the 55 treated neonates with hsPDA, 32 (58%) received paracetamol and 23 (42%) received ibuprofen as first line therapy. The primary closure rate for paracetamol was 59.4% (n=19). Paracetamol was started at a mean age of 22.66±14.35 days of life with a 95% CI of (17.48 – 27.83 days). In comparison, the primary closure rate for ibuprofen was 39.1% (n=9). Ibuprofen was started at a mean age of 18.00±9.35 days of life with a 95% CI of (10.18 – 25.82 days). 37.5% (n=12) of infants received IV paracetamol whereas the remaining 62.5% (n=20) received oral paracetamol. 95.7% (n=22) of the infants received oral ibuprofen as compared to only 4.3% (n=1) who received IV ibuprofen.

c) Repeat course of first line therapy

40.6% (n=13) of the infants in the paracetamol subgroup failed primary treatment. Out of these, 10 were treated again with a second course of paracetamol and only 4 infants achieved closure with a corresponding closure rate of 40.0%. In comparison, 60.9% (n=14) of the infants in the ibuprofen

subgroup failed primary treatment. Out of these, 8 were treated again with a second course of ibuprofen and subsequent closure was achieved in 5 infants with a corresponding closure rate of 62.5 %.

d) Second line management

Out of the 13 infants in the paracetamol subgroup who failed primary treatment, 30.7% (n=4) received second line treatment with ibuprofen. The secondary closure rate for ibuprofen was 75.0% (n=3). These infants received second line therapy with ibuprofen after failing to respond to two courses of paracetamol. In comparison, out of the 14 infants in the ibuprofen subgroup who failed primary treatment, 57.1% (n=8) received second line treatment with paracetamol. The secondary closure rate for paracetamol was 87.5% (n=7). Out of the 8 infants, 6 received second line treatment after failing to respond to single course of ibuprofen and 2 after failing to respond to two courses of ibuprofen.

e) Reopened PDA

The proportion of infants where the PDA reopened after initial closure (n=23) in the paracetamol subgroup was 13.0% (n=3). The PDA reopened in 2 infants after primary closure and in 1 infant after secondary closure with ibuprofen. In comparison, the proportion of infants where the PDA reopened after initial closure (n=12) in the ibuprofen subgroup was 16.7% (n=2). In one of them, the reopened PDA was treated with paracetamol as second line therapy.

f) Surgical ligation

Among the infants in the paracetamol subgroup, 18.75% of infants (n=6) underwent surgical ligation. Out of these, 50% (n=3) underwent surgical ligation after failure with single course of paracetamol, 33.3% (n=2) after failure with two courses of paracetamol and 16.7% (n=1) after failing both first- and second-line treatment with paracetamol (2 courses) and ibuprofen, respectively. Whereas, in the ibuprofen subgroup, 13.0% (n=3) infants underwent surgical ligation. Out of these, 33.3% (n=1) underwent surgical ligation after failure with single course of ibuprofen, 33.3% (n=1) after failure with two courses of ibuprofen and 33.3% (n=1) after failing both first- and second-line treatment with ibuprofen (2 courses) and paracetamol, respectively.

g) Time to primary closure (number of days needed for closure/constriction of PDA from last dose of drug)

The time to primary closure for the paracetamol subgroup ranged between 1 day and 25 days with median of 3 days. In comparison, the time to primary closure for the ibuprofen subgroup ranged between 2 days and 10 days with median of 5 days.

h) Time to definitive closure (number of days from diagnosis to complete closure of PDA)

The time to definitive closure for the paracetamol subgroup ranged between 10 days and 300 days with median of 45 days. In comparison, the time to definitive closure for the ibuprofen subgroup ranged between 18 day and 180 days with median of 45 days.

i) Relation of PDA closure to gestational age

Out of the 42 infants who had gestational age less than 28 weeks, 85.7% (n=36) failed first line treatment with single/repeat courses of either drug and 25% (n=2) failed second line treatment.

The outcome of the patients treated with paracetamol and ibuprofen, as mentioned above, is demonstrated in the flowchart in Figure 6. The comparison between the outcomes of the two treatment groups is summarized in Table 5. The results of our study demonstrate that the difference between the primary closure rates of paracetamol versus ibuprofen is statistically insignificant (59.4% vs. 39.1%; respectively, P = 0.176). Similarly, no significant difference was found between the closure rates after repeat course (40.0% vs. 62.5%; P = 0.637) and after second line treatment (87.5% vs. 75.0%; P = 0.584) between the two groups. Additionally, the re-opening rate of the PDA was similar (10.0% vs. 16.7%; P = 0.931) in infants both in the paracetamol and ibuprofen groups, as the need for surgical ligation (18.75% vs. 13%; P = 0.720). The time to primary closure (3 days vs. 5 days, P = 0.686) and the time to definitive closure (45 days vs. 45 days, P = 0.543) was similar between the paracetamol and ibuprofen groups. Among the infants in the paracetamol subgroup, the primary closure rate of oral paracetamol versus IV paracetamol was 70.0% (n=14) versus 41.6% (n=5) with p value of 0.114, which suggests that there is no significant difference of closure rates between the two groups. This shows that the efficacy of paracetamol for closure of hsPDA is similar to that of ibuprofen.

Management of hsPDA	**Paracetamol (n= 32)**	**Ibuprofen (n=23)**	***P* value**
Primary closure rate, % (n)	59.4% (19)	39.1% (9)	0.176
Closure rate after repeat course, % (n)	40.0% (4)	62.5 % (5)	0.637
Secondary closure rate, % (n)	87.5% (7)	75.0% (3)	0.584
Surgical ligation, % (n)	18.75% (6)	13.0% (3)	0.720
PDA reopening rate, % (n)	13.0% (3)	16.7% (2)	0.931
Time to primary closure (in days), median (range)	3 (1 - 25)	5 (2 - 10)	0.686
Time to definitive closure (in days), median (range)	45 (10-300)	45 (18-180)	0.543

Table 5. Comparison between the outcomes of paracetamol and ibuprofen groups

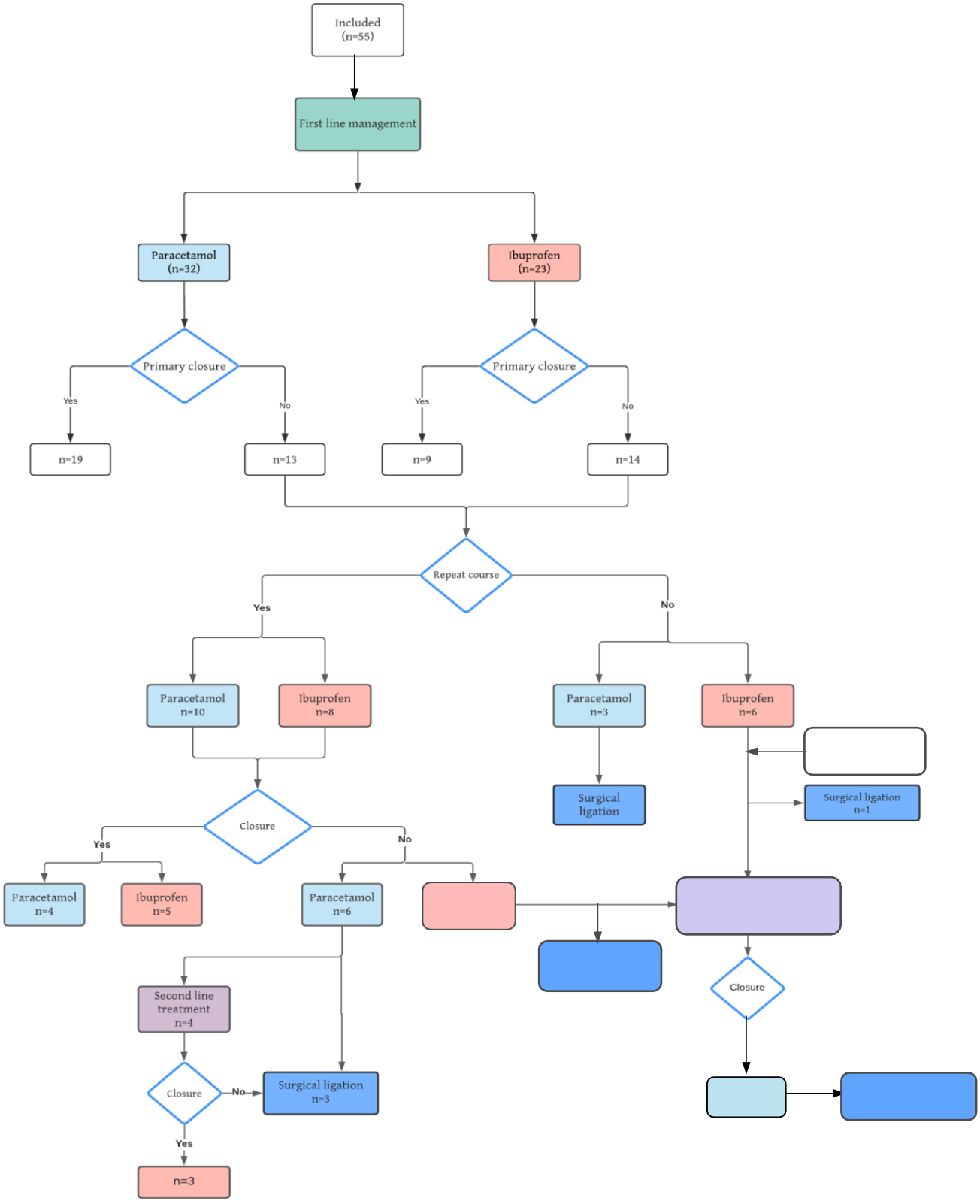

Figure 6. Outcome of the patients treated with paracetamol and ibuprofen

The closure rates between the two groups is compared in Figure 7. The time to closure (in days) between the two treatment groups is compared in Figure 8.

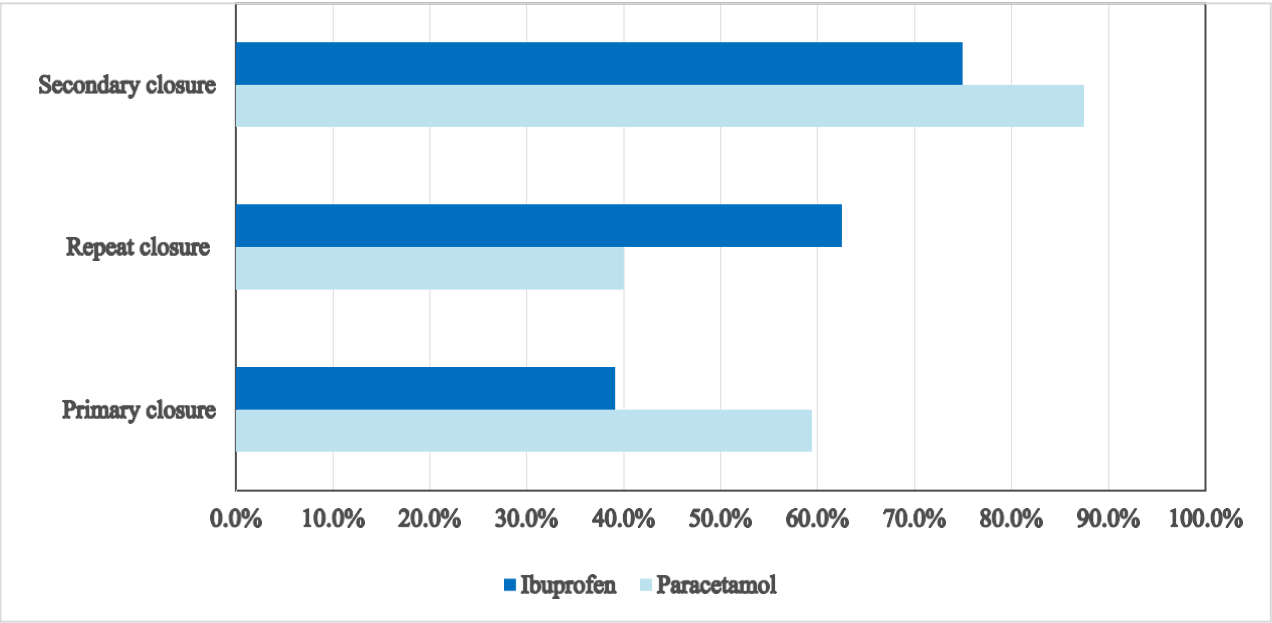

Figure 7. Closure rates (%) between paracetamol and ibuprofen

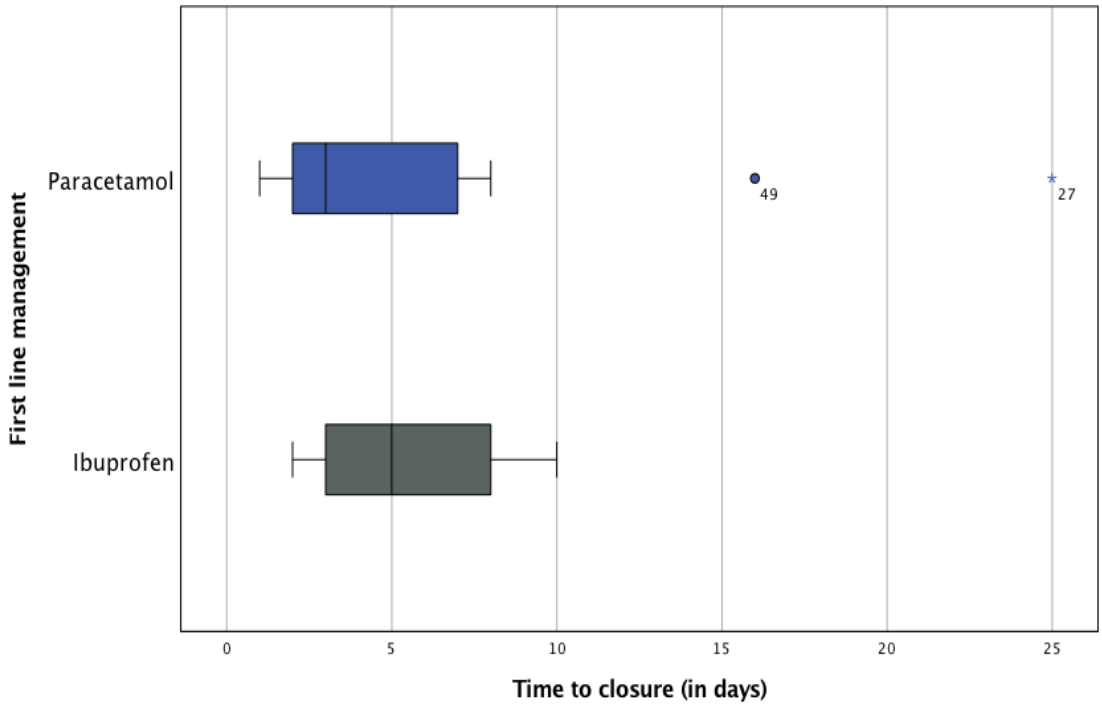

Figure 8. Time to closure (in days) between paracetamol and ibuprofen

v. Adverse effects of hsPDA and medications

The comparison of adverse effects of both hsPDA and the medications between the two drugs in the enrolled infants (n=55) is mentioned in Table 6. The proportion of infants with bronchopulmonary dysplasia (59.4%), intraventricular hemorrhage (71.9%) and necrotizing enterocolitis (9.4%) was higher in the paracetamol subgroup. Only 1 out of 32 infants, developed elevated liver transaminases after treatment with paracetamol. The proportion of infants with feeding intolerance (17.4%), acute kidney injury (13.0%) and platelet dysfunction (13.0%) was higher in the ibuprofen subgroup. The proportion of infants affected with retinopathy of prematurity was similar in both groups (paracetamol 68.8% versus ibuprofen 60.9%). As the P value for all the adverse events was >0.05, the occurrence of adverse events was similar in paracetamol and ibuprofen groups as no statistically significant difference was observed among the 2 groups.

Adverse event	**Paracetamol (n= 32)**	**Ibuprofen (n=23)**	***P* value**
Bronchopulmonary dysplasia, % (n)	59.4% (19)	34.8% (8)	0.102
Retinopathy of prematurity, % (n)	68.8% (22)	60.9% (14)	0.577
Intraventricular hemorrhage, % (n)	71.9% (23)	56.5% (13)	0.264
Feeding intolerance, % (n)	9.4% (3)	17.4% (4)	0.686
Necrotizing enterocolitis, % (n)	9.4% (3)	0	0.257
Acute kidney injury, % (n)	6.3% (2)	13.0% (3)	0.639
Deranged liver transaminases, % (n)	3.1% (1)	0	0.392
Platelet dysfunction, bleeding tendency, % (n)	3.1% (1)	13.0% (3)	0.298

Table 6. Comparison of adverse events between paracetamol and ibuprofen groups

The comparison of the adverse events between the two groups is also demonstrated in Figure 9.

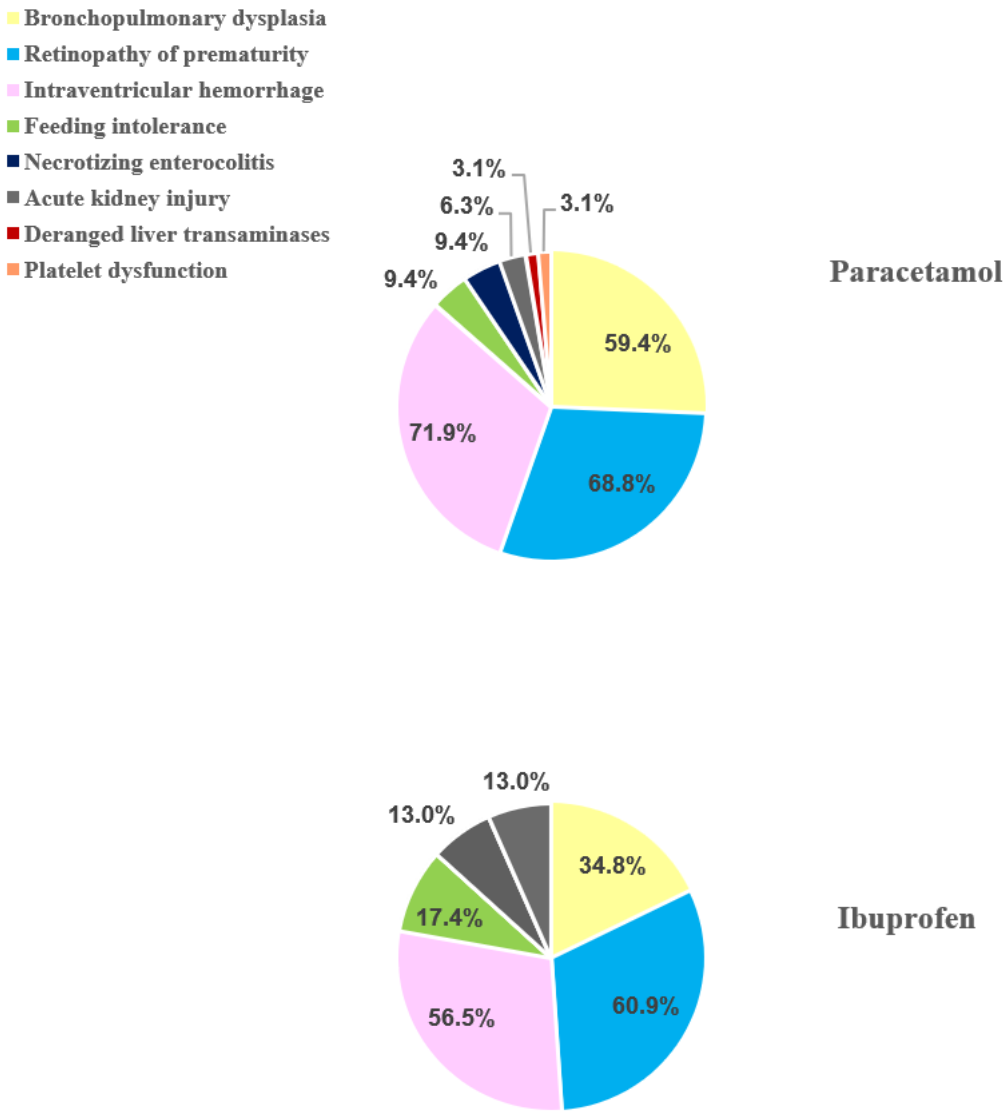

Figure 9. Occurrence of adverse events between paracetamol and ibuprofen groups

Discussion

NSAIDs (indomethacin and ibuprofen) have been the standard medical therapy for PDA closure. Both are successful in promoting ductal closure in 70–80 % of cases. However, these drugs can cause severe adverse effects, inducing the development of gastrointestinal perforations, acute renal failure, and bleeding disorders.

Administration of oral or intravenous paracetamol (acetaminophen) has recently gained attention, appearing as effective as traditional nonsteroidal anti-inflammatory drugs (NSAIDs) in PDA closure, with lower toxicity. Several studies, both RCTs and observational studies, comparing the efficacy and

safety profile of paracetamol and ibuprofen have been reported. In this study, we assessed the efficacy of paracetamol in comparison with ibuprofen for the treatment of hsPDA in preterm infants and we found that paracetamol had similar efficacy to ibuprofen. The results of our study demonstrated that the primary closure rate after single course of paracetamol was higher compared to those treated with ibuprofen (59.4% vs. 39.1%; respectively, P = 0.176) and the closure rate after repeated courses of paracetamol was found to be lower compared to that of ibuprofen (40.0% vs. 62.5%; P = 0.637). We also found that the secondary closure rate of paracetamol after failing treatment with single/repeat course of ibuprofen was higher compared to those in whom ibuprofen was given after failing treatment with single/repeat course of paracetamol (87.5% vs. 75.0%; P = 0.584). However, the difference between the closure rates was statistically insignificant which shows that paracetamol is not superior or inferior to ibuprofen and both have similar efficacy in closing hsPDA. Additionally, the re-opening rate of the PDA was similar (10.0% vs. 16.7%; P = 0.931) in infants both in the paracetamol and ibuprofen groups, as the need for surgical ligation (18.75% vs. 13%; P = 0.720).

Dang et al (6), Oncel et al(10) and Bagheri et al (5) are randomized controlled trials comparing the efficacy of oral paracetamol versus oral ibuprofen, conducted in the year 2013, 2014 and 2016, respectively. The rates of primary closure between paracetamol and ibuprofen were reported as 81.2% versus 78.8% (95% CI [−0.080,0.128]), 72.5% versus 77.5% (P= 0.6) and 82.1%

versus 75.8% (P=0.38) by Dang et al (6, Oncel et al(10) and Bagheri et al (5) , respectively. These trials reported that paracetamol and ibuprofen have similar efficacy for closure of hsPDA, which is similar to the findings of our study. Similarly, Karabulut et al .(20), a retrospective cohort study conducted in 2019, also found that both drugs have similar efficacy. Dani et al.(20) conducted an RCT in 2016 that compared IV paracetamol and IV ibuprofen and they resulted that paracetamol was less effective in closing hsPDA than ibuprofen, however, it had similar constriction rate to ibuprofen, which resulted in similar outcomes between the two groups of either closed PDA or not hemodynamically significant PDA.

The time to primary closure (3 days vs. 5 days, P = 0.686) and the time to definitive closure (45 days vs. 45 days, P = 0.543) was also similar between the paracetamol and ibuprofen groups. Among the 3 infants in the paracetamol subgroup in whom PDA reopened, the PDA reopened in 2 infants after primary closure and in 1 infant after secondary closure with ibuprofen. All these 3 infants were followed in the outpatient clinic after discharge. There was spontaneous closure of PDA in 2 of them and 1 of them underwent transcatheter PDA closure at 2 years of age. In the ibuprofen subgroup, the PDA reopened in 2 infants. In one of them, the reopened PDA was successfully closed after second

line treatment with paracetamol and the other infant underwent transcatheter PDA closure at 3 years of age. In comparison, the proportion of infants where the PDA reopened after initial closure (n=12) in the ibuprofen subgroup was 16.7% (n=2). In one of them, the reopened PDA was treated with paracetamol as second line therapy.

We also compared the primary closure rate between oral and IV paracetamol, was 70.0% (n=14) versus 41.6% (n=5), respectively, with p value of 0.114. This suggests that there is no significant difference of closure rates between the two groups. Our results agree with the previous findings of Hossain et al.(22) that showed that the rates of PDA closure are similar between the two groups.

Out of the 42 infants who had gestational age less than 28 weeks, 85.7% (n=36) failed first line treatment with single/repeat courses of either drug and 25% (n=2) failed second line treatment. Among the 9 patients who underwent surgical ligation, 8 of them had gestational age less than 28 weeks. These results confirm previous findings that hsPDA occurrence is inversely related to gestational age probably due to the increase of DA reactivity to oxygen and decrease of circulating vasodilator concentration occurring as gestational age progresses.

Regarding the safety profile of the medications, our study also compared the rate of adverse events between the two drugs. The proportion of infants with bronchopulmonary dysplasia, intraventricular hemorrhage and necrotizing enterocolitis was higher in the paracetamol subgroup. Only 1 out of 32 infants, developed elevated liver transaminases after treatment with paracetamol. The proportion of infants with feeding intolerance, acute kidney injury and platelet dysfunction was higher in the ibuprofen subgroup. However, no statistically significant difference was observed among the 2 groups and the occurrence of adverse events was similar in both drugs. These results are similar to findings of Dani et al.(6) and Karabulut et al.(20), who also found no significant different in adverse events between the two groups. Dang et al.(11) and Oncel et al(10), reported significantly lower incidence of adverse events in the paracetamol group.

Limitations

Firstly, the limitations of our study included the sample size, as a larger sample is needed to have more statistical and clinical significance of the results. Secondly, our study is a retrospective cohort study which can cause inaccuracy in obtaining the historical data and can cause way for selection or memory bias to occur in the results. Additionally, for the purpose of assessing the efficacy and safety profile between two treatment groups, some key statistics such as pharmacokinetics, relative risk and intention to treat cannot be measured. Another limitation is that our echocardiographic criteria for hsPDA

diagnosis (i.e., left atrium-to-aortic root ratio > 1.4 or a ductal size > 1.5 mm), although they are widely diffused, may have significant variability between observers. The incidence of safety outcomes such as acute renal failure might be insufficient to detect any significant difference between the paracetamol and ibuprofen groups at given small sample size.

Conclusion

The use of paracetamol as an effective and safer alternative to ibuprofen for the first line management of hsPDA in preterm infants, has been established in several studies. Our study also showed that paracetamol is as effective as ibuprofen for the closure of hsPDA in preterm infants. In addition, both drugs had similar safety profile, with the finding of deranged liver enzymes in only 1 patient after treatment with paracetamol. Hence, our study concludes that paracetamol can be used as first line therapy for management of hsPDA as the efficacy and safety profile is comparable to ibuprofen.

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