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# Safety and Efficacy of Oral Paracetamol Versus Oral Ibuprofen in Closure of Pda Among Premature Neonates Admitted to Neonatal Care Unit in Al-Ramadi Teaching Hospital for Maternity and Childhood

**[1]Khamees M. Al-Dulaimy, [2]Saif Farooq Noori, [3]Wael Wajeeh Al.Rawi**
Al-Ramadi Teaching Hospital for Maternity and Childhood

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**KEYWORDS**
Patent Ductus Arteriosus, paracetamol, ibuprofen, preterm, neonate.

**ABSTRACT**:
Patent ductus arteriosus (PDA) is one of the most common congenital heart defects in preterm neonates. In the last years, paracetamol has been proposed for the treatment of PDA. The aim of this study was to evaluate the efficacy and safety of oral paracetamol in the closure of the Patent Ductus Arteriosus in preterm infants and to compare it with oral ibuprofen. A randomized controlled trial study was conducted in the neonatal care unit (NCU) at Al-Ramadi Teaching Hospital for Maternity and Childhood with 46 preterm children, divided into two groups. The first included 23 children treated with oral ibuprofen. The second included 23 children treated with oral paracetamol, were randomly assigned to receive either oral paracetamol or ibuprofen. After the initial treatment course in both groups, the need for a second course was determined by echocardiographic evaluation This study was extended throughout 2021 from 1st of January to 1st of July. Paracetamol after 1st course of treatment was able to achieve a success rate of (17 cases 73.9%) against the success rate of ibuprofen treatment, which reached (18 cases 78.3%), but without significant difference between the two treatments P = 0.823. this result demonstrating that the effectiveness of paracetamol treatment was not inferior to that of ibuprofen. In fact, the incidence of gastrointestinal bleeding in the paracetamol group (0 case 0%) was significantly lower than that of the ibuprofen group (4 cases 17.4%) with significant association found between both groups (P= 0.045) .This comparison of drug efficacy and safety profiles in premature infants with PDA revealed that oral paracetamol was comparable to ibuprofen in terms of the rate of ductal closure and even showed a decreased risk of gastrointestinal bleeding. Therefore, paracetamol may be accepted as a first-line drug treatment for PDA in preterm infants.

## Introduction

Patent ductus arteriosus (PDA) is one of the most common congenital heart defects. A PDA, defined as failure of the ductus arteriosus (DA) to close within 72 hours after birth[1].PDA is associated with 4- to 8-fold increase in the mortality of preterm infants [2]. Potential complications of a persistently patent DA after birth include heart failure, renal dysfunction, necrotizing enterocolitis (NEC), intraventricular hemorrhage, and altered postnatal nutrition and growth[3,4]. In addition, PDA is a risk factor for the development of chronic lung disease (CLD)[5].The reported incidence of PDA in term neonates is only 1 in 2,000 births, accounting for 5%–10% of all congenital heart disease[6]. The incidence of PDA in preterm neonates is far greater, with reports 30% (depending on population and diagnostic criteria)[3]. The increased incidence of PDA in the preterm infant is attributable to the lack of normal closure mechanisms due to immaturity[7]. Gestational age and weight are intimately linked to PDA in preterm neonates. Specifically, PDA is present in 80% of infants weighing less than 1,200 g at birth, compared to 40% of infants weighing less than 2,000 g at birth[1].

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Furthermore, symptomatic PDA is present in 48% of infants with a birth weight of less than 1,000 g [8].

Approximately 80% of preterm infants presenting with respiratory distress syndrome (RDS) also have a PDA, which may be due to the increased circulating prostaglandins (PGE2) associated with RDS.[2] Several birth factors have been shown to increase the incidence of PDA, including high altitude at birth, genetic factors, and in utero exposure to rubella.[9,10] For reasons that have not been elucidated, PDA is more common among female infants than males (2:1).[2]

Hemodynamically significant PDAs have been associated with significant morbidity and mortality, which can be as high as 30%.[2]

The Pathophysiology of DA is derived from the distal dorsal sixth aortic arch and is completely formed by the eighth week of gestation.[6]

The patency of the DA is primarily controlled by low fetal oxygen tension and the circulation of prostanoids produced from the metabolism of arachidonic acid by COX, with PGE2 producing the most profound ductal relaxation among the prostanoids.[12,13]

The main provider of nutrients to the DA is the lumen; however, the vasa vasorum is also a substantial provider to the outer wall of the ductus. The vasa vasorum grows toward the lumen and extends 400–500 μm from the outer wall of the ductus. The distance between the lumen and the vasa vasorum (40–500 μm) is referred to as the avascular zone and represents the maximum distance allowable for effective nutrient diffusion. In full-term infants, this avascular zone is expanded beyond the effective diffusion distance, therefore contributing to cell death. In preterm infants, the avascular zone does not sufficiently expand, resulting in cell survival and maintenance of ductal patency. If the levels of circulating PGE2 and other prostaglandins are decreased through COX inhibition, closure is facilitated. In response to the nutritional deficit and ischemic hypoxia, vascular endothelial growth factor and transforming growth factor beta (both of which contribute to endothelial proliferation), in combination with other inflammatory mediators, contribute to the remodeling of the DA into the non-contractile ligament commonly referred to as the ligamentum arteriosum.[12]

Diagnostic and laboratory testing further enhances the clinical picture. Either left or right ventricular hypertrophy, or both, may be revealed with an electrocardiogram (ECG); however, this is dependent on the degree of left-to-right shunting, and ECG does not provide any information on ductal-dependent lesions. Additionally, cardiomegaly and increased pulmonary markings are often appreciated with chest radiography.

Symptoms are dependent on the size of the ductus, which also dictates the degree of left-to-right shunting. Infants with small PDAs may exhibit minimal or no symptoms.

Three main strategies are currently available to neonatologists to treat PDAs in preterm infants: fluid restriction and “watchful waiting”; pharmacologic management; and surgical ligation , each option has its advantages and disadvantages.

A conservative approach to the treatment of PDA involves fluid restriction and “watchful waiting.” Diuretics lack evidence justifying routine use, but they may be useful if the neonate is exhibiting signs of CHF while waiting for spontaneous closure of the DA.[26] The loop diuretic furosemide may contribute to patency of the DA through renal stimulation of renal PGE2. There have not been sufficient studies addressing this concern; however, a meta-analysis demonstrated an increase in treatment failure by 7% with use of furosemide, although this did not reach statistical significance[27] Advantages to the “watch-and-wait” approach include limiting the infant's exposure to a pharmacologic agent that may have significant side effects and avoiding the risk of surgery. This is a viable option in some cases, considering that approximately 34% (42 of 122 neonates) of extremely low birth weight preterm infants (≤ 1,000 g; estimated gestational age 26 ± 2 weeks) with a PDA demonstrated spontaneous closure at 4.3 ± 2 days postnatal age in a recent study by Koch et al.[4]

The major drawback to this conservative treatment modality is the potential diminished efficacy of alternate treatment options, particularly pharmacologic management with COX inhibition. In the same study cited above, 68 of 80 preterm infants with a persistent PDA were treated with indomethacin 6.2 ± 4 days postnatally. The failure rate was 41%, suggesting that earlier treatment might be associated

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with improved outcomes in extremely low birth weight neonates.

Although COX-2 is intrinsic to the DA, studies have shown that PGE2 derived from COX-1 predominates in the maintenance of patency of the DA. Based on the literature to date, non-selective COX inhibitors are the treatment of choice for pharmacologic closure of PDA.[13]

Currently, there are 2 United States Food and Drug Administration (FDA)-approved nonselective COX inhibitors indicated in the closure of PDAs. Both IV indomethacin and IV ibuprofen lysine are equally effective in the closure of PDA, achieving closure rates of 75%-93%.[28]

More recently, oral or iv administration of paracetamol (acetaminophen) gained attention in PDA treatment; the first case report on this topic has been published by Hammerman et al. on 2011 [29, 30]. Successively, this drug has been evaluated through many trials as safe and effective compared to traditional NSAIDs in PDA closure, with fewer side effects [31].

Before paracetamol introduction, in case of contraindication for NSAIDs, such as active or recent intracerebral hemorrhage (<48 h), thrombocytopenia (<50,000/mm3), bleeding diathesis (meaning INR > 1.5 and/or hematuria, blood in the stool, tracheal secretions or at the injection site), sepsis, NEC, intestinal perforation, pulmonary hemorrhage, hepatic damage with severe hyperbilirubinemia, renal dysfunction (oliguria <1 ml/kg/h also after adequate hydration, serum creatinine >110–140 µmol, and BUN > 14 mmol/l), and hypersensitivity to ibuprofen [32], the only available solution was surgical ligation with all the connected risks [33].

However, further studies are needed before this drug can be recommended as first-line therapy; long-term outcomes of treatment and its possible late side effects at 18 or 24 months of postnatal age must be fully clarified [34].

Yang et al. [35] demonstrated a probably higher renal safety of this drug describing a significantly lower reduction in PGE2 urinary excretion and minor incidence of oliguria comparing two groups of infants treated with paracetamol versus ibuprofen.

These advantages would be related to the different drug mechanism of action, because paracetamol is not a classical NSAID, having only a weak antiplatelet and anti-inflammatory activity. It exerts mainly central effects (analgesic, antipyretic) and reduces the synthesis of prostaglandins through the inhibition of prostaglandin synthetase (PGHS), as it happens with NSAIDs, but acting in a different enzyme site, called peroxidase region (POX) [36].

However, some hepatic side effects have been described after iv paracetamol administration, which may determine a transient increase in liver enzymes concentration [37] or, according to other studies, more serious acute liver toxicity events [38].

Hepatotoxicity in neonates is not determined directly by paracetamol itself but can be caused by N-acetyl-p-benzoquinone imine (NAPQI) metabolite production by hepatic cytochrome P450 (CYP)-dependent mixed function oxidase enzyme. The mechanisms of NAPQI formation, sulphate elimination, and glucuronide production rate are still not exactly known in preterms [39].

The hepatic paracetamol metabolism occurs through sulphation, glucuronidation, and oxidation. Administering therapeutic doses of paracetamol, glucuronidation, or sulphation is activated as first mechanism, producing nontoxic metabolites. Also hepatic oxidation of paracetamol by CYP1A2, 3A4, and 2E1 generates the highest reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) which is conjugated by glutathione into a renal metabolite that becomes safe. Instead, after an excessive dose of paracetamol, sulphation and glucuronidation pathways saturate and the resulting excessive dose of NAPQI consumes glutathione reserves becoming toxic [40]. It is well known that, in adults, the toxic paracetamol dose is about ten times higher than therapeutic concentration and paracetamol metabolism changes with the growth [41]; further evaluations could allow us to fully understand the extremely premature neonates metabolism [40].

It is described that neonates show an extremely variable glucuronidation rate and a limited ability for glutathione conjugation [42], with the predominance of sulphation [43], and that CYP is expressed early in postnatal life in full-term neonates while this is not well known in preterms [44].

However, clinical evidence shows a low or absent hepatic toxicity in neonates, suggesting the existence of a large therapeutic serum concentration range for paracetamol [45].

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This could depend on some mechanisms that seem to protect neonates in case of overdose such as slow oxidative metabolism and slow hepatic production of toxic metabolites and high rate of glutathione synthesis [46].

N-acetylcysteine can detoxify NAPQI and becomes safe in neonates, so that it is used in case of subtoxic serum paracetamol concentration [47] but there are no studies investigating its administration in PDA treatment [48].

For this lack of clear information about neonatal paracetamol metabolism, Cook et al. [39] performed a population pharmacokinetic model in order to define intravenous paracetamol effects and toxicity determinants and successively evaluated its predictive value with the aim of generalizing this knowledge to the whole neonates population. Their results evidenced that body weight (instead of gestational age, postmenstrual age, and unconjugated bilirubin levels) represents the principal predictor of intravenous paracetamol pharmacokinetics and the only covariate showing the adequate features to be included in the final proposed model, influencing both clearance and volume of drug distribution. According to these findings, the author suggests that the use of a parsimonious intravenous paracetamol dosage based on equivalent per kilogram (in all neonates, from extremely preterms to full-term newborns) could accommodate pharmacokinetics maturational changes, without the necessity to modify dosages and administration times according to gestational or postmenstrual age, as previously proposed by other studies. Cook et al. [39] also conclude with the observation that further studies will confirm if this simplified regimen really becomes unable to induce hepatotoxicity in all subcategories of neonates, considering the limited number of participants to the mentioned study but also the poor available knowledge about the real drug pharmacodynamics in neonates [39].

Serum paracetamol levels were evaluated in three studies of PDA management. In the study of Oncel et al. [49], these became 7.3 mcg/mL, 15.5 mcg/mL, and 14.7 mcg/mL during the three days of therapy. In the study of Yurttutan et al. [50], serum paracetamol levels after 24 h from administration became lower than 18 mcg/mL [51].

Härkin et al. [52] analyzed 87 serum samples from 21 paracetamol treated patients and detected concentrations lower than 25.2 mg/L, without relevant accumulation. All these values resulted in therapeutic range for children (10–30 mcg/mL) [51].

To examine the possible side effects of this drug, treated patients should be evaluated for alimentation disturbances, abdominal distension, oliguria, hypertension, and renal and hepatic functionality both during and after the treatment, also considering long-term consequences of clinical and subclinical side effects [53].

According to Tan and Baral [54], acetaminophen protein adducts or long chain acylcarnitines can be considered sensitive biomarkers helpful in monitoring the occurrence of potential hepatotoxic effects.

The effects of prophylactic paracetamol administration on PDA closure have been retrospectively evaluated by Aikio et al. [55] on 102 neonates born with <32 weeks of GA, demonstrating a reduction in PDA incidence from 30,7% to 14,7% after paracetamol introduction before the age of 72 hours of life, without an increase in adverse effects. However, more studies are needed to attest efficacy and safety of early PDA closure with paracetamol [55].

The aim of this study was to evaluate the efficacy and safety of oral paracetamol in the closure of the Patent Ductus Arteriosus in preterm infants and to compare it with oral ibuprofen at Neonatal Care unit at Al-Ramadi Teaching Hospital for Maternity and Childhood.

## Patients and Methods

### Study Design, Setting and Data Collection Time

A randomized controlled trial study was done on neonates admitted to the neonatal care unit in Al-Ramadi Teaching Hospital for Maternity and Children, Al Ramadi city, Anbar governorate west of Iraq from 1st of January to 1st of July 2021.

### Study patients and number of patients

All studied neonates were preterm with gestational age less than 37 week. A sample size of 46 neonates would be enrolled.

The study was done on two groups of preterm babies, group A and group B , neonate were randomly assigned and put into two groups by computer-generated random numbers.

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All studied babies were diagnosed with echocardiography test as having patent ductus arteriosus.

Before giving treatment, each case had done liver function test (LFT), renal function test (RFT), complete blood picture (CBC) and head ultrasound.

**Group A** was treated with giving them ibuprofen (piofen™ 200mg/5ml "Pioneer company") orally for three days administered in a dose of 10 mg per kg per dose /day on day 1 and 5 mg per kg per dose/day at 24 and 48 hours from the first dose (total 3 doses)[61].

**Group B** were giving oral paracetamol (Panadol™ 120mg/5ml "GSK company") for three days administered in a dose of 15 mg per kg per dose every 6 hours for 3 consecutive days [62].

All cases receive the same drug company for both drugs oral paracetamol or oral ibuprofen given by NG feeding by medical doctor.

Postnatal aged of neonate at starting of treatment was ranging from 4 - 7 days.

Repeated echocardiography was done after three days of giving the drugs to the two groups to show the closure rate of the PDA.

In cases with failure of closure, another trial therapy in the same doses for three days was given, another echocardiography was done after three days form starting second course to show the closure rate of PDA.

In cases with failure of closure after complete second course of treatment surgical ligation may be considered according to hemodynamically significant PDA .

Cases with PDA that was chosen for closure was according to Presence of a haemodynamically significant PDA .

haemodynamically significant PDA (hsPDA)[63] is defined if any one of the below-mentioned clinical/biochemical sign is present in the presence of a PDA with a transductal diameter of ≥1.6 mm (or) in the presence of any one of the below-mentioned echocardiographic sign suggestive of haemodynamic significance even in the absence of any of the below-mentioned clinical/ biochemical sign.

- ❖ signs of significant left→right shunt: hyperdynamic pulsatile precordium, bounding peripheral pulses and wide pulse pressure (>25 mm Hg)
- ❖ signs of systemic underperfusion: poor peripheral pulse volume, prolonged capillary refill time, decreased urine output, deranged renal function test, metabolic acidosis and hypotension
- ❖ signs of pulmonary overperfusion: abnormal weight gain, increase in liver size, 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 haemorrhagic pulmonary oedema

Echocardiographic features indicative of hsPDA [63]:

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

►► Evidence of left atrial enlargement (Left atrium: Aortic root diameter ratio ≥1.4)

►► Ductal velocity <2 m/s

►► Antegrade main pulmonary artery (MPA) diastolic flow >20 cm/s

►► E wave: A wave ratio >1

►► Isovolemic relaxation time (IVRT) ≤45 ms

►► Absent or reversed diastolic blood flow pattern in descending thoracic aorta.

**Data collection tool**

A list of information was taken from each studied case and recorded in a special prepared paper include:

1.Gestational age. 2.Gender. 3.Birth weight. 4.Type of delivery. 5.Patient clinical condition.

6.Size of PDA, (tiny, small, Moderate, or large). 7.Closure rate for each group in both trials.

8. Side effects of using both drugs (gastrointestinal perforation or bleeding, necrotizing enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage, thrombocytopenia, hepatic or renal dysfunction, etc..).

**Exclusion criteria**

1. Patent ductus dependents patients.

2. Contraindication for enteral feeding.

3. Contraindication for administration of any one of the study drugs such as blood urea >60 mg/dL, serum creatinine level >1.6 mg/ dL, platelet count <60 x 109/L, clinical bleeding from any site, deranged coagulogram, clinical or radiological evidence of necrotizing enterocolitis, intraventricular hemorrhage, and hyperbilirubinemia within 2 mg/dL from the exchange transfusion cut-off value.

**Ethical approval**

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1- Permission (Informed consent) was obtained from the parents or family member accompanying the patients, clarifications and basic orientation on the objectives of the study were given beforehand. All information's were anonymous. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes.

2- The council of Arab Board of Health Specialization.

3- Approval and agreement from AL Ramadi teaching hospital for maternity and childhood.

**Statistical Analysis**

The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables between study groups. Chi square test was used to assess the comparison between study groups in certain information, while fisher exact test was used instead when the expected frequency was less than 5. A level of P – value less than 0.05 was considered significant.

**Results**

The total number of study patients was 46. All of them were preterm neonates diagnosed with PDA by echocardiography and divided into two groups: group A (ibuprofen group) included 23 patients received ibuprofen suspension, group B (Paracetamol group) included 23 patients received paracetamol suspension.

**General characteristics**

The distribution of study patients by general characteristics is shown in figure and table (3.1). Study patients' gestational age was ranging from 32 – 36 weeks with a mean of 34.13 weeks and a standard deviation (SD) of ± 2.1 weeks. The highest proportion of study patients in paracetamol and ibuprofen groups was delivered at GA > 32 weeks (87% and 74% respectively). Regarding gender, 56.5% of paracetamol group were females; while 56.5% of ibuprofen group were males. In paracetamol group, 52.2% had birthweight < 2.5 kg and 60.9% of them were delivered by C/S. In ibuprofen group, 78.3% had birthweight < 2.5 kg and 52.2% of them were delivered by NVD.

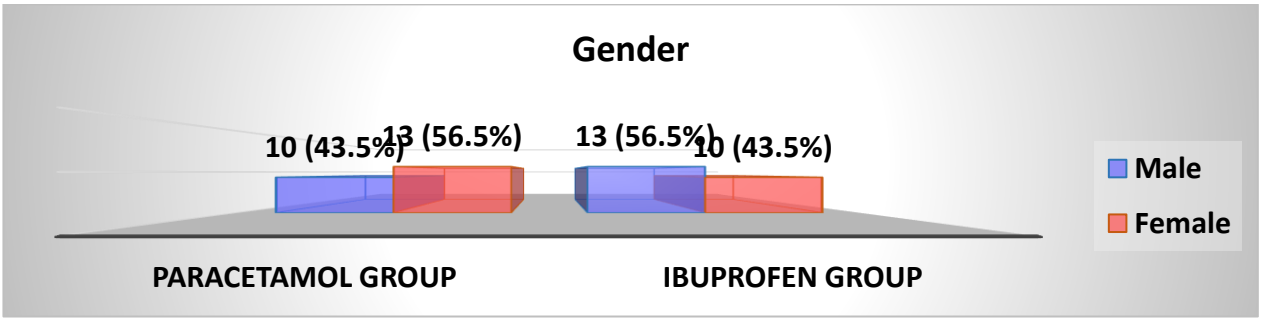


**Figure 1:** Distribution of study groups by gender

**Table 3:** Distribution of study groups by general characteristics

| General Characteristics | Study Groups | | Total (%) n= 46 | P - Value |
|---|---|---|---|---|
| | Paracetamol (%) n= 23 | Ibuprofen (%) n= 23 | | |
| **GA (Weeks)** | | | | |
| **≤ 32** | 3 (13.0%) | 6 (26.0%) | 9 (19.6%) | 0.317 |
| **> 32** | 20 (87.0%) | 17 (74.0%) | 37 (80.4%) | 0.624 |
| **Birthweight (Kg)** | | | | |
| **< 2.5** | 12 (52.2%) | 18 (78.3%) | 30 (65.2%) | 0.273 |
| **≥ 2.5** | 11 (47.8%) | 5 (21.7%) | 16 (34.8%) | 0.133 |

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|---|---|---|---|---|
| **Mode of delivery** | | | | |
| **NVD** | 9 (39.1%) | 12 (52.2%) | 21 (45.7%) | 0.51 |
| **C/S** | 14 (60.9%) | 11 (47.8%) | 25 (54.3%) | 0.548 |

In comparison between study groups, mean of birthweight was significantly lower in ibuprofen group than that in paracetamol group (2.07 ± 0.38 versus 2.45 ± 0.41 kg , P= 0.002).

No statistical significant difference in GA between study groups (P= 0.067).

**Table 4 :** Comparison between study groups by certain characteristics

| **Variable** | **Study groups** | | **P - Value** |
|---|---|---|---|
| | **Paracetamol Mean ± SD** | **Ibuprofen Mean ± SD** | |
| **GA (Week)** | 34.69 ± 1.8 | 33.56 ± 2.3 | **0.067** |
| **Birthweight (Kg)** | 2.45 ± 0.41 | 2.07 ± 0.38 | **0.002** |

**Size of PDA**

Table 3.3 shows the comparison in size of PDA between study groups. We noticed that the highest proportion of study patients in both groups had small PDA (( 43.5% in paracetamol group (group B ) and 56.5% in ibuprofen group (group A) )) and this difference in percentage was statistically not significant (P= 0.531).

**Table 5 :** Distribution of study groups by size of PDA

| Size of PDA | Study Groups | | Total (%) n= 46 | P - Value |
|---|---|---|---|---|
| | **Paracetamol (%) n= 23** | **Ibuprofen (%) n= 23** | | |
| Tiny | 4 (17.4%) | 3 (13.0%) | 7 (15.2%) | 0.706 |
| Small | 10 (43.5%) | 13 (56.5%) | 23 (50.0%) | 0.531 |
| Moderate | 6 (26.1%) | 5 (21.7%) | 11 (23.9%) | 0.764 |
| Large | 3 (13.0%) | 2 (8.7%) | 5 (10.9%) | 0.654 |

**Closure of PDA**

Comparison between study groups by closure of PDA after 1st trial of drugs is shown in table (3.4). After 1st trial of drug, PDA was closed in 73.9% of paracetamol group and in 78.3% of ibuprofen group and this difference in percentage was statistically not significant (P= 0.823).

**Table 6 :** Comparison between study groups by PDA closure after 1st trial of drugs

| **Status of PDA after 1st trial** | | **Study Groups** | | **Total (%) n= 46** | **P - Value** |
|---|---|---|---|---|---|
| | | **Paracetamol (%) n= 23** | **Ibuprofen (%) n= 23** | | |
| **Closed** | | 17 (73.9) | 18 (78.3) | 35 (76.1) | **0.823** |
| **Not closed** | **Tiny** | 2 (8.7) | 3 (13.0) | 5 (10.9) | **0.654** |

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| | | | | | |
|---|---|---|---|---|---|
| | **Small** | 4 (17.4) | 2 (8.7) | 6 (13.0) | 0.413 |
| | **Moderate** | 0 (0%) | 0 (0%) | 0 (0%) | 1 |
| | **Large** | 0 (0%) | 0 (0%) | 0 (0%) | 1 |

After 2nd trial of drugs, PDA of all patients in both groups were closed.

**Side effect**

In the current study, no side effects detected among patients of paracetamol group; while 17.4% of patients in ibuprofen group showed side effects and this difference was statistically significant (P= 0.045)

There is no any death during this study and any case who leave the study was excluded and not enter the study.

**Table 7 :** Comparison between study groups by side effect

| **Side effect** | | **Study Groups** | | **Total (%) n= 46** | **P - Value** |
|---|---|---|---|---|---|
| | | **Paracetamol (%) n= 23** | **Ibuprofen (%) n= 23** | | |
| **No Side effect** | | 23 (100.0%) | 18 (78.3%) | 41 (89.1) | 0.435 |
| **Side effect** | **gastrointestinal bleeding** | 0 (0%) | 4 (17.4%) | 4 (8.7) | **0.045** |
| | **Elevation in RFT** | 0 (0%) | 1 (4.3%) | 1 (2.2) | 0.317 |
| | **Elevation in LFT** | 0 (0%) | 0 (0%) | 0 (0%) | 1 |

**DISCUSSION**

In the current study, 46 neonates were enrolled. All of them were diagnosed with Patent ductus arteriosus (PDA) and divided into two groups: 23 patients received ibuprofen suspension (ibuprofen group or group A) and 23 patients received paracetamol suspension (paracetamol group or group B).

In the current study, mean and a standard deviation (SD) of gestational age was 34.13 ± 2.1 weeks (ranging from 32-36 weeks). The highest proportion in paracetamol and ibuprofen groups was delivered at GA > 32 weeks (87% and 74% respectively). Regarding gender, 56.5% of paracetamol group were females; while 56.5% of ibuprofen group were males. In paracetamol group, 52.2% had birthweight < 2.5 kg and 60.9% of them were delivered by C/S. In ibuprofen group, 78.3% had birthweight < 2.5 kg and 52.2% of them were delivered by NVD.

In this study and by comparison between study groups, mean of birthweight was significantly lower in ibuprofen than that in paracetamol group (P= 0.002). No significant difference in GA between study groups (P= 0.067).

Regarding the size there was no statistically significant difference between pre- and post-treatment PDA size in both groups as regard ECHO findings after 1st course (73.9% in paracetamol group and 78.3% in ibuprofen group) (P= 0.823). and after the 2nd course all the cases in both groups were closed.

Differently, El-Farrash study in 2019 (Cairo , Egypt) there was no statistically significant difference between both groups as regard ECHO findings after of 1st course of treatment (p>0.05),the mean difference between pre- and post- treatment PDA size was significantly higher in the paracetamol group compared with ibuprofen group after the 2nd course of treatment (p=0.024) [64].

Regarding closure of PDA this study reported after 1st trial of drug, that PDA was closed in 73.9% of paracetamol group and in 78.3% of ibuprofen group and this difference in percentage was statistically not significant (P= 0.823).

After 2nd trial , PDA of all patients were closed.

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In El-Farrash study in 2019 (Cairo , Egypt) , The closure rate of oral paracetamol was comparable to that of oral ibuprofen after the first course of the treatment (66.7% vs. 40%, p=0.272) and after second course of treatment (80.0% vs. 66.7%, p=0.929), with no significant correlation between both treatment group [64]. Huang and colleagues in a study done in 2019 (Zhumadian , China) , concluded that Paracetamol may confer comparable efficacy for PDA closure as ibuprofen, since they observed after five randomize control trails with 677 neonates, that efficacies for the primary ( p = 0.56) and overall PDA closure were comparable between oral paracetamol and oral ibuprofen, with no significant relation between them ( p = 0.62) [65].

Also, in Bagheri study in 2016 (Kerman, Iran) , as reported after the 1st course of treatment, PDA closed in 82.1 % patients who received oral paracetamol vs. 75.8 % of those given oral Ibuprofen, despite non-significant relation between both groups (P=0.38). After 2n course, PDA closed in 50 % of oral paracetamol group and 73.3% of oral Ibuprofen group, with no significant relation between both groups (P= 0.21). Finally, closure rates after two courses were 91% in oral paracetamol and 90.3% in oral Ibuprofen group [66]. Moreover, Ibuprofen and Paracetamol was compared a trial conducted by Oncel study (Ankara, Turkey) compared the efficacy and safety of oral Paracetamol and oral Ibuprofen for the closure of PDA in 90 preterm infants with a gestational age less than or equal to thirty weeks of gestation. After the 1st course of treatment, PDA closed in 77.5% (31 of 45 patients) of infants assigned to oral Ibuprofen group vs. 72.5% ( 29 of 45 patients) in the oral Paracetamol group, with no significant relation between both treatment (P = 0.6) [67]. Finally, Dang and other co-authors (Changchun, China) published a randomized control trial comparing the efficacy of oral ibuprofen and oral paracetamol in the treatment of PDA, they found that, the ductus was closed in 81.2% of infants in paracetamol group compared with 78.8% of the infants in ibuprofen group with no significant difference between the two treatments (p =0.693). After the 1st course of treatment, PDA occurred in 45 infants (56.3%) given oral paracetamol and in (47.5%) received oral ibuprofen (p=0.268) [68].

Regarding side effect in the current study, no side effects detected in paracetamol group; while 17.4% of patients in ibuprofen group had side effects (gastro-intestinal bleeding) , with significant association found between both groups (P= 0.045) .

El-Farrash and colleagues in 2019 (Cairo , Egypt) , observed that all the studied neonates tolerated the received treatment well without side effects. The incidence of oliguria, in Yang study in 2016 (Xuzhou, China) , was less among infants with PDA of the paracetamol group (2.3%) than observed among the PDA in infants of the ibuprofen group (14.0%); however, this difference was not-significant (P=0.108) [69]. Concerning the safety of oral paracetamol, the current results were similar to those of Oncel study in 2014 (Ankara, Turkey) [67], Allegaert study in 2008 (Leuven, Belgium) [70], Yurttutan study in 2013 (Ankara, Turkey) [53], who declared that there were no side effects or signs of hepatic or renal intolerance during and following administration of paracetamol [71].

In Huang study in 2017 (Zhumadian , China) , results showed that PDA neonates that received paracetamol were associated with a trend of reduced risk of renal failure (P<0.07) and a significantly reduced risk of gastro-intestinal bleeding (P<0.009) as compared with those received ibuprofen [65].

### 5.1. Conclusions

The rate of closure of PDA with paracetamol administration was not different from that of oral ibuprofen. In addition, the incidence of side effects was higher in ibuprofen than paracetamol administration.

### References

1. Clyman RI. Ibuprofen and patent ductus arteriosus. New Engl J Med. 2000;343:728-739. [PubMed] [Google Scholar]
2. S. Noori, M. McCoy, P. Friedlich., “Failure of ductus arteriosus closure is associated with increased mortality in preterm infants,” Pediatrics, vol. 123, no. 1, pp. e138–e144, 2009.
3. Thébaud B, Lacaze-Mazmonteil T. Patent ductus arteriosus in premature infants: A never-closing act. Paediatr Child Health [Internet]. 2010 [cited 2022 May 1];15(5):267. Available from: /pmc/articles/PMC2912622/.

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JCHR (2023) 13(4), 352-365 | ISSN:2251-6727

4. Koch J, Hensley G, Roy L. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics. 2006;117:1113–1121. [PubMed] [Google Scholar]
5. Adrouche-Amrani, L., Green, R.S., Gluck, K.M. Failure of a repeat course of cyclooxygenase inhibitor to close a PDA is a risk factor for developing chronic lung disease in ELBW infants. BMC Pediatr 12, 10 (2012). https://doi.org/10.1186/1471-2431-12-10.
6. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation. 2006;114:1873–1882. [PubMed] [Google Scholar]
7. El Hajjar M, Vaksmann G, Rakza T, Severity of the ductal shunt: a comparison of different markers Archives of Disease in Childhood - Fetal and Neonatal Edition 2005;90:F419-F422.
8. Fanaroff AA, Hack M, Walsh MC. The NICHD Neonatal Research Network: changes in practice and outcomes during the first 15 years. Semin Perinatol. 2003;27:281–287. [PubMed] [Google Scholar]
9. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: Current knowledge - A scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young. Circulation [Internet]. 2007 Jun 12 [cited 2022 Apr 13];115(23):2995–3014.Availablefrom: https://www.ahajournals.org/doi/abs/10.1161/circulationaha.106.183216
10. Bernati N, Nova R, Tasli JM, Theodorus T. Risk factors for patent ductus arteriosus in preterm neonates. Paediatr Indones [Internet]. 2014 Jun 30 [cited 2022 Apr 13];54(3):132–6.Availablefrom: https://paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view
11. Ivey KN, Srivastava D. The paradoxical patent ductus arteriosus. J Clin Invest. 2006;166:2863–2866. [PMC free article] [PubMed] [Google Scholar]
12. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol. 2006;26:S14–S18. [PubMed] [Google Scholar]
13. VanOvermeire B, Chemtob S. The pharmacologic closure of the patent ductus arteriosus. Semin Fetal Neonatal Med. 2005;10:177–184. [PubMed] [Google Scholar]
14. Bernard T, Michelakis ED, Wu X. Oxygen-sensitive Kv channel gene transfer confers oxygen responsiveness to preterm rabbit and remodeled human ductus arteriosus: implications for infants with patent ductus arteriosus. Circulation. 2004;110:1372–1379. [PubMed] [Google Scholar]
15. Hamrick SE, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent ductus arteriosus of the preterm infant. Pediatrics. 2020;146(5).
16. Levin M, McCurnin D, Seidner SR. Postnatal constriction, ATP depletion, and cell death in the mature and immature ductus arteriosus. Am J Physiol Regul Integr Comp Physiol. 2006;290:R359–R364. [PubMed] [Google Scholar]
17. Kajino H, Goldbarg S, Roman C. Vasa vasorum hypoperfusion is responsible for medial hypoxia and anatomic remodeling in the newborn lamb ductus arteriosus. Pediatr Res. 2002;51:228–235. [PubMed] [Google Scholar]
18. Kajino H, Chen Y, Chemtob S. Tissue hypoxia inhibits prostaglandin and nitric oxide production and prevents ductus arteriosus reopening. Am J Physiol Regul Integr Comp Physiol. 2000;279:R278–R286. [PubMed] [Google Scholar]
19. Moore P, Brook MM, Heyman MA. Patent ductus arteriosus. In: Allen HD, Gutgesell HP, editors. Moss & Adams' Heart Disease in Infants, Children & Adolescents: Including the Fetus and Young Adults. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. pp. 653–663. eds. [Google Scholar]
20. Zipes DP, Libby P, editors. Braunwald's Heart Disease. In: MACC Douglas P. Zipes, M.D., M.D. Peter Libby, M.D. Robert O. Bonow.A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005. Patent ductus arteriosus; pp. 1511–1513.
21. Sanjeev S, Pettersen M, Lua J. Role of plasma B-type natriuretic peptide in screening for hemodynamically significant patent ductus

arteriosus in preterm neonates. J Perinatol. 2005;25:709–713. [PubMed] [Google Scholar]

22. El-Kuffash A, Molloy EJ. Are B-type natriuretic peptide (BNP) and N-terminal-pro-BNP useful in neonates? Arch Dis Child Fetal Neonatal Ed. 2007;92:320–324. [PMC free article] [PubMed] [Google Scholar]
23. Mann D, Qu JZ, Mehta V. Congenital heart diseases with left-to-right shunts. Int Anesthesiol Clin. 2004;42:45–58. [PubMed] [Google Scholar]
24. Skinner J. Patent ductus arteriosus. Semin Neonatol. 2001;6:49–61. [PubMed] [Google Scholar]
25. Ramesh Arora, Vijayalakshmi IB.Patent Ductus Arteriosus Ramesh. In:IB Vijayalakshmi, P Syamasundar Rao, Reema Chugh. A Comprehensive Approach to Congenital Heart Diseases.1st ed. India; 2013.p307-331.
26. Wyllie J. Treatment of patent ductus arteriosus. Semin Neonatol. 2003;8:425–432. [PubMed] [Google Scholar]
27. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Cochrane Database of Systematic Reviews. 2001. Art. No.:CD001148. DOI: 10.1002/14651858.CD001148. [PubMed]
28. Aranda JV, Thomas R. Intravenous ibuprofen for preterm infants. NeoReviews. 2005;6:e516–e523. [Google Scholar]
29. Terrin G., Conte F., Oncel M. Y., Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: A systematic review and meta-analysis. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2016;101(2):F127–F136. doi: 10.1136/archdischild-2014-307312. [PubMed] [CrossRef] [Google Scholar]
30. Hammerman C., Bin-Nun A., Markovitch E., Schimmel M. S., Kaplan M., Fink D. Ductal closure with paracetamol: A surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011;128(6):e1618–e1621. doi: 10.1542/peds.2011-0359. [PubMed] [CrossRef] [Google Scholar]
31. Dani C., Poggi C., Mosca F., Efficacy and safety of intravenous paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: Study protocol for a randomized control trial. Trials. 2016;17(1, article no. 182) doi: 10.1186/s13063-016-1294-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. Valerio E., Valente M. R., Salvadori S., Frigo A. C., Baraldi E., Lago P. Intravenous paracetamol for PDA closure in the preterm: a single-center experience. European Journal of Pediatrics. 2016;175(7):953–966. doi: 10.1007/s00431-016-2731-9. [PubMed] [CrossRef] [Google Scholar]
33. Rheinlaender C., Helfenstein D., Walch E., Berns M., Obladen M., Koehne P. Total serum bilirubin levels during cyclooxygenase inhibitor treatment for patent ductus arteriosus in preterm infants. Acta Paediatrica, International Journal of Paediatrics. 2009;98(1):36–42. doi: 10.1111/j.1651-2227.2008.01007.x. [PubMed] [CrossRef] [Google Scholar]
34. Allegaert K., Anderson B., Simons S., Van Overmeire B. Paracetamol to induce ductus arteriosus closure: Is it valid? Archives of Disease in Childhood. 2013;98(6):462–466. doi: 10.1136/archdischild-2013-303688. [PubMed] [CrossRef] [Google Scholar]
35. Yang B., Gao X., Ren Y., Wang Y., Zhang Q. Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial. Experimental and Therapeutic Medicine. 2016;12(4):2531–2536. doi: 10.3892/etm.2016.3676. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
36. El-Mashad A. E.-R., El-Mahdy H., El Amrousy D., Elgendy M. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. European Journal of Pediatrics. 2016;176(2):233–240. doi: 10.1007/s00431-016-2830-7. [PubMed] [CrossRef] [Google Scholar]
37. Alan S., Kahvecioglu D., Erdeve O., Atasay B., Arsan S. Is Paracetamol a useful treatment for ibuprofen-resistant patent ductus arteriosus? Neonatology. 2013;104(3):168–169. doi:

10.1159/000352068. [PubMed] [CrossRef] [Google Scholar]

38. Dart R. C., Rumack B. H. Intravenous acetaminophen in the United States: Iatrogenic dosing errors. Pediatrics. 2012;129(2):349–353. doi: 10.1542/peds.2011-2345. [PubMed] [CrossRef] [Google Scholar]
39. Cook S. F., Roberts J. K., Samiee-Zafarghandy S., Population Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) in Preterm and Term Neonates: Model Development and External Evaluation. Clinical Pharmacokinetics. 2016;55(1):107–119. doi: 10.1007/s40262-015-0301-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
40. Rostas S. E., McPherson C. C. Pharmacotherapy for patent ductus arteriosus: Current options and outstanding questions. Current Pediatric Reviews. 2016;12(2):110–119. doi: 10.2174/1573396312021605060028. [PubMed] [CrossRef] [
41. Allegaert K., Anderson B. J., Naulaers G., Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates. European Journal of Clinical Pharmacology. 2004;60(3):191–197. doi: 10.1007/s00228-004-0756-x. [PubMed] [CrossRef] [Google Scholar]
42. Allegaert K., de Hoon J., Verbesselt R., Vanhole C., Devlieger H., Tibboel D. Intra- and interindividual variability of glucuronidation of paracetamol during repeated administration of propacetamol in neonates. Acta Paediatrica. 2005;94(9):1273–1279. doi: 10.1080/0803525051002952. [PubMed] [CrossRef] [Google Scholar]
43. Manyike P. T., Kharasch E. D., Kalhorn T. F., Slattery J. T. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clinical Pharmacology and Therapeutics. 2000;67(3):275–282. doi: 10.1067/mcp.2000.104736. [PubMed] [CrossRef] [Google Scholar]
44. Kearns G. L., Abdel-Rahman S. M., Alander S. W., Blowey D. L., Leeder J. S., Kauffman R. E. Developmental pharmacology - Drug disposition, action, and therapy in infants and children. New England Journal of Medicine. 2003;349(12):1157–1167. doi: 10.1056/NEJMra035092. [PubMed] [CrossRef] [Google Scholar]
45. Jacqz-Aigrain E., Anderson B. J. Pain control: Non-steroidal anti-inflammatory agents. Seminars in Fetal and Neonatal Medicine. 2006;11(4):251–259. doi: 10.1016/j.siny.2006.02.009. [PubMed] [CrossRef] [Google Scholar]
46. Palmer G. M., Atkins M., Anderson B. J., I.V. acetaminophen pharmacokinetics in neonates after multiple doses. British Journal of Anaesthesia. 2008;101(4):523–530. doi: 10.1093/bja/aen208. [PubMed] [CrossRef] [Google Scholar]
47. Beringer R. M., Thompson J. P., Parry S., Stoddart P. A. Intravenous paracetamol overdose: Two case reports and a change to national treatment guidelines. Archives of Disease in Childhood. 2011;96(3):307–308. doi: 10.1136/adc.2010.192005. [PubMed] [CrossRef] [Google Scholar]
48. Oncel M. Y., Erdeve O. Oral medications regarding their safety and efficacy in the management of patent ductus arteriosus. World Journal of Clinical Pediatrics. 2016;5(1):75–81. doi: 10.5409/wjcp.v5.i1.75. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
49. Oncel M. Y., Yurttutan S., Degirmencioglu H., Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. Neonatology. 2013;103(3):166–169. doi: 10.1159/000345337. [PubMed] [CrossRef] [Google Scholar]
50. Yurttutan S., Oncel M. Y., Arayici S., A different first-choice drug in the medical management of patent ductus arteriosus: Oral paracetamol. Journal of Maternal-Fetal and Neonatal Medicine. 2013;26(8):825–827. doi: 10.3109/14767058.2012.755162. [PubMed] [CrossRef] [Google Scholar]
51. Kratz A., Ferraro M., Sluss P. M., Lewandrowski K. B. Case records of the massachusetts general hospital. weekly clinicopathological exercises. laboratory reference values. The New England Journal of Medicine. 2004;351(15):1548–1563. doi:

Journal of Chemical Health Risks

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JCHR (2023) 13(4), 352-365 | ISSN:2251-6727

10.1056/NEJMcpc049016. [PubMed] [CrossRef] [Google Scholar]

52. Härkin P., Härmä A., Aikio O., Paracetamol Accelerates Closure of the Ductus Arteriosus after Premature Birth: A Randomized Trial. Journal of Pediatrics. 2016;177:72–77.e2. doi: 10.1016/j.jpeds.2016.04.066. [PubMed] [CrossRef] [Google Scholar]
53. Oncel M. Y., Erdeve O. Safety of therapeutics used in management of patent ductus arteriosus in preterm infants. Current Drug Safety. 2015;10(2):106–112. doi: 10.2174/1574886309999141030142847. [PubMed] [CrossRef] [Google Scholar]
54. Tan Z. H., Baral V. R. Principles of clinical management of patent ductus arteriosus in extremely preterm neonates. Current Pediatric Reviews. 2016;12(2):83–97. doi: 10.2174/1573396312021605060013 09. [PubMed] [CrossRef] [Google Scholar]
55. Aikio O., Härkin P., Saarela T., Hallman M. Early paracetamol treatment associated with lowered risk of persistent ductus arteriosus in very preterm infants. Journal of Maternal-Fetal and Neonatal Medicine. 2014;27(12):1252–1256. doi: 10.3109/14767058.2013.854327. [PubMed] [CrossRef] [Google Scholar]
56. Malviya M, Ohlsson A, Shah S. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database of Systematic Reviews. 2003. Art. No.:CD003951. DOI: 10.1002/14651858.CD003951. [PubMed]
57. Kabra NS, Schmidt B, Roberts RS. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. J Pediatr. 2007;150:229–234. [PubMed] [Google Scholar]
58. McCurnin DC, Yoder BA, Coalson J. Effect of ductus ligation on cardiopulmonary function in premature baboons. Am J Respir Crit Care Med. 2005;172:1569–1574. [PMC free article] [PubMed] [Google Scholar]
59. Chorne N, Leonard C, Piecuch R. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics. 2007;119:1165–1171. [PubMed] [Google Scholar]
60. Koehne PS, Bein G, Alexi-Meskhishvili V. Patent ductus arteriosus in very low birthweight infants: complications of pharmacological and surgical treatment. J Perinat Med. 2001;29:327–334. [PubMed] [Google Scholar]
61. Poon G. Ibuprofen lysine (NeoProfen) for the treatment of patent ductus arteriosus. Proc (Bayl Univ Med Cent). 2007;20: 83-5.
62. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011 Dec;128(6):e1618-21. doi: 10.1542/peds.2011-0359. Epub 2011 Nov 7. PMID: 22065264.
63. Kumar A, Sundaram V, Yadav R, Oleti TP, Murki S, Krishna A, Sundaram M, Saini SS, Dutta S. Oral paracetamol versus oral ibuprofen for closure of haemodynamically significant patent ductus arteriosus in preterm neonates (<32 weeks): a blinded, randomised, active-controlled, non-inferiority trial. BMJ Paediatr Open. 2017 Aug 11;1(1):e000143. doi: 10.1136/bmjpo-2017-000143. PMID: 29637155; PMCID: PMC5862198.
64. El-Farrash RA, El Shimy MS, El-Sakka AS, Ahmed MG, Abdel-Moez DG. Efficacy and safety of oral paracetamol versus oral ibuprofen for closure of patent ductus arteriosus in preterm infants: a randomized controlled trial. The Journal of Maternal-Fetal & Neonatal Medicine. 2019;32(21):3647-54.
65. Huang X, Wang F, Wang K. Paracetamol versus ibuprofen for the treatment of patent ductus arteriosus in preterm neonates: a meta-analysis of randomized controlled trials. The Journal of Maternal-Fetal & Neonatal Medicine. 2018;31(16):2216-22.
66. Bagheri MM, Niknafs P, Sabsevari F, Torabi MH, Bijari BB, Noroozi E, et al. Comparison of oral acetaminophen versus ibuprofen in premature infants with patent ductus arteriosus. Iranian journal of pediatrics. 2016;26(4).
67. Oncel MY, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, et al. Oral paracetamol versus oral ibuprofen in the management of

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 352-365 | ISSN:2251-6727

patent ductus arteriosus in preterm infants: a randomized controlled trial. The Journal of pediatrics. 2014;164(3):510-4. e1.

68. Dang D, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. PloS one. 2013;8(11):e77888.
69. Yang B, Gao X, Ren Y, Wang Y, Zhang Q. Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial. Experimental and therapeutic medicine. 2016;12(4):25316.
70. Allegaert K, Rayyan M, De Rijdt T, Van Beek F, Naulaers G. Hepatic tolerance of repeated intravenous paracetamol administration in neonates. Pediatric Anesthesia. 2008;18(5):388-92.
71. Yurttutan S, Oncel MY, Arayıcı S, Uras N, Altug N, Erdeve O, et al. A different first-choice drug in the medical management of patent ductus arteriosus: oral paracetamol. The Journal of Maternal-Fetal & Neonatal Medicine. 2013;26(8):825.