

# Double Case Control Study on Effect of Ibuprofen and Acetaminophen in Premature Neonate with Patent Ductus Arteriosus in Neonatal Intensive Care Unit in Sulaimania Maternity Hospital

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## Abstract

**Backgrounds and objectives:** Persistent patency of the ductus arteriosus is a major cause of morbidity and mortality in premature infants. Cyclooxygenase inhibitors remain the mainstay of medical therapy for patent ductus arteriosus. The aim of this study is to evaluate pharmacological closures of Patent Ductus Arteriosus in premature babies. Patients and **Methods:** Double case control study done on sixty premature neonates with a gestational age (25-37) weeks, who were admitted to the Sulaimania maternity hospital from February to September 2017. Patent ductus arteriosus diagnosis was confirmed by echocardiography. Twenty neonates received oral ibuprofen, an initial dose of 20mg/kg, followed by 10mg/kg at 24 or 48 hours later, twenty cases received oral acetaminophen in dose of 20mg/kg as initial dose, followed by 15mg/kg every eight hours for 3 days. Twenty cases not received treatment after taking consent from their family. The second echo was done after completed treatment. **Results:** In sixty premature neonates with patent ductus arteriosus; twenty cases received ibuprofen 14 cases responded to the treatment (70%), and 7 cases (35%) developed side effects, twenty cases received acetaminophen 11 cases responded to the treatment (55%), and side effects developed in just 3 cases (15%). lastly twenty cases received no treatment patent ducts arteriosus closed in just 8 cases (40%). **Conclusions:** Ibuprofen is slightly more effective on the closing of the PDA in preterm infants than acetaminophen, but the latter has fewer side effects and using medication is preferred on using no medication **Keywords:** Patent ductus arteriosus, Ibuprofen, Acetaminophen, Premature neonates.

## Introduction

In the developing fetus, the pulmonary artery and the aortic arch are connected via the ductus arteriosus, a vascular shunt that diverts the right ventricular output away from the fetus's fluid-filled lungs and into the systemic circulation<sup>1</sup>. Whereas this ductal shunt closes spontaneously within a few hours of birth in full-term infants, this process is frequently delayed/ interrupted in premature infants and is associated with increased risk of clinical complications<sup>2-5</sup>. The incidence of persistent PDA correlates inversely with birth weight and gestational age; it is seen in about 30% of infants born with a birth weight less than 1500 grams, 40% of infants weighing 751-1000 grams, and more than 50% of those weighing 501-750 grams<sup>4,6,7</sup>. Although spontaneous ductal closure occurs eventually in nearly a third of extremely premature neonates, more than 60% of all preterm infants born prior to 28 weeks' gestation receive medical or surgical treatment.

PDA can be asymptomatic, symptomatic, 'hemodynamically-non-significant' (no cardiovascular dysfunction), or 'hemodynamic ally-significant' (with cardiovascular dysfunction).

Echocardiography is the mainstay of diagnosis and assessment of PDA. It allows direct visual assessment of the ductus originating from the descending aorta distal to the left subclavian artery and connecting to the main pulmonary artery. Among the treatment modalities used: indomethacin which is nonselective COX inhibitors, it was the first drug used for PDA treatment, presenting a closure rate of about 70–85% without any other short-term benefits<sup>8</sup>. Since indomethacin has been used as a prophylaxis in PDA management, it has been shown to reduce the incidence of intraventricular hemorrhage (IVH  $\geq$  grade 3 by 30%) and severe pulmonary hemorrhage by 35%, symptomatic PDA development, and necessity of surgical ligation<sup>8-10</sup>, without effects on mortality or long-

term neurodevelopmental outcome<sup>9</sup>.

However, for its high vasoconstrictor power, this drug has been associated with several side effects such as impairment in renal function until acute or chronic renal failure, oliguria, proteinuria, hyperkalemia, cerebral white matter damage, necrotizing enterocolitis, intestinal perforation (especially when coadministered with corticosteroids), and platelet dysfunction.

Recognizing these indomethacin related side effects, ibuprofen was subsequently introduced in the clinical practice, either orally or in iv manner; each course of therapy is composed of the standard dose of 10 mg/Kg/dose/day on the first day of treatment followed by two subsequent doses of 5 mg/Kg/dose/day on second and third days<sup>11</sup>.

Ibuprofen shares with indomethacin the mechanism of action and the efficacy in PDA closure (success rate 70–85%)<sup>8</sup>, but its lower vasoconstrictor effect leads to a reduced impact on microcirculation and consequent less impairment of renal function; this difference could be partly determined by a preferential effect of indomethacin on COX-1 instead of COX-2 but also by other mechanisms not exactly known<sup>12</sup>.

However, ibuprofen is not free from other significant side effects, such as pulmonary hypertension and hyperbilirubinemia<sup>9</sup>. Paracetamol; more recently, oral or IV administration of paracetamol (acetaminophen) gained attention in PDA treatment<sup>13,14</sup>.

Surgical closure of PDA is another choice, after failure of drug therapy or in case of contraindications to available drugs.

The aim of this study was to evaluate the effect of ibuprofen and paracetamol in premature babies with PDA, and their side effects.

## Methods

A double case control study performed in the neonatal intensive care unit (NICU) of the maternity hospital in Sulaimani city from February to September, 2017.

This trial was approved by the ethics committee of Kurdistan Board for Medical Specialties & neonates were included in the study after parental consent was obtained. The inclusion criteria were gestational age less than

37 weeks, postnatal age less than 1 month, gender, residency and an echocardiographically diagnosed PDA following an echocardiographic detection of the duct size (small: <0.5mm, medium 0.5-1 mm, large 1-1.5 mm, huge: >1.5 mm) (15) by same echo machine (Envies Phillip probe 8 MHz), & by the same operator.

Exclusion criteria were as follow: a major complex CHD especially duct dependent CHD, IVH, NEC, sepsis, evidence of bleeding or platelet count <50000 per microliter & renal insufficiency (S.creatinine >1.6 mg/dl).

All patients were evaluated with complete blood count, renal and liver function tests, abdominal & cranial ultrasound.

We divided patients into three groups:

Twenty cases received oral acetaminophen (120 mg/5ml) at dose of 20 mg/kg loading dose followed by 15 mg/kg every 8 hrs for 3 doses (on the base of BNF guideline).

Twenty cases were received oral ibuprofen (100mg/5ml) at dose of 10mg/kg followed by 5mg/kg after 24 and 48 hours (on the base of BNF guideline).

Twenty cases did not receive treatment (after refusal by the family) just follow up echo done 1 week and 3 months after the first echocardiography.

Success rate of treatment was defined as closure of the patent duct on echocardiography after completing the course of the drug.

Secondary outcome was safety of both drugs and developing any adverse effects.

## Results

In this study we have 60 cases of PDA, 37 were male (61.7%), 23 were female (38.3%).

The gestational age of cases in the study ranged from 25 weeks to 37 weeks but most of them 63.3% were more than 27 weeks.

Postnatal age of the patients classified from less than 1 week to 2 weeks but most of them were less than 1 week 70%.

Most of the cases in the study came from rural areas 53.3%, while 46.7% of them were from inside Sulaimani city which regarded as urban area.

Most of the cases presented with respiratory distress which included 51 cases (85%), 2 cases (3.3%) presented

with meconium aspiration syndrome( MAS), 2 cases (3.3%) with hypoglycemia, and 5 cases (8.3%) had no any presentation just admitted or follow up and PDA was found accidentally.

Five cases (8.3%) needed no any airway support, 36 of them (60%) needed oxygen, and 19 cases (31.7%) were on CPAP, but none of them needed ventilator.

Among twenty cases that received ibuprofen: 5 of them (25%) their gestational age GA was less than 27 weeks, 2 (10%) of them their PDA was closed & 3 (15%) of them was not closed, while 15 (75%) Of them their gestational age GA more than 27 weeks 12 (60%) of them were responded to ibuprofen.

Among those twenty cases that were received acetaminophen 9(45%) of them their gestational age was less than 27 weeks and only 4(20%) of them were responding, but among those 11(55%) cases their gestational age was more than 27 weeks 7 (35%) of them responded to the treatment, as shown in the table 1) which means that PDA closure is more among those cases their gestational age more than 27 weeks.

**Table (1):** Association between treatments and PDA closure according to gestational age

	Ibuprofen			P value
	Closed PDA	Not closed	Total	
G.A<27 weeks	2 (10%)	3 (15%)	5 (25%)	0.091
G.A>27 weeks	12 (60%)	3 (15%)	15 (75%)	
Total	14 (70%)	6 (30%)	20(100%)	
	Acetaminophen			P value
	Closed PDA	Not closed	Total	
G.A<27 weeks	4 (20%)	5 (25%)	9 (45%)	0.391
G.A>27 weeks	7 (35%)	4 (20%)	11 (55%)	
Total	11 (55%)	9 (45%)	20(100%)	

In the table (2) twenty patients did not received any treatment, 8 (40%) of them their G.A <27 weeks and PDA closed in only 3 (15%) cases, while among those 12 (60%) cases that their G.A was more than 27 weeks PDA closed in 5 (25%) of them.(in the total twenty cases PDA closed in just 40% and it is small number in comparison with those forty cases received treatment PDA closed in 62.5% of them).

**Table (2):** Closure of the PDA in those patients not received treatment according to G.A:

	No Treatment			P value
	Closed PDA	Not closed	Total	
G.A<27 weeks	3 (15%)	5 (25%)	8(40%)	0.457
G.A>27 weeks	5 (25%)	7 (35%)	12(60%)	
Total	8 (40%)	12 (60%)	20(100%)	

As shown in the table (3); PDA closed in 70% of cases received ibuprofen and closed in 55% of cases received acetaminophen, so there is no significant difference between two groups in PDA closure (P value 0.01).

**Table(3):** Comparison between ibuprofen and acetaminophen in PDA closure.

PDA Closure	Ibuprofen	Acetaminophen	P value
closed	14 (70%)	11 (55%)	0.01
Not closed	6 (30%)	9 (45%)	
Total	20 (100%)	20 (100%)	

In the table (4) shown that among twenty patients who received ibuprofen, 13 (65%) of them did not develop any side effects, 2 (10%) of them developed decrease platelet. Count, in 3 cases (15%) had increased renal function test, & 2 cases (10%) developed necrotizing enterocolitis (NEC); while those twenty cases who received acetaminophen 17 (85%) cases did not develop any side effects, platelet count decreased in just 1 case (5%), and liver function test LFT was increased in 2 (10%) cases.

**Table (4):** association between treatment and side effects:

Treatment		Side effects					P value
		No SE	Decrease plt count	Increase RFT	NEC	Increase LFT	
Ibuprofen	Yes	13(65%)	2 (10%)	3 (15%)	2 (10%)	0 (0%)	0.097
	No	17(85%)	1 (5%)	0 (0%)	0 (0%)	2 (10%)	
Acetaminophen	Yes	17(85%)	1 (5%)	0 (0%)	0 (0%)	2 (10%)	0.097
	No	13(65%)	2 (10%)	3 (15%)	2(10%)	0 (0%)	

## Discussion

In our study, the average age of the newborns at birth was  $6 \pm 31$  weeks and this is comparable with a study was done by Habibi<sup>16</sup>; the total of 77 preterm infants with PDA, 51.9 percent ( $n = 40$ ) of patients with acetaminophen and 48.1% (37 patients) were treated with ibuprofen. The average age of the newborns at birth was  $4 \pm 31.8$  weeks. Also another research was done by Dang<sup>17</sup>, they had one hundred and sixty infants (gestational age 34 weeks) with echocardiographically confirmed PDA were randomly assigned to receive either oral paracetamol ( $n=80$ ) or ibuprofen ( $n=80$ ), the ductus was closed in 65 (81.2%) infants of the paracetamol group compared with 63 (78.8%) of the ibuprofen. Demonstrating that the effectiveness of paracetamol treatment was not inferior to that of ibuprofen.

In our study; among those twenty cases that received paracetamol PDA was closed in 11 cases (55%), while among those twenty cases received ibuprofen PDA was closed in 14 cases (70%). According to our research, the ibuprofen has a good effect on closing of ductus arteriosus. These results are in agreement with another study that done in by Ghanem<sup>18</sup>; to determine whether orally administered ibuprofen treatment is efficacious in PDA closure in premature infants with respiratory distress syndrome RDS, which showed oral ibuprofen to be effective and safe in PDA closure, with 31 of 33 (93.9%) study infants achieving a successful outcome .

In our study, there was no significant difference between two groups of infants treated with paracetamol and ibuprofen in PDA closure, this also comparable to the study done by Habibi<sup>16</sup>; in two groups of infants showed that 75.7 percent ( $n = 28$ ) of infants treated with ibuprofen, and 87.5 percent (35) of the infants treated with acetaminophen have been recovered at the end of the first period, and the rest were treated by another treatment period. Statistically;

the difference was not significant.

In our study, shown that among twenty patients were received ibuprofen,13 (65%) of them not developed any side effects, while 7 of them (35%) developed side effects, 2 (10%) of them decreased platelet count, in 3 (15%) of them RFT impaired, & 2 of them developed NEC While those twenty cases in our study received acetaminophen 17(85%) of them did not develop any side effects, platelet count decreased in just 1 case (5%), and LFT was increased in 2 cases (10%).

However; other studies showed some other side effects such as study done by Yang<sup>19</sup>, who showed the clinical efficacy of oral ibuprofen and acetaminophen in the treatment of preterm infants with PDA, the results of ibuprofen side effects were impaired renal function in 14% Of cases, necrotizing enterocolitis (NEC) in11.6%, and side effects of paracetamol were impaired renal function in 2.3% of cases, (NEC) in 4% of cases, while platelet count not decreased in both groups.

## Conclusions

In comparison of drug efficacy and safety profiles in premature infants with PDA, the study showed that using medication is preferred on using nothing. Also; it revealed that oral paracetamol was comparable to ibuprofen in terms of the rate of ductal closure and even showed lesser side effect, therefore; paracetamol may be accepted as a first-line drug treatment for PDA in preterm infants.

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