



**ORIGINAL RESEARCH PAPER**

**Paediatrics**

**“EFFECT OF ORAL IBUPROFEN AND ORAL ACETAMINOPHEN IN THE TREATMENT OF SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS: A HOSPITAL BASED STUDY”**

**KEY WORDS:** PDA, NICU, Acetaminophen and Ibuprofen,

**Dr Jagdish Solanky**

(MBBS, MD), Assistant Professor, Department of Paediatrics, K D Medical College and Hospital, Mathura, UP

**Dr Harish Kumar Agrawal\***

(MBBS, MD), Assistant Professor, Department of Paediatrics, K D Medical College and Hospital, Mathura, UP \*Corresponding Author

**ABSTRACT**

Patent ductus arteriosus (PDA) is a common cause of morbidity. The aim of this study was to compare the efficacy of oral Acetaminophen and oral Ibuprofen for the closure of patent ductus arteriosus (PDA) in preterm infants. This study demonstrated that, there was no significant difference between treatment of PDA with either oral Acetaminophen or oral Ibuprofen in preterm neonates. Oral Ibuprofen can effectively close PDA but is unfortunately associated with some adverse effects limiting its utility thus we studied an alternative drug with similar efficacy and less adverse effects and contraindication.

**Introduction:**

The patency of ductus arteriosus (PDA) is a frequent complication in preterm infants suffering from respiratory distress syndrome (RDS), and 60% to 70% of preterm infants of < 28 weeks' gestation receive medical or surgical therapy for a PDA.<sup>1</sup> Neonates with a left-to-right shunt through the ductus complicating their RDS have higher respiratory failure, lower survival rate, and increased risk of intracranial haemorrhage (ICH), chronic lung disease (CLD) and necrotizing enterocolitis (NEC).<sup>2</sup> Therefore, closure of PDA is indicated before a significant left-to-right shunting occurs. Ductus arteriosus is a great communication way which naturally in the fetus has been Patent, and connects the main pulmonary artery to the descending aorta and causes the main part of the right heart's blood is not entered the lungs and transferred into the systemic circulation. In infants, the closure of the functionality of ductus arteriosus has happened in the first few hours of birth and almost the blood does not pass the duct in any babies born after 96 hours.<sup>3</sup> Closure of the ductus after birth occurs for various reasons, and it has been shown that an increase in arterial oxygen pressure, which along with the ventilation of the lungs occurs after birth leads to the closure of the duct.<sup>4</sup> In the meantime, the role of prostaglandins is known, and in fact, the balance between the effects of oxygen retractor and prostaglandins vasodilator plays a major role on the patency of ductus.<sup>4</sup> On the other hand, the effects of these materials depend on the gestational age of babies, and in preterm infants, the ductus sensitivity is more to the effects of the patency due to prostaglandins and decreases with age.<sup>5</sup> Patent ductus arteriosus (PDA) occurs in 50% of infants with gestational age less than 28 weeks.<sup>6</sup> Most doctors prefer that treat this problem in infants, but some experts have said that, in this case, treatment is not necessary.<sup>7-9</sup>

Hemodynamic consequences of the patent ductus arteriosus include higher than normal pulmonary circulation that is related to the increased risk of respiratory failure, pulmonary edema and decreased alveolar growth associated with chronic lung disease, and systemic hypoperfusion.<sup>10-13</sup> Patent ductus arteriosus also can reduce the oxygenation of the brain and tissues, which in turn may put babies at risk of neurological damage.<sup>14</sup> Treatment options of patent ductus arteriosus mainly include urethral obstruction with surgery or drug therapy with the cyclooxygenase inhibitors. Previous research has revealed some negative and serious consequences of treatment through surgery, of which can be note to pneumothorax, chylothorax and infection.<sup>15</sup> Also, in more than 40% of cases, paralysis of the vocal cords and its effect on feeding and breathing disorders also have been reported.<sup>16</sup> More recent studies have confirmed the association between closure of patent ductus arteriosus through surgery with neurological developmental disorders, chronic lung disease, and severe retinopathy of premature infants.<sup>17-18</sup> Also, in some cases, closure of patent ductus arteriosus, through surgery has failed to improve clinical status of infants with the disease.<sup>19</sup> But, in contrast, closure

of it through medication can prevent the disturbances in alveolar growth.<sup>20-21</sup> In most countries, there are two types of inhibitors of cyclooxygenase are used to close a patent ductus arteriosus. These include: Indomethacin and ibuprofen lysine. When the standard dose of each drug is applied, the success rate of patent ductus arteriosus closure is the same for both drugs.<sup>22-23</sup> The real response in very low birth weight infants is estimated between 40 to 60 percent, while the figure in infants with older age is more than 80 percent.<sup>4,9,22,24,25</sup> On the other hand, the patency of ductus may occur again for 20 percent of the treated infants.<sup>26</sup> Also, aging baby more than 10 days, reduces their response.<sup>27</sup> Relatively low rate of closure of patent ductus arteriosus in very low birth weight babies, not because of pharmacodynamic differences, but rather is caused by differences in the pharmacokinetics of the two drugs.<sup>27</sup> Both of these drugs in closure of patent ductus arteriosus have a significant impact, and their optimal dose can be permanent in more than 90 percent of premature babies. Toxicity is the most important issue that distinguishes these two drugs. Side effects of these can be divided into two categories reversible short-term effects (such as reduced organ perfusion and decreased kidney function) and long-term effects (such as chronic lung disease and the destruction of nerve growth). Comparison of short-term side effects of these drugs shows the benefits of ibuprofen to indomethacin. But given the potential side effects of these two drugs, as well as large cases of a contraindication to the use of them, finding a safe and effective alternative medicine seems necessary.

**Material and Methods:**

This present study was conducted in the Department of neonatal intensive care unit (NICU) of K D Medical College and Hospital, Mathura during the period from May 2017 to September 2017. The study population included all preterm infants born at K D Medical College and Hospital, with PDA and diagnosis age less than 14 days. All preterm infants have been examined in terms of the dependence on oxygen; increased PCO<sub>2</sub>, heart murmur, heart failure symptoms, Bounding Pulse, and suspecting PDA, echocardiography was done for them. In case of confirmation of disease, they entered the study. A total of 82 infants with PDA were eligible for the study, after obtaining parental consent, were included in the study, and were randomly divided into two groups:

**Group A:** was treated with ibuprofen at a dose 10 mg / kg / stat, and then 5 mg/kg/ 12h for two doses.

**Group B:** were evaluated for two days, were treated with acetaminophen at a dose 15 mg/kg/6h (8 doses).

At the end of the three-day treatment period, patients were re-echocardiography. In case, Echocardiographic findings of each patient indicated the lack of closure of the ductus arteriosus, patients for a longer period, was treated with the drug, and at the end of the third day, were re-echo. Those patients who did not

respond to two courses of drug treatment, were selected as candidates for surgical treatment. Throughout the treatment period, patients with a review of the 24-hour urine output, any blood, serum bilirubin and creatinine levels were followed in terms of the occurrence of side effects. Data was analyzed using statistical software SPSS 22 and with the help of independent t-test (in the case of normal distribution of data) or Mann-Whitney (nonnormal distribution of the data), and chi-square tests.

**Results and Discussion:**

This present study consists of 82 preterm infants born in K D Medical College and Hospital, who suffered from PDA. 51.2 percent (n = 42) of patients with acetaminophen and 48.7% (40 patients) were treated with ibuprofen. The average age of the newborns at birth was 4.2 ± 21.06 weeks. Significant differences in mean age of infants were observed in both groups (0.485 = P). Average weight of infants treated with ibuprofen was 821 ± 1562 g, and the average weight of infants treated with acetaminophen was 889 ± 1668 g (0.657 = P). Table-1 showed that 32(80.0%) of infants treated with ibuprofen, and 36(85.7%) 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. Of course, based on the results of the chi-square test, the difference, 5.7%, was not statistically significant (0.146 = P).

**Table 1: Distribution of the number of treatment periods of infants with PDA by the type of treatment received.**

Treatments	Treatment Periods		Total
	One period	Two periods	
Acetaminophen	36(85.7%)	6(14.3%)	42(100%)
Ibuprofen	32(80.0%)	8(85.7%)	40(100%)
Total	68(82.9%)	14(17.1%)	82(100%)

In Table 2, the closure of PDA in newborns at the end of the first period of their treatment has been shown by their groups. As seen in the table, at the end of the first period of treatment in 2(5.0%) of the cases treated with ibuprofen, and 1(2.4%) of the cases treated with acetaminophen, it was not observed any change in the situation of patent ductus arteriosus (0.31 = P).

**Table 2: Closure of PDA in babies at the end of the first period by the type of treatment received.**

Treatments	PDA at the end of first period			Total
	Perfect	Imperfect	Unchanged	
Acetaminophen	36(85.7%)	5(11.9%)	1(2.4%)	42(100%)
Ibuprofen	32(80.0%)	6(15.0%)	2(5.0%)	40(100%)
Total	68(82.9%)	11(13.4%)	3(3.6%)	82(100%)

Table-3 shows that the ductus arteriosus of all 6 infants treated with acetaminophen, and 6 patients of 8 infants treated with ibuprofen, who received the second course of treatment, was fully closed (0.20 = P). Based on the results, no statistically significant difference was observed between the side effects of prescribed two drugs of acetaminophen and ibuprofen (0.62 = P).

**Table 3: Closure of PDA in babies at the end of the second period by the type of treatment received.**

Treatments	PDA at the end of second period			Total
	Perfect	Imperfect	Unchanged	
Acetaminophen	6(100%)	0	0	6(100%)
Ibuprofen	6(75.0%)	1(12.5%)	1(12.5%)	8(100%)
Total	12(85.7%)	1(7.1%)	1(7.1%)	14(100%)

The results of a recent study showed that the results of use of oral acetaminophen have been comparable with ibuprofen in closure of the PDA, and both of them to the same extent are effective on the closing of the PDA in preterm infants. Also, there was no difference between the incidences of complications from prescribing these drugs in the treatment of this group of babies. Ductus arteriosus in most newborns at the first day of life will be closed functionally, and patent ductus arteriosus for permanent (PDA) is abnormal. Since, in 30-60% of infants with very low birth

weight, there is patent ductus arteriosus, and their own permanent closure of the ductus in the first four days of life occurs in only one third of infants with less than 1000 grams, therefore, the overwhelming majority of these infants are potential candidates for medical or surgical interventions.<sup>33</sup> Therefore, one of the most important topics in babies' science is methods of closure of patent ductus arteriosus. Although the use of drugs such as indomethacin and ibuprofen are considered as common medical methods, but the side effects and obstacles to use them always has made experts interested in finding new approaches with less complications. So far, few studies have been done on evaluating the effect of the use of acetaminophen in the treatment of patent ductus arteriosus, and comparing it with other medicines. In many cases, acetaminophen has been ineffective as a supplement, not as a first-line treatment, in cases where COX inhibitors are ineffective, contraindications are used. In the present study, it was not observed a significant difference between the effect of oral ibuprofen and oral acetaminophen in the closure of the PDA in preterm infants. The results of a randomized controlled trial conducted by Dang et al.<sup>34</sup>, aimed to compare the efficacy and safety of oral ibuprofen in front of oral acetaminophen on 160 preterm infants (gestational age less than 34 weeks), showed that, both drugs, alike, were effective in the treatment of patent ductus arteriosus (81.2 versus 77.8 percent). These results are quite consistent with the findings of our study. The results of evaluating the effectiveness and safety of oral acetaminophen vs oral ibuprofen for the treatment of patent ductus arteriosus in 90 premature infants with gestational age less than 30 weeks, and birth weight less than 1250 g, their patent ductus arteriosus was confirmed by echocardiography, after the first course of treatment, patent ductus arteriosus of 77.5 % of babies receiving acetaminophen was closed. The researchers of this study concluded that, oral acetaminophen can be a good alternative for the treatment of patent ductus arteriosus in premature infants.<sup>35</sup> According to the study of Sinha et al.<sup>36</sup>, and also the Terrin et al.<sup>37</sup>, acetaminophen compared to ibuprofen can be considered as a safe and promising drug for the treatment of patent ductus arteriosus in premature infants. Yurttutan et al.<sup>38</sup> also with assessment and treatment of six premature infants with patent ductus arteriosus with oral acetaminophen concluded that, due to the low side effects, low cost and effectiveness of acetaminophen, it can be considered as a main option for the management of patent ductus arteriosus in these infants. This result is quite consistent with the findings of our investigation. Based on the present results, although incidence among infants treated with ibuprofen is more than acetaminophen group by 8.6 percent, but unlike recent study hypothesis, this difference was not statistically significant. According to a study by Dang et al.<sup>34</sup>, which was carried out aimed to compare the efficacy and safety of oral ibuprofen compared oral acetaminophen for 160 preterm infants (gestational age less than 34 weeks), hyperbilirubinemia or gastrointestinal bleeding in acetaminophen group was somewhat lower than ibuprofen. However, in this study, no significant differences were observed between the two groups in terms of side effects or other problems. Based on the results Sinha et al.<sup>36</sup>, contrary to the prescribed ibuprofen, which had left many side effects, after administration of oral acetaminophen, no side effects were observed. According to the results of Terrin et al.<sup>37</sup>, although treatment with ibuprofen or indomethacin had a lot of side effects, but during treatment with acetaminophen, no adverse reactions or serious problems have been seen. Unlike the results of a recent study, the findings of the studies above suggest the incidence of more side effects of ibuprofen compared with acetaminophen. It seems that, no significant differences in the current study, despite the high incidence of complications among infants treated with ibuprofen probably are due to the low number of samples studied.

**Conclusion:**

These findings suggest that the oral Ibuprofen can effectively close PDA but is unfortunately associated with some adverse effects limiting its utility thus we studied an alternative drug with similar efficacy and less adverse effects and contraindication. On the basis of identical efficacy of Ibuprofen and Acetaminophen and higher safety of Acetaminophen it is recommended to use

Acetaminophen as the drug of first choice. Although we have demonstrated that Acetaminophen may be utilized as the drug of choice for PDA in preterm infants with good efficacy, further studies are warranted.

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