

# Comparison of Gastrointestinal Complications of Paracetamol and Ibuprofen in the Management of Infants with Patent Ductus Arteriosus: A Randomized Clinical Trial Study

## Abstract

**Background:** Patent ductus arteriosus (PDA) is one of the more common congenital heart defects in preterm neonates. The closure of PDA can be done with ibuprofen; however, this drug is associated with many contraindications and potential side-effects. In the past years, paracetamol has been proposed for the treatment of PDA. This study was designed to evaluate the efficacy and gastrointestinal complications of paracetamol and ibuprofen for the pharmacological closure of PDA in preterm infants. **Methods:** In a clinical trial study, 40 preterm infants with echocardiographically confirmed PDA were randomly assigned to receive either paracetamol ( $n = 23$ ; 15 mg/kg every 6 h for 2 days) or ibuprofen ( $n = 17$ ; initial dose of 10 mg/kg, followed by 5 mg/kg every 12 h for 2 days). The neonates matched for gestational age and weight. We used *t*-test for parametric, Chi-square for categorical, and Wilcoxon for nonparametric variables. Significant level was considered less than 0.05. **Results:** Platelet count, BUN and creatinine levels, and closure of PDA had not significant difference between two groups ( $P > 0.05$ ). Incidence and severity of GI bleeding, feeding intolerance, and NEC were significantly more in infants who received paracetamol than ibuprofen ( $P < 0.05$ ). **Conclusions:** There were no differences in the rate of PDA closure between the two drugs, but with respect to complications, rate and severity of GI bleeding, feeding intolerance, and NEC were significantly more in infants who received paracetamol than ibuprofen. Therefore, paracetamol could not be used as a proper alternative agent for ibuprofen in the treatment of PDA in preterm infants.

**Keywords:** Acetaminophen, ductus arteriosus, ibuprofen, patent

## Introduction

Patent ductus arteriosus (PDA) is a heart defect in which there is a persistent connection between the aorta and the pulmonary arteries.<sup>[1]</sup> It can also cause low diastolic pressure that leads to other conditions such as necrotizing enterocolitis (NEC), intraventricular hemorrhage, retinopathy of prematurity, periventricular leukomalacia, and renal failure.<sup>[2,3]</sup> It is common in premature neonates and infants following maternal rubella during pregnancy.<sup>[4]</sup> PDA accounts for 2%–7% of all heart abnormality in the united states.<sup>[5]</sup> In Iran, the prevalence of PDA has been reported approximately 15% of all congenital heart defects.<sup>[6]</sup>

There are currently three approaches in PDA treatment including fluid intake restriction, drug therapy, and surgical method. Conservative therapy involves restricting fluid intake, which may be

associated with the administration of diuretics. In this method, 34% of cases, PDA is closed within 3 to 6 days.<sup>[7]</sup> In surgical repair, PDA closure is performed by ligation or a combination of ligation and use of surgical clips or stitches.<sup>[8]</sup> The most important drugs in PDA treatment are nonselective COX inhibitors including indomethacin and ibuprofen, with success rates of 75% to 93%. Both of these drugs are injected through intravenous because of decreased gastric perfusion and gastrointestinal complications. Both drugs also are associated with nervous system complications, necrotizing enterocolitis, and reducing cerebral and mesenteric blood flow.<sup>[9-12]</sup> However, they are less common in ibuprofen administration; it may cause bleeding, skin lesions, hypoglycemia, hypocalcemia, heart failure, respiratory failure, IVH, and renal dysfunction.<sup>[13]</sup> Recently, oral or IV administration of paracetamol

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(acetaminophen) has been considered in the treatment of PDA, which is first recommended by Terrin *et al.* (2016).<sup>[14]</sup> In many studies, it has been defined as a safe, effective and with less side effects than other conventional antiinflammatory drugs in PDA closure.<sup>[15-19]</sup> However, routine use of that has been limited due to some side effects including transiently increase in hepatic enzymes, acute hepatic toxicity, retinopathy of prematurity, gastrointestinal bleeding, necrotizing enterocolitis, pulmonary hemorrhage, IVH, sepsis, and death.<sup>[20-27]</sup> Hence, the best treatment option for PDA drug therapy is still controversial.

Several studies indicated that the overall complication rate for PDA treatment with acetaminophen is lower than other drugs.<sup>[9,19]</sup> Results of other studies suggest that there is no difference in the incidence of complications in neonates treated with acetaminophen or ibuprofen.<sup>[17,18]</sup> Some studies also recommend further studies, while pointing out the efficacy of acetaminophen, which has proven to be superior to other conventional PDA drug therapies.<sup>[7]</sup>

This study aimed to evaluate the efficacy and gastrointestinal complications of acetaminophen and ibuprofen for the pharmacological closure of PDA in preterm infants.

## Methods

In this clinical trial study, all premature neonates with diagnosis of PDA who born at Amiralmomenin Hospital, Semnan, Iran between May 2018 and May 2019 were included in the study. Ethical approval was obtained for this study from the Ethics Committee of the Semnan University of Medical Sciences.

Inclusion criteria were the age of less than 14 days at the time of diagnosis and hospitalizing in neonates intensive care unit during follow-up of the patients. In addition, neonates with congenital heart defects that maintaining the openness of the ductus is vital for them such as pulmonary atresia and major or chromosomal congenital abnormalities, history of nonsteroidal antiinflammatory use during pregnancy, persistent pulmonary hypertension in the neonates (PPHN), 5-min Apgar score <5, having PDA symptom and need for supplementary treatment (in control group), presence of vomiting or hematemesis in first three days of birth, and G6PD deficiency were excluded from the study.

The patients were selected through convenience sampling and then were randomly divided into two groups of paracetamol and ibuprofen by block permuted randomization. Patients in two groups homogenized in terms of weight and gestational age at delivery time. In paracetamol group, in the first 24 h of birth, 15 mg/kg paracetamol at six-hour intervals for 48 h was injected intravenously. Patients in ibuprofen group orally received 10 mg/kg at first day of birth and then followed by 5 mg/kg at next 48 h.

Data collection was done by a questionnaire and were gender, birth weight, gestational age at delivery, type of delivery, and single or multiple pregnancy. Ultrasonic cardiogram platelet count, BUN, serum creatinine, and potential blood in the stool were evaluated before and after 3 days of taking first dose of drugs. In addition, the incidence of NEC, OB, and feeding intolerance were recorded using medical records of patients. The diagnosis of NEC was confirmed by the presence of gas or air bubbles in the wall of the intestine on an abdominal X-ray and symptoms such as inability to tolerate feeding, bloody stools, and distention of the abdomen.<sup>[28]</sup> OB test was performed through checking stool samples for occult blood.<sup>[29]</sup> In addition, PDA was diagnosed, if in echocardiography, the ratio of the left atrium to the aortic root was greater than 1.3 mm and the internal duct diameter was more than 1.5 mm.<sup>[30,31]</sup>

Data obtained were analyzed using SPSS version 22 software (IBM Corporation, Armonk, NY, USA). The *t*-test was used to compare the normally distributed data, whereas the Wilcoxon's test was used to compare the nonnormally distributed data. In addition, Chi-square test was used for test the association between categorical variables. The level of statistical significance was set at *P* value <0.05.

## Results

In this study, neonates with diagnosis of PDA were evaluated at two groups of paracetamol (*n* = 23) and ibuprofen (*n* = 17). The mean of neonatal gestational age was 30.43 ± 4.28 weeks in paracetamol group and 32.29 ± 3.25 weeks in the ibuprofen group. The mean of neonatal weight was 1566.73 ± 752.84 g in paracetamol group and 1773.05 ± 663.05 g in neonates receiving ibuprofen. In addition, the mean of hospitalization group was 23.00 ± 18.88 days in the paracetamol group and 17.64 ± 12.50 days in the ibuprofen group.

The mean of first minute Apgar scores was 6.3 ± 2.7 and 7.7 ± 2.2, in paracetamol and ibuprofen groups, respectively. Table 1 shows history of preeclampsia and gestational diabetes and death of neonates during the study.

Data analysis showed that there was no significant difference between pre and posttreatment in PLT count, and creatinine and BUN levels in the two groups receiving paracetamol and ibuprofen (*P* < 0.05) [Table 2].

There was no statistically significant relationship between PDA closure and type of treatment (paracetamol and ibuprofen) (*P* < 0.05) [Table 3].

Feeding intolerance and NEC were significantly higher in paracetamol group than ibuprofen group (*P* > 0.05). Table 4 shows the complications of both treatments.

## Discussion

In this study, there was no significant difference between the paracetamol and ibuprofen groups in platelet count and

**Table 1: History of preeclampsia and gestational diabetes in mothers and death of neonates during study**

| Variables                      | Groups             |                  |
|--------------------------------|--------------------|------------------|
|                                | Paracetamol (n=23) | Ibuprofen (n=17) |
| Have a history of preeclampsia | 1 (4)              | 1 (6)            |
| Having gestational diabetes    | 2 (8)              | 0 (0)            |
| Death of neonates (yes)        | 4 (18)             | 0 (0)            |

**Table 2: PLT count, and creatinine and BUN levels in the two groups receiving paracetamol and ibuprofen at before and after treatment**

| Variables                          | Groups             |                  | P     |
|------------------------------------|--------------------|------------------|-------|
|                                    | Paracetamol (n=23) | Ibuprofen (n=17) |       |
| Plt count (mean±SD) [×103 µ/L]     |                    |                  |       |
| Before                             | 213.34±128.54      | 263±114.05       | 0.205 |
| After                              | 211.56±125.55      | 259.05±105.56    | 0.203 |
| BUN level (mean±SD) [mg/dl]        |                    |                  |       |
| Before                             | 15.39±11.53        | 12.48±5.66       | 0.346 |
| After                              | 18.01±20.78        | 11.87±4.48       | 0.340 |
| Creatinine level (Mean±SD) [mg/dl] |                    |                  |       |
| Before                             | 0.9±1.77           | 0.58±0.19        | 0.392 |
| After                              | 0.57±0.23          | 0.56±0.15        | 0.797 |

creatinine and BUN levels at before and after treatment. In addition, ductal closure was not significantly different between neonates with PDA in the two groups. However, there was a higher incidence of feeding intolerance and NEC between the neonates with paracetamol therapy in comparison with ibuprofen therapy.

In the study by Dang *et al.* conducted on 160 preterm infants (gestational age less than 34 weeks) showed that both paracetamol and ibuprofen had a significant effect on the closure of PDA (81.2% vs. 78.8%). These results are consistent with the findings of our study.<sup>[19]</sup>

In Oncel *et al.* study, PDA closure was not significantly different between neonates receiving ibuprofen and paracetamol, which is similar to the findings of our study.<sup>[32]</sup> Sinha *et al.* indicated that administration of ibuprofen had no effect on the closure of PDA. But after the oral administration of paracetamol in these neonates, PDA closure was seen for 48 h, without any adverse events.<sup>[33]</sup> The finding of this study is opposite to the current study. In the other study by Terrin *et al.*, treatment with ibuprofen or indomethacin produced many side effects, but treatment with paracetamol had no adverse effects or serious complications.<sup>[14]</sup> Dang *et al.* also revealed that hyperbilirubinemia or gastrointestinal bleeding was slightly lower in the paracetamol group than in the ibuprofen group and no other side effects or problems were observed between the two groups.<sup>[19]</sup> Results of these studies are also

**Table 3: Relationship between PDA closure and type of treatment (paracetamol and ibuprofen)**

| Variables             | Groups             |                  | χ <sup>2</sup> | P     |
|-----------------------|--------------------|------------------|----------------|-------|
|                       | Paracetamol (n=23) | Ibuprofen (n=17) |                |       |
| PDA closure (mean±SD) |                    |                  |                |       |
| Yes                   | 22 (96)            | 16 (94)          | 0.048          | 0.826 |
| No                    | 1 (4)              | 1 (6)            |                |       |

**Table 4: Occurrence of gastrointestinal bleeding, OB, feeding intolerance, and NEC after treatment**

| Variables                     | Groups             |                  | χ <sup>2</sup> | P     |
|-------------------------------|--------------------|------------------|----------------|-------|
|                               | Paracetamol (n=23) | Ibuprofen (n=17) |                |       |
| Gastrointestinal bleeding (n) |                    |                  |                |       |
| yes                           | 4 (17)             | 1 (6)            | 5.04           | 0.08  |
| no                            | 15 (66)            | 16 (94)          |                |       |
| Missing data                  | 4 (17)             | 0 (0)            |                |       |
| OB                            |                    |                  |                |       |
| yes                           | 5 (22)             | 3 (18)           | 2.68           | 0.159 |
| no                            | 14 (60)            | 14 (82)          |                |       |
| Missing data                  | 4 (18)             | 0 (0)            |                |       |
| Feeding intolerance           |                    |                  |                |       |
| yes                           | 4 (18)             | 1 (6)            | 6.17           | 0.046 |
| no                            | 15 (60)            | 16 (94)          |                |       |
| Missing data                  | 5 (22)             | 0 (0)            |                |       |
| NEC                           |                    |                  |                |       |
| yes                           | 4 (18)             | 0 (0)            | 7.39           | 0.025 |
| no                            | 15 (64)            | 17 (100)         |                |       |
| Missing data                  | 4 (18)             | 0 (0)            |                |       |

contrary to the finding of the current study, in which side effects of paracetamol was lower than ibuprofen in PDA closure.

In the study of Habibi *et al.*, total PDA closure in the ibuprofen group was 75.7% (n = 28) and in the paracetamol group 87.5%, which was not significantly different (P = 0.179). In addition, in this study, there were no significant differences between the two groups in drug side effects and other clinical complications (P = 0.611).<sup>[27]</sup> In our study, the closure of the PDA was in patients receiving paracetamol nearly 95% and ibuprofen 94%, which was higher than the percentages in Habibi *et al.* study. The incidence of complications in the Habibi *et al.* study was similar in the two groups receiving paracetamol and ibuprofen, but in our study, there was a significant difference in gastrointestinal bleeding and feeding Intolerance between groups, indicating ibuprofen is a preferred treatment option in our study.

The results of a meta-analysis study by Souvik *et al.* indicated that high doses of oral ibuprofen may increase the risk of death and complications such as enterocolitis; however, it may increase PDA closure compared to standard doses of intravenous ibuprofen or intravenous

indomethacin and paracetamol.<sup>[15]</sup> In the Ohlsson and Shah study, the incidence of complications was lower in the paracetamol than ibuprofen.<sup>[34]</sup> In addition, Dani *et al.* reported that incidence of complications in the two groups receiving paracetamol and ibuprofen was not significantly different and the same therapeutic efficacy was obtained for both drugs and paracetamol was suggested as a suitable drug for PDA treatment.<sup>[17]</sup> In the study of Al-lawama *et al.*, there was no statistically significant difference in short-term neonatal outcomes in the both drug therapies.<sup>[26]</sup>

The results of Yang *et al.* study also indicated the same rate of DA closure ( $P = 0.506$ ) and the same complications such as oliguria, blood in stool, intraventricular hemorrhage, NEC, and bronchopulmonary dysplasia in the paracetamol and ibuprofen groups.<sup>[35]</sup> However, in Yang *et al.*, both drugs were administered orally, whereas in our study paracetamol was injected and ibuprofen was administered orally. El-Mashad *et al.* also indicated, there was no significant difference in PDA closure in paracetamol, indomethacin, and ibuprofen groups ( $P = 0.868$ ), which is similar to the results of our study. Furthermore, serum creatinine and BUN increased significantly in the ibuprofen and indomethacin groups ( $P < 0.001$ ) and there was a significant decrease in platelet count and urinary output in both the ibuprofen and indomethacin groups ( $P < 0.001$ ).<sup>[36]</sup> This is opposite with the results in our study since no significant differences were found in platelet count, creatinine, and BUN between the two groups.

The limitation of our study was the low sample size. Thus, it is recommended to conduct a multicenter study with a larger sample size of neonates with PDA. In addition, it is recommended studies aimed to compare different drugs with different administration methods (orally and injectable).

## Conclusions

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

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## Conflicts of interest

There are no conflicts of interest.

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