

Low-dose intravenous acetaminophen versus oral ibuprofen for the closure of patent ductus arteriosus in premature neonates

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Background: Patent ductus arteriosus (PDA) is a common disease in premature neonates, which could occur in up to 50% of the neonates weighting <1000 g. PDA might induce hemodynamic and respiratory disorders and increase mortality and morbidity. This study aimed to compare the effectiveness of oral ibuprofen and a low dose of intravenous acetaminophen in the management of PDA. **Materials and Methods:** This randomized double-blind clinical trial was conducted on the preterm neonates with an equal gestational age of <34 weeks and weight of >1000 g with symptomatic PDA, who were admitted in Shahid Beheshti and Al-Zahra Hospitals Affiliated to Isfahan University of Medical Sciences, Iran. In total, 40 preterm neonates were examined, 20 of whom received 15 mg/kg/6 h of intravenous acetaminophen for 2 days and 20 infants received 10 mg/kg of intravenous ibuprofen on the 1st day and 5 mg/kg for the next 2 days, and the results include vital signs and echocardiography findings were compared. **Results:** In the acetaminophen and ibuprofen groups, 16 (80%) and 17 neonates (85%) responded (PDA closure rate) to the treatment, respectively ($P = 0.68$). Furthermore, acetaminophen and ibuprofen have a similar effect on vital signs. Both drugs did not change in blood pressure, but they reduced the respiratory rate and heart rate after treatment. **Conclusion:** Low-dose acetaminophen compared to ibuprofen has an equal effectiveness in the closure of PDA.

Key words: Acetaminophen, ductus arteriosus, ibuprofen, preterm

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INTRODUCTION

Ductus arteriosus is the connection between the pulmonary artery and descending aorta during the neonatal period, which shunts the main portion of the pulmonary arterial blood into the aorta and naturally closes with the increased arterial oxygen within a few days after birth. If the ductus arteriosus remains open until the reduction of the pulmonary vascular resistance, the blood flow is reversed, and the aortic blood is shunted through the pulmonary artery. If the reduction of vascular resistance is higher, the shunt would be more as well.

Patent ductus arteriosus (PDA) is detected in 1/2000–1/2500 term neonates, and the prevalence

increases in the regions with higher altitude. PDA is common problem in preterm neonates, so that 50% of the neonates weighting <1000 g are diagnosed with this disorder.^[1] Furthermore, spontaneous PDA closure occurs in a high proportion of preterm infants (24%–58%).^[2,3]

In premature infants, PDA might lead to severe hemodynamic and respiratory complications. Indomethacin and ibuprofen have been used in the treatment of PDA.^[4-6] The medication therapy of PDA began with the administration of indomethacin, which led to various complications.^[5] On the other hand, the treatment of PDA by ibuprofen has been shown to be equally effective, while causing fewer

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side effects, lowering serum creatinine (Cr), increasing the urinary volume, and alleviating the adverse outcomes associated with the decreased blood flow to the organs and vasoconstriction.^[3,5,6]

In 22%–30% of the preterm neonates with PDA, who receive a course of indomethacin and ibuprofen treatment, PDA closure does not occur, leading to the need for the higher medication doses or repeated courses of treatment.^[2] Moreover, surgical interventions have been recommended to the patients with no response to the second medication therapy or those with the symptoms of heart failure.^[7]

Reports are variable with regard to the administration of ibuprofen in term neonates.^[8,9] The use of ibuprofen has been associated with potential adverse effects and failure of PDA treatment in a number of patients as well as the cases of neonates with contraindications (e.g., gastrointestinal or brain hemorrhage, thrombocytopenia, coagulopathies, necrotizing enterocolitis, and renal failure). As such, researchers have been concerned with finding an alternative treatment, and some reports have mentioned the positive effects of acetaminophen on PDA.^[10-13] According to the literature, ibuprofen has been prescribed at the therapeutic doses of 10, 5, and 5 mg/kg of body weight during 3 consecutive days,^[14] while acetaminophen is prescribed at the dosage of 15 mg/kg every 6 h for 3 days. Such effectiveness has also been reported in the cases with ibuprofen resistance.^[15-17] Using low-dose acetaminophen (2-day dose vs. 3-day dose) can cause fewer side effects, and it can also reduce the cost of treatment. Considering that when we decided to do the study, limited articles on low-dose acetaminophen were published in this regard, and in Iran, there were no similar studies until then. Therefore, according to the necessity of the study described earlier, this study was first performed at Isfahan University of Medical Sciences, Iran.

The present study aimed to compare the effectiveness of lower acetaminophen doses with ibuprofen in preterm neonates with PDA requiring treatment.

MATERIALS AND METHODS

Study design and participants

This noninferiority randomized double-blind clinical trial was conducted on the 40 preterm neonates randomly allocated to acetaminophen group ($n = 20$) and ibuprofen group ($n = 20$), who were born in Al-Zahra and Shahid Beheshti hospitals in Isfahan University of Medical Sciences, Iran.^[12,16,17] Neonates with the diagnosis of PDA in echocardiography were enrolled in the study. Sampling of the study is fully shown in Figure 1.

This study was approved by the University Ethical Committee with ethical code 396047 and conducted with the parents of patients' informed consent.

Inclusion criteria of the study were as follows:

- Preterm infants with gestational age of ≤ 34 weeks
- Parental consent
- Weight of ≥ 1000 g.

Exclusion criteria of the study were as follows:

- Sepsis
- Diagnosis of ductal-dependent complex congenital heart diseases
- Presence of major or congenital chromosome life-threatening anomalies
- Platelet count of $< 50,000/\text{mm}^3$
- Severe coagulopathies
- Severe asphyxia at birth.

Procedures and assessment of variables

All the preterm neonates aged < 34 weeks and weighting of ≥ 1000 g who had heart murmur or cardiovascular, respiratory, and hemodynamic disturbance were examined and echocardiography was done by a pediatric cardiologist. In addition, echocardiography was performed using a 4MH2 transducer (model: MEDISON ACCUVIIXV100, South Korea); in the case of PDA diagnosis, they were randomly divided into two groups.

The randomized trial was as follows: neonates whose number of hospital records were paired were selected as the first group or the acetaminophen group and neonates whose number of hospital records were odd were selected as the second group or the ibuprofen group.

Neonates in the first group received 15 mg/kg/dose of intravenous acetaminophen every 6 h for 2 days and for 1–2 courses, and the patients in the second group received oral ibuprofen (10mg/kg/day first day and 5mg/kg/day for second and third day) orally for 3 days and for 1–2 courses. Neonates of acetaminophen group not received oral acetaminophen. Three days after the medication therapy, the study groups were examined again, and echocardiography was repeated. Moreover, we evaluated the respiratory, cardiovascular, and hemodynamic indices of the infants.

The second course of choice drug was initiated in the symptomatic neonates of both study groups, in whom PDA closure did not occur after the first course of choice drug. In the case that PDA remained open after the second course of choice drug, it was known as drug resistant (4 patients in acetaminophen group and 3 patients in ibuprofen group); the medications were replaced with other alternatives; on the other hand, in the presence of ibuprofen resistance,

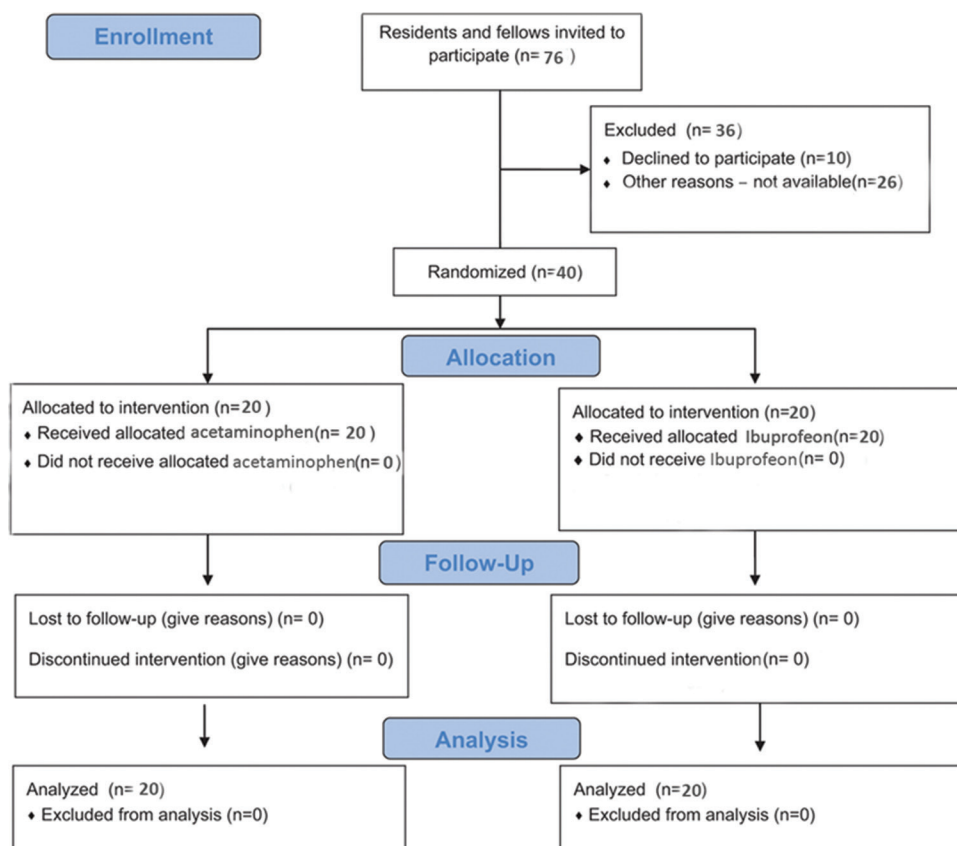


Figure 1: Flow diagram of patients' recruitment

acetaminophen was administered, and in the cases of acetaminophen resistance, ibuprofen administration was initiated course; the second treatment courses were prescribed if necessary, and the results were assessed.

The basis of PDA closure in this study was echocardiography after each course of medication by a pediatric cardiologist, so that for each neonate, at least 2 times to 5 times during the treatment, echocardiography was performed.

Finally, the obtained results were compared between the two study groups. Before and after the research, complete blood count, blood urea nitrogen (BUN), Cr, serum bilirubin level, and urine test were conducted and recorded. In previous studies and this study, the drug is administered at least 1–2 courses maximum, and the overall effectiveness of drug administration is assessed by considering the results of both courses from a single drug.

The neonatologist was aware of the administered medication in the neonates, whereas the pediatric cardiologist and the patients and his parents were blinded to the administered medication of the infants. Hence, this study was done in double blind.

Statistical analysis

Data analysis was performed in Excel version 2010 and SPSS version 19 (IBM, Armonk, NY, USA) at the significance level

of 0.05; quantitative and categorical data were presented as mean \pm standard deviation (minimum–maximum) and frequency (percentage), respectively. Normality of data was evaluated using Q-Q plot and Kolmogorov–Simonov test.

Within-group comparisons based on quantitative data were conducted using paired samples *t*-test while between-group analyses were performed using independent samples *t*-test. Between-group analyses based on categorical data were done using Chi-square test.

RESULTS

In total, 40 patients were studied in two groups, 20 of whom received ibuprofen and 20 neonates received acetaminophen. Demographic characteristics of the infants are presented in Table 1, and no significant differences were observed between the groups in this regard.

In neonates who received acetaminophen, 12 cases (60%) had a positive response after one treatment course ($P < 0.001$) and 4 cases (20%) had a positive response after two treatment courses. In this group, 16 neonates (80%) positively responded to 15 mg/kg of acetaminophen, and 4 patients needed a second agent (ibuprofen). Among these four cases, PDA closure occurred in two infants (10%) with one treatment course, while in one case (5%), it occurred with

two ibuprofen treatment courses. Furthermore, one of the neonates in this group had no response to either of the drugs, and PDA closure did not occur.

In the group of neonates who were administered with ibuprofen, 13 cases (65%) showed a positive response with one treatment course, 4 cases (20%) with two treatment courses, and overall, in this group, 17 neonates were responded positively and the rate of positive response to ibuprofen drug was 85%. In addition, three neonates needed a second agent (acetaminophen) in this group. Among these three patients, two cases (10%) experienced PDA closure with one course of acetaminophen treatment, whereas one infant (5%) in this group showed no response to the prescribed medications, and PDA remained open.

Comparison of the groups after administrating the first dose of the medication, $P = 0.80$ indicates that the prescribed agent was equally effective in both groups, with no significant difference in this regard. In the patients with open PDA who received the second treatment course, PDA closure occurred in four cases in each group ($P < 0.001$ for both drugs), and in the comparison of the two drugs, $P = 0.38$ indicates no significant difference in this regard.

In the third and fourth stage, where the medication was changed, no statistically significant differences was found between two studied groups in terms of respond to treatment,

in which in the acetaminophen group, 3 neonates (15%) responded to ibuprofen, while in ibuprofen group, 2 (10%) neonates responded to acetaminophen ($P = 0.86$).

Information of PDA closure rate in this study is presented in Figure 2 and Table 2.

According to the results showed in Table 3, there was no significant difference in the blood pressure of the neonates within acetaminophen ($P = 0.24$) and ibuprofen ($P = 0.91$) before and after treatment; also, no significant difference was observed between two groups ($P = 0.35$). In terms of the heart rate, a significant decrease was observed within each group after the treatment with a significant difference ($P < 0.001$), while the comparison of the groups showed no significant difference in this regard ($P > 0.05$). Moreover, respiratory rate reduced within both groups with a significant difference before and after the treatment ($P < 0.001$), while the comparison of the groups showed no significant difference in this regard ($P > 0.05$). In this study, no complications were observed in both groups.

DISCUSSION

The ductus arteriosus starts to close after birth with the sudden increase of the arterial oxygen, and this process is completed within a few days after birth. Reduction of the endogenous prostaglandins could accelerate this process. Synthesis of prostaglandins is possible through the cyclooxygenase and peroxidase pathways. Acetaminophen inhibits the peroxidase

Table 1: Basic characteristics of participants in study groups

Variable	Ibuprofen group	Acetaminophen group	P
Gestational age (week)	29±4 (24.3-33.5)	29±3 (26-34)	0.91*
Weight (g)	1300±81 (1000-2500)	1263±90 (1000-2500)	0.76*
Sex (%)			
Boy	12 (60)	10 (50)	0.52**
Girl	8 (40)	10 (50)	
Delivery type (%)			
Cesarean section	17 (85)	13 (65)	0.14**
Vaginal	3 (15)	7 (35)	

Values are mean±SD (minimum–maximum) for quantitative and frequency (%) for categorical data. *Based on t-test; **Based on Chi-square test. SD=Standard deviation

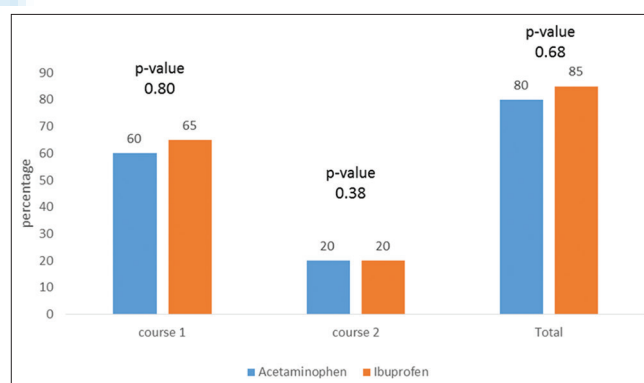


Figure 2: The rate of closed patent ductus arteriosus in study groups

Table 2: Patent ductus arteriosus closure rate in acetaminophen group and ibuprofen group

Variable	Ibuprofen group	Acetaminophen group	P
PDA closure rate after first course of first drug (choice drug)	13 (65)	12 (60)	0.80
PDA closure rate after second course of first drug (choice drug)	4 (20)	4 (20)	0.38
PDA closure rate after a total of two courses of choice drug	17 (80)	16 (80)	0.68
PDA closure rate after first course of alternative drug (acetaminophen for ibuprofen group and vice versa)	2 (10)	2 (10)	0.86
PDA closure rate after second course of alternative drug (acetaminophen for Ibuprofen group and vice versa)	0 (0)	1 (5)	0.88

PDA=Patent ductus arteriosus

Table 3: Mean of vital signs in ibuprofen and acetaminophen groups

Variable	Ibuprofen group	Acetaminophen group	P
Blood pressure			
Before treatment	45.40±1.31	49.95±1.23	0.35**
After treatment	45.50±0.101	49.10±0.9	
Difference	+0.1±3.57	-0.85±2.68	
P	0.91*	0.24*	
Heart rate			
Before treatment	182.90±1.38	172.90±5.40	0.59**
After treatment	165.90±3.09	159.40±3.29	
Difference	-17.00±14.59	-13.5±25.10	
P	<0.001*	<0.001*	
Respiratory rate			
Before treatment	72.56±1.12	70.40±1.29	0.57**
After treatment	56.90±2.18	56.40±2.07	
Difference	-15.90±11.04	-14.00±10.17	
P	<0.001*	<0.001*	

*Resulted from paired samples t-test; **Resulted from independent t-test or Mann-Whitney U-test

and ibuprofen inhibits the cyclooxygenase pathway. The present study aimed to evaluate and compare the effects of ibuprofen and acetaminophen on the closure of ductus arteriosus in premature neonates.

The effectiveness of acetaminophen in this study was estimated at 80% compared to the previous studies. Several studies have investigated the effects of ibuprofen on the closure of PDA in patients.^[6,18] For instance, Linder *et al.* compared 46 patients receiving indomethacin and 73 patients receiving ibuprofen, reporting the drugs to be equally effective. Furthermore, the indomethacin groups experienced more side effects comparatively.^[6] In the mentioned study, the groups were evaluated and compared at different times.

In another study by El-Mashad *et al.*, three patient groups were compared, receiving indomethacin, ibuprofen, and acetaminophen. In the mentioned study, BUN and Cr of the patients in the indomethacin group and bilirubin level in the ibuprofen group increased, while all the groups equally benefited from the drug therapy with regard to PDA closure.^[19] Other studies have also reported the effectiveness of acetaminophen. In 2011, PDA closure was confirmed after acetaminophen therapy, which was followed by other reports in this regard. In patients who are not allowed to use ibuprofen, acetaminophen administration for 3 days began with the mechanism of peroxidase pathway inhibition.^[16,17,19]

However, in this study, no increase was observed in the BUN and Cr and hepatic enzymes of our patients, which was measured at the beginning and end of treatment.

The main difference between the present research and other studies is the doses of prescribed medications. In

previous studies, acetaminophen was administered as one to two courses which each course of drug was administered with the dosage of 15 mg/kg/6 h for 3 days, while we administered the drug for a shorter duration (2 days for each course). In previous studies and also this study, the overall effectiveness of drug administration is assessed by considering the results of both courses from a single drug, and thus, the effectiveness of acetaminophen in this study was estimated at 80% compared to the previous studies. Dang *et al.* studied 160 infants with gestational age ≤34 weeks treated with 15 mg/kg every 6 h for 3 days of paracetamol or ibuprofen at standard dose. They found that the ductus was closed in 81.2% of infants in the paracetamol group compared with 78.8% of infants in the ibuprofen group.^[20] In this regard, using the binomial test and considering the chance of success rate of 81.2% of the study, there was no significant difference in the closed PDA between the current study and the standard dose ($P=0.53$).

Furthermore, in the present study, patients who did not respond to one of the drugs were treated with another drug, as three out of four neonates which not response to the acetaminophen responded to ibuprofen treatment in the next stage, and two out of three out of four neonates which not response to the acetaminophen responded to ibuprofen treatment in the next stage, and two out of three neonates which not response to the ibuprofen responded to acetaminophen treatment after replacing the drugs, and thus, surgical closure of PDA was not necessary, while in previous research, surgical interventions were the main solution after resistance to the first drug.^[7] This change of the drug regime can be the subject of further research.

According to the results of the current research, shorter duration of treatment caused no changes in the effectiveness of acetaminophen, which can be confirmed by further studies. Moreover, we observed that in the case of resistance to one of the medications, an alternative drug could be considered in order to increase the response rate of the patients to the treatment. Our findings are in line with the results of the previous studies regarding the equal effectiveness of ibuprofen and acetaminophen in PDA closure. In addition, if confirmed by other investigations, it can be recommended lower doses of these drugs for the treatment of PDA.

One of the issues to be addressed and difficult to answer is that whether further investigation would distort research findings when many studies have confirmed that PDA closure occurs spontaneously in a high proportion of the cases.^[2,3] In this regard, accurate selection of patients could minimize errors, since without the treatment, some of various respiratory and cardiovascular symptoms could occur and the disorder may progress and lead to adverse complications in the patient.

One of the limitations of the present study was the small sample size because of the prevalence of 12%–15% of preterm infant birth in Isfahan and also the prevalence 14% of PDA in preterm infants of Isfahan, and this issue led to the sampling of this study prolonged for 2 years. Furthermore, a total of 76 preterm infants with gestational age of ≤ 34 weeks with weight of ≥ 1000 g who had a PDA were identified for study. However, unfortunately, 36 of them for medical reasons (sepsis, coagulopathy, ductal dependent cyanotic congenital heart disease, gastrointestinal bleeding (GIB)) drug administration was contraindication and could not be entered in the study; finally, the above issues led to a small sample size due to the limited resources available, and the findings have to be examined on larger samples sizes. Furthermore, the use of alternative drugs has to be further studied and approved by future investigations.

CONCLUSION

According to the results, 15 mg/kg/dose q 6 h of acetaminophen for 2 days had the same effects as the previously recommended 3-day dose and was equally effective in the closure of PDA, if confirmed by other investigations, can be recommend lower doses of these drugs for the treatment of PDA. Furthermore, low-dose acetaminophen compared to ibuprofen has an equal effectiveness in the closure of PDA. In the case of resistance to one of the medications, an alternative drug could be considered in order to increase the closure rate of the PDA which can approved by future investigations.

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Conflicts of interest

There are no conflicts of interest.

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