

The Effect of Oral Ibuprofen on Closure of Patent Ductus Arteriosus in Term Neonates: A Clinical Trial Study

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Abstract

Background

The function of ductus arteriosus closes within a few minutes to a few days after birth in term neonates. In some cases, the duct remains open after birth, a condition which is called patent ductus arteriosus (PDA). PDA is associated with high rates of neonatal mortality and morbidity. The present study aims to evaluate the effect of oral ibuprofen on closure of PDA in term neonates.

Materials and Methods

In this clinical trial, 40 neonates (at the gestational age of 37 weeks and more) aged 5 to 30 days, with confirmed PDA through echocardiography, were randomly divided into two groups (n= 20). One group received ibuprofen syrup (10 mg/kg body weight) in the first 24 hours, followed by 5 mg/kg body weight for the next four days. The other group received placebo in the same manner. On the seventh day after the beginning of intervention, neonates underwent echocardiography for examination of PDA closure. Side effects of ibuprofen were evaluated. Symptoms of kidney failure, such as oliguria, edema, and proteinuria and increased creatinine, as well as gastrointestinal side effects such as gastrointestinal bleeding and recurrent vomiting, were assessed for one month.

Results

According to the results, PDA diameter was not significantly different in ibuprofen compared to the placebo groups before ($p>0.05$) and after ($p>0.05$) intervention. Frequency of PDA closure was 13 (65%) in the ibuprofen group and 10 (50%) in the placebo group with no significant difference ($p>0.05$). There was no significant difference in the mean systolic and diastolic pressure gradient after intervention and in mean changes in pulmonary arterial hypertension between the two groups ($p>0.05$). No side effects were observed in any of the groups.

Conclusion: Based on the results, oral ibuprofen did not significantly affect PDA closure in term neonates.

Key Words: Ibuprofen, Patent ductus arteriosus, Term neonate.

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1- INTRODUCTION

The ductus arteriosus is a blood vessel that connects the pulmonary artery to the aorta. In the mother's uterus, blood is shunted from the pulmonary aorta due to higher pressure in the lungs. Therefore, blood exits from the right ventricle and enters the ductus arteriosus through which it can finally enter the aorta. Prostaglandins are strong vasodilators that keep the ductus arteriosus open in the uterus. In normal conditions, the resistance of the pulmonary artery gradually decreases after birth under the influence of respiratory oxygen. Subsequently, blood enters the pulmonary circulation and takes the prostaglandins into the lungs, where they metabolize and eliminate from the circulation. Oxygenated blood also plays an important role in the closure of the ductus arteriosus. Normal fetal circulation depends on the placenta and patent ductus arteriosus (PDA), and changes after birth due to placenta abruption and the onset of pulmonary circulation. The ductus arteriosus immediately starts to close after birth (1, 2).

The equilibrium between the contractile effects of oxygen and dilating effects of prostaglandin plays an essential role in the PDA (3). The effects of these substances depend on the intrauterine age of the neonate; in preterm neonates, the susceptibility of the ductus arteriosus to the effects of prostaglandin-induced PDA is higher, yet decreases as age advances. Therefore, PDA prevalence is high in preterm infants, and up to 65% in extremely premature infants (4). In term neonates with normal birth weight, the ductus arteriosus usually closes within three days after birth (5). The PDA occurs in 1 term neonate per 2,000 live births (6). The clinical outcome of PDA is associated with the size of left-to-right shunt through the ductus arteriosus, which is related to changes in blood flow in the lungs, kidneys, and intestines (7-11). Currently,

the first choice of treatment for PDA in preterm infants is drug therapy using cyclooxygenase inhibitors (12). The use of injectable or oral indomethacin for closure of ductus arteriosus has led to successful non-surgical closure of PDA in many neonates (15-13). However, indomethacin therapy is associated with adverse complications such as decreased cerebral, mesenteric, and renal perfusion (16, 17). Ibuprofen has been considered as a possible alternative to indomethacin (18-23). Available evidence shows a comparable rate of PDA closure after ibuprofen therapy (24-26).

Unlike indomethacin, Ibuprofen has a lower effect on urine output and renal function (18, 19). Additionally, ibuprofen has a greater effect on brain blood flow, but has not yet been reported to reduce intraventricular hemorrhage (IVH) risk (20, 22, 23). Because of the availability and cost-effectiveness of oral ibuprofen compared to injectable ibuprofen, many physicians use this therapeutic regimen to close PDA (16, 17, 27). If drug therapy is not possible or successful, surgery or coil catheterization can be performed. PDA is due to physiological developmental disorder in preterm infants, whereas abnormal PDA closure is associated with a major structural anomaly in term neonates.

For term neonates, treatments of choice include catheterization and surgery, of which catheterization is preferred due to fewer complications and shorter recovery time. Indomethacin is not effective in treating PDA in term neonates, and, therefore, is not recommended for this purpose (12). The use of intravenous or oral indomethacin and ibuprofen has been approved for preterm infants, but their use for term neonates has only been investigated in experimental research. Currently, the traditional treatment of PDA in term neonates is surgery, which is associated with high rates of mortality and morbidity and huge costs (28). Adverse

effects such as recurrent laryngeal nerve injury, chylothorax (thoracic duct injury), and pneumothorax have also been reported (29). As for the coil catheterization, the shunt is more likely to remain after the closure of the large arterial duct, which in some cases leads to the destruction of red blood cells and consequently, hemolysis and acute renal failure (30). Besides, coil embolization into the pulmonary circulation is likely done in the large arterial duct (31). Nevertheless, few studies have been conducted on the efficacy of cyclooxygenase inhibitors such as ibuprofen for the closure of PDA in term neonates (28). Since previous studies have come up with controversial findings, and ibuprofen remains to be used as a widely acceptable treatment for PDA in term neonates, further studies are needed to prove or rule out ibuprofen's efficacy and provide evidence to support or reject ibuprofen therapy for PDA in term neonates, in order to minimize the use of catheterization and surgical procedures and associated risks. This study is aimed to investigate the effect of oral ibuprofen as a safer, cheaper, and more available method for treating PDA in term neonates.

2- MATERIALS AND METHODS

2-1. Study design

The present study is a clinical trial (IRCT20190204042618N1), performed on 40 neonates referred to Imam Ali Clinic or admitted to Hajar Hospital in Shahrekord, Iran.

2-2. Methods

The samples were gradually selected by simple convenience sampling. Term infants (at the gestational age of 37 weeks) aged 5 to 30 days showing PDA symptoms such as tachycardia, full pulses, decreased blood oxygen saturation, hemodynamic, respiratory, murmur, and other problems related to the ductus arteriosus by the

physician decision, underwent echocardiography.

2-3. Measuring tool

After confirmation of PDA by echocardiographic examination and measurement of the ductus arteriosus size, systolic and diastolic blood pressure gradient, pulmonary hypertension, and other inclusion criteria in the neonates were examined. The neonates were randomly divided into two groups (n= 20). Physical examinations were performed for signs of congestive heart failure including cardiomegaly, tachycardia and tachypnea tachycardia, gallop rhythm, dyspnea, tachypnea, and heart murmur in both groups. Intervention group received the oral ibuprofen syrup and control group received placebo only.

2-4. Intervention

Intervention group received oral ibuprofen (initial dose of 10 mg/kg/day, then four doses of 5 mg/kg/day for the next four days). Control group received placebo in the same manner. The neonates were examined for the side effects of the drug, including gastrointestinal, renal, dermal, and other potential complications. The drug was given by the mothers on the advice of the researcher, but the echo technician did not know the type of drug administered and echocardiography was performed in two different centers.

2-5. Ethical considerations

The study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (Ethics code: IR.SKUMS.REC.1397.1). It should be noted that the development of any of the complications is indicated in the patient's symptoms, and in case of outpatient visits, parents were advised to refer to the specialist if they noticed any changes in their infant's conditions. Echocardiography was performed on all infants seven days after beginning of the

intervention and the size of the ductus arteriosus, systolic and diastolic blood pressure gradient, and pulmonary hypertension were examined. If the ductus arteriosus had closed and no other complication was developed after the first therapeutic intervention, an additional ibuprofen therapeutic regimen would start in the similar scheme to the first. Echocardiography was then performed again in this group at 30 days of age to examine the closure of PDA.

2-6. Inclusion and exclusion criteria

The infants were included in the study by the parents’ consent for their participation. The infants would be excluded if they had gastrointestinal bleeding, increased creatinine, and decreased urine output.

3- RESULTS

In this clinical trial, with the aim of investigating the effect of oral ibuprofen on PDA closure in term neonates, 40 neonates (at the gestational age of 37 weeks and over) aged 5 to 30 days who had PDA were randomly assigned into two groups (n= 20). One group received ibuprofen tablets (10 mg/kg/day on the first day and 5 mg/kg/day in the next four days), and one group was given a placebo syrup. The general characteristics of the patients in the two groups are presented in **Table.1** and **Figure.1**. There was no significant difference in gestational age, chronological age and weight between the two groups (p<0.05). There was also no significant difference in gender between the two groups (p>0.05, **Figure.1**).

Table-1: General characteristics of the patients under study.

Variables	Ibuprofen	Control	P-value
	Mean ± SD	Mean ± SD	
Gestational age	1.2±38.65	1.4±38.55	0.69
Chronological age	4.15±11.15	5.41±13.35	0.19
Weight (g)	698±3040	442±3042	0.06

SD: Standard deviation.

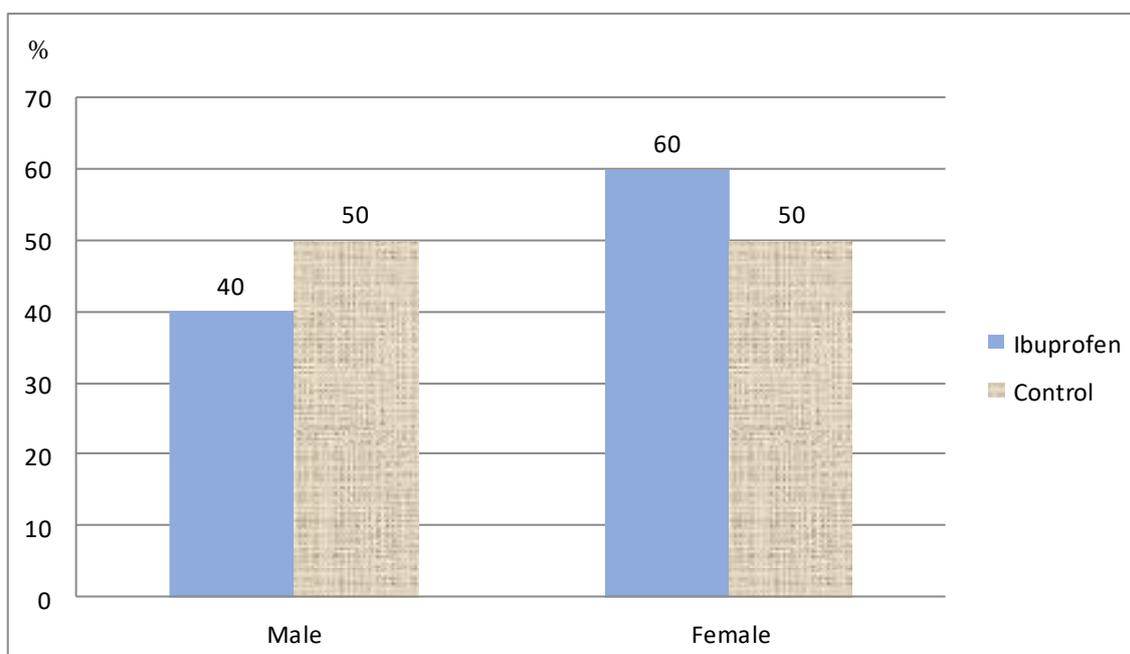


Fig.1: Qualitative general characteristics (gender) of the patients under study.

The results regarding the frequency and percentage of closure of the PDA on the 7th day after the beginning of the intervention in the studied groups are shown in **Figure.2**. In our study, PDA closure occurred in 13 patients (65%) in the case group and 10 (50%) in the placebo group with no statistically significant difference ($p < 0.05$). As previously mentioned, in case of PDA closure after the first therapeutic regimen and no drug-related complications, an additional regimen was performed in the ibuprofen group similar to the first regimen. Afterwards, echocardiography was performed again at 30 days of age in the ibuprofen group to examine PDA closure. The results showed that PDA closed after

the second therapeutic regimen at age 30 days in two out of seven neonates (28.6%) in the ibuprofen group whose ductus arteriosus had remained open after the first therapeutic regimen. The diameter of PDA in the group receiving ibuprofen and the control group were not significantly different before and after the intervention ($p > 0.05$, **Table.2**). The decrease in the diameter of PDA after intervention was more pronounced in the ibuprofen group than in the control group by an average of 0.57 mm, but the difference in PDA reduction between the two groups was not statistically significant. No gastrointestinal, renal, and skin complications were observed in either of the groups after intervention.

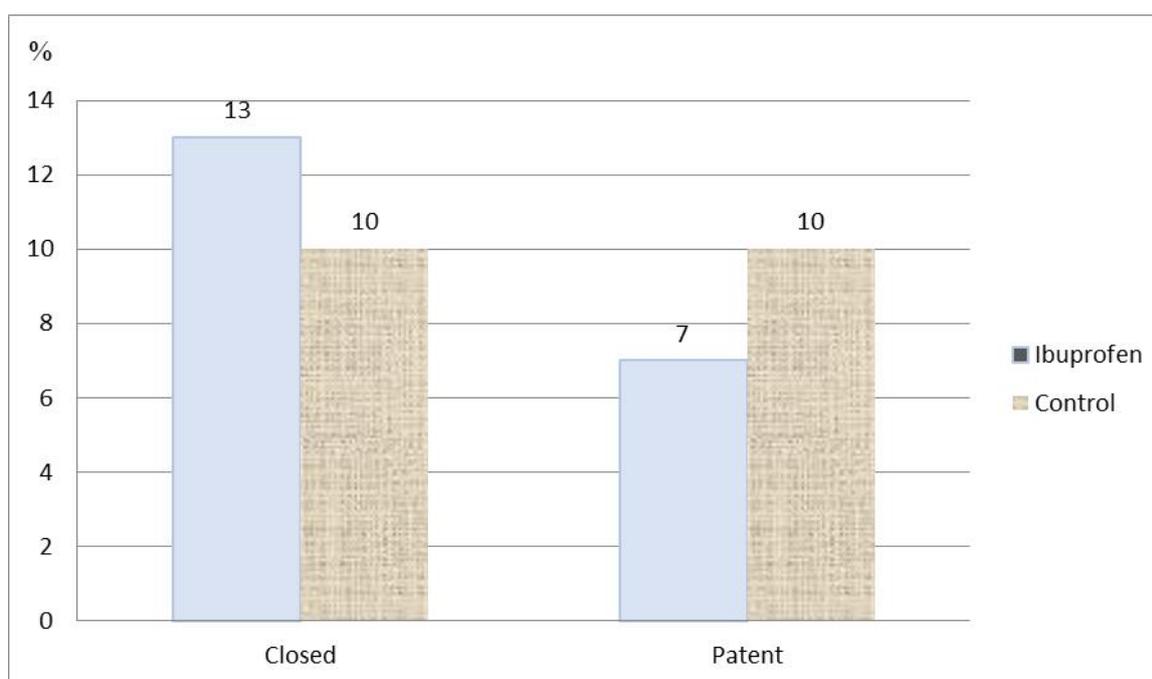


Fig.2: Frequency and percentage of patent ductus arteriosus closure after intervention in the studied groups.

Table-4: Comparison of mean patent ductus arteriosus diameter before and after intervention.

Variables	Ibuprofen, n=20 Mean \pm SD	Control, n=20 Mean \pm SD	P value
PDA diameter (mm) before intervention	0.33 \pm 2.7	0.40 \pm 2.53	0.18
PDA diameter (mm) after intervention	1.11 \pm 0.75	1.23 \pm 1.15	0.34
Change of PDA diameter (mm)	1.06 \pm 1.95	1.16 \pm 1.38	0.09

PDA: Patent ductus arteriosus, SD: Standard deviation.

4- DISCUSSION

The present study aimed to evaluate the effect of oral ibuprofen on closure of PDA in term neonates. PDA diameter was not significantly different between ibuprofen and placebo groups before and after intervention. Frequency of PDA closure was 13 (65%) in the ibuprofen group and 10 (50%) in the placebo group with no significant difference. Usually, in term neonates the ductus arteriosus closes within a few days after birth. In some cases, however, it does not, a condition which is referred to as PDA (32). The incidence rate of PDA in term neonates varies from 1 in 2000 to 1 in 2500 (33). Mortality and morbidity in neonates with PAD are increased due to heart failure and, in rare cases, infective endocarditis. In addition, pulmonary vascular disease may also develop in these patients. Ductus arteriosus closure is important in treatment of cardiovascular and respiratory problems in neonates (34). Therefore, more clinical trials are needed to recommend certain drugs such as indomethacin and ibuprofen for closure of PDA in term neonates (28).

In the present study, PDA closed in 13 neonates (65%) receiving ibuprofen and 10 (50%) receiving placebo on the 7th day after the beginning of intervention. In our study, which is consistent with the study of Amoozgar et al. (28), the rate of PDA closure was higher in the ibuprofen group than in the placebo group, but the difference was not statistically significant, probably due to the lower sample size and the higher age of neonates in our study compared to Amoozgar et al. These inconsistencies in the findings suggest that the effect of ibuprofen on PDA closure may vary on different days after the onset of intervention. In our study, ibuprofen did not cause any side effects, which is consistent with the findings of Amoozgar et al. (28). The findings of Pour Arian et al. (2015) were compared with those of the study by Amoozgar et al. using the

standard dose of ibuprofen. The 29 neonates in the study of Pour Arian et al. received the highest dose of ibuprofen (initial dose of 20 mg/kg on the first day, two doses of 10 mg/kg /day in the next two (second and third) days). In 18 newborns, the PDA closed 4 days after the beginning of the treatment (62.1% vs. 43.3% for standard dose and 4.7% for the control group in the previous study). In our study, this rate was 65% on day 7, which is roughly the same as the rate in the study of Pour Arian et al. Despite the high dose of ibuprofen used in the study of Pour Arian et al., the similarity of PDA closure rate in both studies is probably due to the longer period of treatment in our study.

Similarly, although the ibuprofen administered in the study of Pour Arian et al. was twice the dose of our study, PDA size decreased by 1.95 mm in our study compared 1.32 mm in that of Pour Arian et al. This may be due to the fact that, although our administered dose was half the dose of Pour Arian et al., the drug was administered for 5 days in our study but only for 3 days in the study by Pour Arian et al. (37). In our study, PDA closed in 65% of the neonates in the ibuprofen group and 50% in the control group with no statistically significant difference, which is similar to the study by Alipour et al. It appears that the lack of significant effects of ibuprofen in our study was due to the small sample size.

In the study of Alipour et al. where the sample size was larger, this result was probably due to delayed echocardiography and examination of PDA closure (on day 21) compared to other studies (38). In a study by Yantie et al. (2017) in Indonesia, term neonates with PDA were divided into two groups (n: 16): the case group (receiving ibuprofen at 10 mg/kg on the first day, and two doses of 5 mg/kg/day in the next two days) and the control group (receiving placebo). PDA closed in 8 neonates in the ibuprofen group and 10 in

the control group with no statistically significant difference. In our study, PDA closed in 13 neonates in the ibuprofen group and 10 neonates in the control group with no statistically significant difference (39). It should be noted that in the mentioned study, the sample size was also small (in each group included 16 neonates). The sample size in a study by Deng et al. (40) was similar to our study, and the times of echocardiography and the examination for PDA closure were almost the same in both. Contrary to our study, however, the rate of PDA closure was significantly different between indomethacin (76%) and control (25%) groups. In our study, the rate of PDA closure was 65% in the ibuprofen group and 50% in the control group without any statistically significant difference. In many studies as already mentioned, ibuprofen has been observed to have a similar efficacy as indomethacin in preterm neonates (23, 24).

However, compared to those, indomethacin was found to be highly efficient to close the PDA in term neonates, whereas ibuprofen was not as effective. More studies are needed on the effects and efficacy of different drugs in term neonates. Drug responses can also vary in different individuals. For example, genetic polymorphism can cause different clinical responses and side effects in different individuals. Pharmacokinetic and pharmacodynamic characteristics of ibuprofen in full-term infants can have an impact on the interpersonal differences in response to the drug (39).

It should therefore be noted that, despite the similarities in their design, the cited study was conducted in China and ours in Iran, and the genetic differences in drug responses of the two studies might have led to different rates of drug response and, subsequently, different observations in the two studies. In our study, no gastrointestinal, renal or skin

complications were observed in any of the samples, which is consistent with other studies with ibuprofen. Finally, the differences in the findings of the two studies might be due to differences in study populations, sample size, dosage, and the duration of the therapeutic regimen, as well as difference in the time of echocardiography. However, since ibuprofen did not cause any side effects in our study, it can be further studied for PDA closure treatment in term neonates before surgery.

5- CONCLUSION

According to the results of this study, there was no significant difference in PDA closure rate and mean change in PDA diameter between ibuprofen and placebo groups. In addition, there was no significant difference in mean changes in systolic and diastolic pressure gradient and mean change in pulmonary hypertension between the two groups after intervention. Finally, the results of this study showed that oral administration of ibuprofen did not significantly affect PDA closure in term neonates.

6- CONFLICT OF INTEREST: None.

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