

Comparison of Therapeutic Effects and Side Effects of Oral Ibuprofen and Indomethacin on the Closure of Patent Ductus Arteriosus in Premature Infants

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ABSTRACT

BACKGROUND AND OBJECTIVE: Patent ductus arteriosus (PDA) is a common problem in premature infants. Indomethacin is the first effective drug used to treat this problem and due to the side effects of this drug, intravenous ibuprofen is one of the recommended drugs in this field. Due to the unavailability of intravenous form of these drugs in Iran, this study was conducted to compare therapeutic effects and side effects of the oral form of ibuprofen and indomethacin on the closure of PDA in premature infants.

METHODS: In this randomized clinical trial, 80 premature infants (less than 32 weeks) with symptomatic PDA, who required treatment were randomly divided into two groups of 40 and were treated with indomethacin or oral ibuprofen. Results (changes in PDA size and percentage of recovery) and complications (changes in creatinine and serum bilirubin, intraventricular hemorrhage, necrotizing enterocolitis and death) of treatment were recorded and compared between the two groups. (IRCT: 2015111024977N1)

FINDINGS: There was no significant difference between the two groups in terms of confounding variables. The treatments had to be repeated for ten percent of patients (four patients) in both groups. PDA size did not change in ten percent of patients (four patients) in indomethacin group and did not change in seven point five percent of patients (three patients) in ibuprofen group. The two groups did not differ significantly in terms of probable side effects. None of the patients in the two groups needed surgery.

CONCLUSION: Considering that in this study, the response rate and side effects of oral ibuprofen and indomethacin did not differ significantly, this drug could be an appropriate alternative for indomethacin when necessary.

KEY WORDS: *Indomethacin, Ibuprofen, Patent Ductus Arteriosus, Infants.*

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Introduction

Ductus arteriosus is a large communication link that is normally open in the embryo and connects the trunk of the pulmonary artery to the descending aorta, and the major part of the heart's blood is transmitted to the systemic bloodstream, and in term infant, the ductus arteriosus is closed functionally in the first few hours after birth and after about 96 hours, the blood does not pass through the duct (1). Ductus arteriosus is 20% closed during the first day, 82% closed during the second day, 96% closed during the third day and 100% closed during the first 96 hours after birth (2). Several causes lead to ductus arteriosus.

As arterial oxygen pressure increases with ventilation of the lungs, the balance between the oxygen contraction effects and prostaglandin stimulating effects plays a significant role in patent ductus arteriosus (PDA) (2). On the other hand, the effects of these substances depend on the intrauterine age of the infant, and in the premature infant, the duct is more sensitive to prostaglandin-induced effects and decreases with age, which is why PDA is more prevalent in premature infants (3).

The first drugs used for the closure of PDA were prostaglandin synthesis inhibitors such as indomethacin, which, given the relatively common side effects, were attempted to be replaced, and the US Food and Drug Administration allowed the use of ibuprofen lysine intravenously in symptomatic cases. Previous studies have shown that ibuprofen is as effective as indomethacin, but ibuprofen decreases renal and mesenteric blood flow less than indomethacin and has fewer renal complications (4). However, long-term studies on the effect of ibuprofen on the brain function of premature babies and their development are not available yet (5).

Most concerns regarding the use of indomethacin are related to drug safety, renal effects, cerebral perfusion and digestion. Some studies suggest that intravenous ibuprofen can be used for the treatment and prevention of PDA in premature infants without a reduction in cerebrospinal fluid flow or hemodynamic damage to the kidneys or reduced digestive perfusion (6). However, ibuprofen itself can also be associated with complications such as bronchopulmonary dysplasia, renal failure, digestive complications (NEC and spontaneous intestinal perforation), and intracerebral and pulmonary hemorrhage and increased bilirubin (1). Considering that all previous studies were conducted on intravenous ibuprofen and indomethacin

or the oral form was compared with the intravenous form, and given that intravenous forms of these drugs are not yet available in Iran, this study was conducted to compare therapeutic effects and side effects of the oral form of ibuprofen and indomethacin on the closure of PDA in premature infants.

Methods

This clinical trial was approved by the Ethics Committee of Qom University of Medical Sciences (IR.MUQ.REC.1393.138) and was conducted in clinical trials registry (IRCT: 2015111024977N1) as a randomized double-blind clinical trial among all premature infants with PDA in Izadi and Hazrat – e – Masoumeh hospitals in Qom. Infants with gestational age less than 32 weeks, birth weight less than 1500 grams, age below one month to initiate treatment, with hemodynamic (LA aortic root diameter ratio > 1.4 or ductal size > 1.5mm) or symptomatic PDA who required treatment, respiratory distress syndrome, requiring respiratory support (NCPAP ventilator or $\text{Fio}_2 > 30\%$), were included in the study.

The PDA was detected by observing the left-to-right shunt through ductus arteriosus in echocardiography (7). Laboratory data, demographic data and clinical outcomes were recorded during the study. Infants with congenital heart defects, life – threatening infection, clinical or radiographic evidence of necrotizing enterocolitis, bleeding, platelet counts less than about 60,000/mL, liver failure, severe intracerebral hemorrhage (grades 3 and 4) and severe hyperbilirubinemia (close to the exchange transfusion), creatinine more than 1.5 or urea nitrogen more than 50, obvious bleeding (bleeding from the trachea, gastric contents, feces, hematuria or from the site of bleeding), and in cases where the mother or the infant was treated with any non-steroidal anti-inflammatory agent or drugs that had an effect on ibuprofen metabolism were excluded from the study.

Convenience sampling was used and the grouping was done based on random allocation using block randomization method. Six quartet blocks were used (including AABB, ABAB, ABBA, BBAA, BABA, and BAAB) and one of the blocks was randomly selected. Sampling continued until sample size was complete. A total of 20 blocks were required. Through the formula for comparing percentages and taking into account the recovery ratio in the indomethacin group 83% and the recovery ratio in the ibuprofen group

100% (8) and the 95% confidence interval and the power of 0.80, the sample size was calculated 40 people for each group. Routine echocardiography was performed for all infants less than 1500 g and gestational age less than 34 weeks. In other high – birthweight infants, an echo was performed in suspicious cases (heart murmur or cardiomegaly). After random allocation, Ibuprofen was administered to a group of patients and indomethacin was administered to another group.

Pharmacotherapy dosage with ibuprofen (7):

1. Age below one week: 10 mg / kg and then 5 mg / kg, 24 hours and 48 hours later
2. Age above one week: 18 mg / kg and then 9 mg / kg, 24 hours and 48 hours later

Pharmacotherapy dosage with indomethacin (7):

1. If the weight of the premature infant is above 1250 g and it is older than 7 days: 0.2 mg / kg and then 0.2 mg / kg in the next 36 and 48 hours
2. If the weight of the premature infant is less than 1250 grams and younger than 7 days: 0.2 mg / kg and then 0.1 mg / kg in the next 24 and 48 hours.

If three days after completion of treatment, the ductus arteriosus is open again, treatment will be repeated below the age of one month, and the need for surgical intervention is evaluated. If 24 hours after 72-hour re-treatment, ductus arteriosus is still open, the surgical consultation is done (for PDA closure). Drug safety was studied over a period of 72 hours. Brain ultrasound, blood test including blood creatinine and blood urea nitrogen were evaluated. Bilirubin, creatinine and platelets were measured 48 hours after birth (before treatment) and the fifth day after birth (after treatment) and entered the checklist.

Brain ultrasound was performed in the first 48 hours of life (before treatment) and on the 7th days (after treatment), and the severity of intraventricular hemorrhage was measured on the basis of ultrasound grade 1–4. After receiving the drug, patients were evaluated in terms of complications and recovery through tests, echocardiography and examinations. All referrals for echocardiography were completely unknown, random, and blind for the echocardiographer. For treatment with indomethacin, its capsule was used. In the entire course of research and dealing with patients, the researchers followed the principles of medical ethics announced by the Helsinki Declaration on Environment and Health and the approval of the Ethics Committee of Qom University of Medical

Sciences. The parents of all patients filled out the informed consent form after being informed about the project. After data collection and entering the data into the computer, independent t-test was used to compare the mean in the two groups under study. Chi-square or Fisher test was used to compare the ratios and $p < 0.05$ was considered significant.

Results

In this clinical trial, of 80 infants with PDA included in the study, all patients passed through the follow-up period and none of the patients were excluded from the study. The gestational age in the indomethacin group was 28.9 ± 1.93 and 29.2 ± 1.8 in the ibuprofen group. The patients had no significant difference in terms of the pre-arrival variables (table 1). There was no significant difference between the two groups in terms of response to treatment, which was determined by two measures of PDA resampling and need for repeat treatment.

Table 1. Distribution of variables when entering the study in two treatment groups

Variable	Group	Indomethacin Mean±SD	Ibuprofen Mean±SD	P-value
Gestational age (weeks)		28.9±1.93	29.2±1.8	0.475
Weight (g)		1166.25±175.12	1182.37±197.25	0.7
Age at onset of treatment (days)		3.6±1.42	3.4±1.27	0.511
Creatinine		0.92±0.23	1.02±1.14	0.605
Platelet		183100±87139	182675±73169	0.981
Bilirubin		6.29±1.18	6.27±1.02	0.944
Male to female ratio		1.5	1.5	1
		N(%)	N(%)	
Large PDA		25(62.5)	23(57.5)	0.648
Infection with IVH Grade 1 or 2		9(22.5)	7(17.5)	0.789
Surfactant administration		30(75)	31(77.5)	0.793
The need for mechanical ventilation		25(62.5)	28(70)	0.478

The size of the PDA did not change in ten percent of patients (four patients) in the indomethacin group and seven point five percent of patients (three patients) in the ibuprofen group (table 2). Two cases of death

occurred in the indomethacin group, and three cases of death occurred in the ibuprofen group, none associated with PDA or treatment complications. There was no statistically significant difference between the two oral medications for the other complications in this study (table 3).

Table 2. Comparison of response to treatment in two treatment groups in infants with PDA who require treatment

Variable	Change rate	Indomethacin N(%)	Ibuprofen N(%)	P-value
Change in PDA size after treatment	-3	16(40)	17(42.5)	-0.96
	-2	15(37.5)	14(35)	
	-1	5(12.5)	6(15)	
	Without change	4(10)	3(7.5)	
Need to repeat the treatment		4(10)	4(10)	1

Table 3. Comparison of deaths and complications in two treatment groups in infants with PDA who require treatment

Variable	Change rate	Indomethacin N(%)	Ibuprofen N(%)	P-value
Change in IVH grade	- 1	2(5)	0	0.336
	0	36(90)	38(95)	
	1	2(5)	1(2.5)	
	2	0	1(2.5)	
Changes in serum creatinine after treatment		0.015±0.227	0.047±1.53	0.894
Change in bilirubin after treatment		0.45±1.7	1.12±1.94	0.105
Death		2(5)	3(7.5)	1
NEC		8(20)	6(15)	0.545

Discussion

The results of this study showed that both oral indomethacin and ibuprofen are effective in the treatments PDA, and none of the infants treated with the two drugs required surgery. The present study did not show any significant difference in the therapeutic effects and side effects of the two drugs. The results of Katakam et al. showed no significant difference in the effect of two drugs on the closure of PDA (9). In a meta-analysis of nine studies with a sample size of 566 people about infants weighing less than 2500 g, it was shown that there was no significant difference in the efficacy of the two drugs in closure of PDA (10). In another study, Su et al. showed that the efficacy of

intravenous ibuprofen and indomethacin is similar (11). In the case of oral ibuprofen, Jafari et al. in a clinical trial on 60 infants with PDA showed that oral ibuprofen is an effective and yet simple treatment with minimal side effects in premature infants (8). Furthermore, Yang et al. used oral ibuprofen syrup versus intravenous indomethacin in very low birth weight infants, and specified that oral ibuprofen was as effective as intravenous indomethacin (2).

In another study by Erdevi et al. in 80 premature infants, it was shown that oral ibuprofen greatly delayed the early closure of PDA, compared with intravenous ibuprofen (12). Comparing the intravenous form of indomethacin versus its oral form, it was shown in a study that its intravenous form is more effective (13). An explanation for the appropriate effect of oral ibuprofen is that the plasma level of therapeutic dose in oral ibuprofen is stable. When plasma levels of oral ibuprofen is maintained at therapeutic size, it can be equivalent to intravenous form of ibuprofen or indomethacin (14).

Regarding the complications in this study, there were no statistically significant differences between the two oral drugs. Previous studies have reported different results in this regard. In a meta-analysis, the data from five studies with a sample size of 443 people showed that the increase in serum creatinine after using ibuprofen was significantly lower than indomethacin, and decreased urine output after using ibuprofen was also significantly less than indomethacin.

There was no significant statistical difference in terms of mortality, intraventricular hemorrhage, necrotizing enterocolitis, PDA surgery, retinopathy of prematurity, sepsis, hospitalization period, gastrointestinal bleeding, periventricular leukomalacia, need for treatment with surfactant, and ventilation requirement period in the two methods of treatment with ibuprofen and indomethacin (10).

In the study of SU et al., the infants treated with intravenous ibuprofen had more creatinine clearance and urine volume, lower serum creatinine, and urea nitrogen compared with indomethacin (11). In the study of Chan et al., spontaneous intestinal perforation in the ibuprofen group was more prevalent than indomethacin and the probability of gastrointestinal bleeding was higher in the ibuprofen group. Serum creatinine and urine volume were similar in the two groups at the beginning of the study and at the end of the study, the effect of two drugs on serum creatinine

and urine volume was similar (1). The results of the study by Yang et al. also showed no difference in the side effects of the two treatments (2). In another study by Katakam et al., there was no significant difference in post-treatment complications including death, necrotizing enterocolitis, spontaneous intestinal perforation, and mean serum creatinine in the two groups (9). Considering the high binding of COX-inhibitors to the protein, increased bilirubin level is one the concerns of treatment with these drugs in preterm infants. However, studies have shown that ibuprofen at concentrations higher than 100 mg/l may increase bilirubin and conventional treatments with ibuprofen do not usually lead to concentrations higher than 50 mg/l (15). In a study among 15 infants, treatment with intravenous ibuprofen did not increase bilirubin (16). However, some researchers believe that the increase in bilirubin in the treatment with indomethacin is less than ibuprofen (15). Differences between the results of this study and previous studies may be due to the use of oral form of both drugs, the

sample size of the present study and the different target population of the studies. In general, the results of this study and its comparison with previous studies showed that oral ibuprofen, like indomethacin, is effective in the treatment of PDA, and given the availability, safety and affordability of the selected drug for treatment at international level, especially for doctors in developing countries, oral ibuprofen appears to be an appropriate option. Especially in cases where indomethacin should be used with caution. Studies with longer follow-up are suggested to compare the long – term side effects of these two drugs.

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References

- 1.Chan NM, Law CW, Kwan KF. Ibuprofen versus indomethacin treatment of patent ductus arteriosus: comparative effectiveness and complications. *Hong Kong Med J*. 2014;20(3):205-12.
- 2.Yang EM, Song ES, Choi YY. Comparison of oral Ibuprofen and intravenous indomethacin for the treatment of patent ductus arteriosus in extremely low birth weight infants. *J Pediatr (Rio J)*. 2013;89(1):33-9.
- 3.Clyman R, Wickremasinghe A, Jhaveri N, Hassinger DC, Attridge JT, Sanocka U, et al. Enteral feeding during indomethacin and ibuprofen treatment of a patent ductus arteriosus. *J Pediatric*. 2013;163(2):406-11.
- 4.Sivanandan S, Bali V, Soraisham AS, Harabor A, Kamaluddeen M. Effectiveness and safety of indomethacin versus ibuprofen for the treatment of patent ductus arteriosus in preterm infants. *Am J Perinatol*. 2013;30(9):745-50.
- 5.Tsui I, Ebani E, Rosenberg JB, Lin J, Angert RM, Mian U. Patent ductus arteriosus and indomethacin treatment as independent risk factors for plus disease in retinopathy of prematurity. *J Pediatr Ophthalmol Strabism*. 2013;50(2):88-92.
- 6.Walther FJ. Oral ibuprofen for patent ductus arteriosus: effective and safe or just cheap? Commentary on R. Neumann et al.: Oral ibuprofen versus intravenous ibuprofen or intravenous indomethacin for the treatment of patent ductus arteriosus in preterm infants: a systematic review and meta-analysis (*Neonatology* 2012;102:9-15). *Neonatology*. 2012;102(1):16-8.
- 7.Parthasarathy A. IAP Textbook of pediatrics: JP Medical Ltd; 2016. Available From: <https://www.abebooks.com/9789352501960/Iap-Textbook-Pediatrics-Parthasarathy-9352501969/plp>
- 8.Jafari Fesharaki H, Nayeri F, Akbari asbaq P, Amini E, Sedaqat M. Different doses of ibuprofen in the treatment of patent ductus arteriosus: a randomized clinical trial. *Teh Univ Med J*. 2012;70(8):488-93. [In Persian]
- 9.Katakam LI, Cotten CM, Goldberg RN, Dang CN, Smith PB. Safety and effectiveness of indomethacin versus ibuprofen for treatment of patent ductus arteriosus. *Am J Perinatol*. 2010;27(5):425-9.
- 10.Neumann R, Schulzke SM, Buhner C. Oral ibuprofen versus intravenous ibuprofen or intravenous indomethacin for the treatment of patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. *Neonatology*. 2012;102(1):9-15.
- 11.Su PH, Chen JY, Su CM, Huang TC, Lee HS. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. *Pediatrics international : Off J Japan Pediatr Soc*. 2003;45(6):665-70.
- 12.Marchal F, Monin P, Vert P, Bianchetti G, Morselli PL. Patent ductus arteriosus in premature newborns. Treatment with indomethacin (author's transl. *Arch Franc Pediatr*. 1981;38(7):503-8.
- 13.Tsao P-C, Chen S-J, Yang C-F, Lee Y-S, Jeng M-J, Soong W-J, et al. Comparison of Intravenous and Enteral Indomethacin Administration for Closure of Patent Ductus Arteriosus in Extremely-low-birth-weight Infants. *J Chin Med Associat*. 2010;73(1):15-20.
- 14.Heyman E, Morag I, Batash D, Keidar R, Baram S, Berkovitch M. Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. *Pediatr*. 2003;112(5): 354.
- 15.Corff KE, Sekar KC. Clinical Considerations for the Pharmacologic Management of Patent Ductus Arteriosus with Cyclooxygenase Inhibitors in Premature Infants. *J Pediatr Pharmacol Thera*. 2007;12(3):147-57.
- 16.Van Overmeire B, Vanhagendoren S, Schepens P, Ahlfors C. The influence of ibuprofen-lysine on unbound bilirubin plasmalevels in preterm neonates. *Pediatr Res*. 2004;55(2004):474.