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Oral Ibuprofen for Closure of Patent Ductus Arteriosus in Full-term Neonates Aged 20-28 days

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ABSTRACT: Patent ductus arteriosus accounts for about 10% of congenital heart disease. Although surgical or catheter closure of patent ductus arteriosus is safe but with some complications and not possible in anywhere. Efficacy of ibuprofen for patent ductus arteriosus closure is shown in preterm neonates. The aim of the current study was to evaluate the efficacy and safety of oral ibuprofen in full- term neonates after the first days of life. This study was a randomized clinical trial on 20-28-day term infants with confirmed patent ductus arteriosus. The sample size was 40 infants divided randomly in case (n = 20) and control group (n = 20). The case group received ibuprofen suspension initially with a dosage of 10 mg/kg, then two 5 mg/kg doses 12 hours apart. If ductal closure did not occur, a second course was repeated after one week. Case group was assessed by adverse effects and complications. The control group received no medication or placebo. To confirm patent ductus arteriosus, diagnosis and follow up by 2 dimensional color Doppler echocardiography was performed. Data was analyzed using SPSS version 16 software. There was no significant difference between the two groups in age, weight, sex, and patent ductus arteriosus size. There wasn't any ductal closure in case group after one course of treatment. Patent ductus arteriosus was closed in 75% of patients in treated group after second course, but no spontaneous closure was reported in control group (P<0.001). None of the patients reported drug complication. The current study indicated that two courses of treatment by oral ibuprofen seem effective with no complications in closing patent ductus arteriosus of full-term infants' aged 20-28 days. However, further research in this field is recommended.

Keywords: Patent ductus arteriosus, Ibuprofen, Full term, Neonates, Medical treatment

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INTRODUCTION

Ductus Arteriosus (DA) is the fetal vascular connection between pulmonary artery and aorta. This duct first closes physiologically and then anatomically after birth. Patent Ductus Arteriosus (PDA) is referred to a situation in which DA does not close completely. Its prevalence is one in every 2000 birth and eight in every 1000 birth in term and premature infants respectively. This disease accounts for about 10 % of all types of congenital heart disease (Moral et al., 2007; O'Rourke et al., 2008; Alipour et al., 2016). The occurrence of PDA has been remarkably increasing during the last two decades because of improved premature infant survival. The most important factor for the potency of PDA in fetal period is hypoxemia and high level of prostaglandin E_2 in circulation. The reason for prescribing prostaglandin synthesis inhibitors such as indomethacin to close the DA in premature infants is based on prostaglandin E_2 role in DA keeping open. The duct gets narrow at birth by increasing arterial oxygen and decreasing prostaglandin E_2 in circulation (Thebaud et al., 2004). Patients with PDA are subjected to complications such as heart failure, pulmonary hypertension and infective endocarditis. Some rare complications in these patients include pulmonary or systemic embolism, aneurismal dilatation of duct or pulmonary artery and ductus calcification (Thebaud et al., 2004; O'Rourke et al., 2008; Pistulli et al., 2014). In case the DA is not closed by medication, PDA can be cured by surgery or cardiac catheterization.

Although surgery has low risk for PDA closure, but it may lead to complications such as nerve paralysis of recurrent laryngeal, respiratory failure, infection, chylothorax and intracranial hemorrhage in preterm infants. Treatment by transcatheter closure has also risks such as embolism, incomplete closing and hemolysis (Pai et al., 2008 and Malviya et al., 2013). Various studies indicated that medicating with ibuprofen and indomethacin

could cure premature infants effectively with similar effects (Lee, 2008). But there are few studies carried out on term infants. In a study conducted by Takami et al. (2007) intravenous indomethacin was given to 41 infants with PDA whose birth weights were above 2500 grams. PDA closed completely in 12 infants and clinical symptoms improved in 13 infants. No severe complication was observed in patients (Takami et al., 2007). Amoozgar et al. (2010) studied the effect of oral ibuprofen on 51 term infants and reported significant difference between treatment and control group in level of PDA closing (Amoozgar et al., 2010). According to the limited studies about term infants especially after early days of birth, the objective of current study is investigating the effect of oral ibuprofen on PDA closing in 20-28 day term newborns.

MATERIALS AND METHODS

This study was a randomized clinical trial on 20-28 day term infants with PDA which has been carried out from 2012 to 2014. The sample size was 40 infants divided randomly in case and control group. The inclusion criteria included term newborns with gestational age of above 37 weeks and after birth age of 20 to 28 days with PDA, and the exclusion criteria were having a history of asphyxia, bleeding, platelets less than 150000, congenital kidney and gastrointestinal disease and congenital heart disease. Complete blood count, Creatinine (Cr), Blood Urea Nitrogen and complete urine test was measured in case group before beginning the treatment. The treatment would start if the results were normal. The case group was medicated by ibuprofen (oral suspension 100 mg/5ml, Hakim Pharmaceutical, Tehran, Iran). The first dose was 10 mg/kg, the second and third doses were 5 mg/kg, 12 h and 24 h after first dose respectively. The control group received no medication or placebo. To confirm PDA diagnosis and follow up 2D, color Doppler echocardiogram was performed with a Vivid S5 ultrasound machine (GE – Vingmed -Norway) using 3 and 7 MHz by pediatric cardiologist twice; before using medication for PDA during and one week after treatment. If PDA didn't close after a week, a treatment of ibuprofen was repeated the same as previous time and one week later echocardiography was carried out. Case group was assessed by adverse effects and complications. Possible complications of drug was told to patients' parents and asked the patients' companions to refer to the hospital if they observed any complications. Infants were excluded from the study if any complication such as bleeding, abdominal distention, feeding intolerance and oliguria occurred. The patients were followed for at least 6 months.

Ethical approval

The study was approved by the ethics committee of Hormozgan University of Medical Sciences, Bandar Abbas, Iran (NO: HEC-2010-6-24), and written informed consent was obtained from all patients' parents. A form was prepared for each patient who contained information about age, weight, sex, echocardiography results and possible complications.

Statistical analysis

Data were analyzed by SPSS version 20, with descriptive statistics (frequency distribution table, percentage, concentration and dispersion indices), chi-square test and Fischer exact test were applied to compare qualitative variants. T test was also applied to compare quantitative variants. The level of significance was considered as $P<0.05$.

RESULTS

The number of investigated patients was totally 40 in this study. In case group, 12 patients (60%) were boys and 8 were girls (40%). In control group, the number of boys and girls were equal. There was no significant difference between two groups in sex (P=0.751). There was also no significant difference between two groups in age, weight and PDA size (P>0.05) (Table 1). No patient in case group responded after one course of treatment but, showed significant response compared to control group after two courses (P<0.001) (Table 2). In case group no difference in sex was observed for treatment response (P=1) (Table 3). Age, weight and PDA size of patients in case group who responded to treatment was not significantly different from patients who did not respond to treatment (P>0.05) (Table 4). At the end of study, none of the patients reported drug complications and all of them had normal BUN and Cr. No thrombocytopenia was observed either.

Table 1. Mean comparison for age, weight and PDA size in case and control groups to investigate the effects of oral ibuprofen on PDA

Variables	Case	Control	P Value
Age (day)	23.85±2.41	23.90±1.94	0.94
Weight (gr)	3162.5±459.65	3380±363.96	0.10
PDA size (mm)	2.82±0.52	2.97±0.37	0.30

Table 2. The relationship between Ibuprofen treatment response among case and control

Treatment Response Group	Yes	No	P Value
Case	15 (75%)	5 (25%)	P<0.001
Control	0 (0%)	20 (100%)	

Table 3. The relationship between sex and treatment response in case group

Treatment Response Sex	Respond to treatment	Not Respond to treatment	P Value
Male	9(60%)	3 (60%)	1.00
Female	6 (40%)	2 (40%)	

Table 4. Comparison of age, weight and PDA size in case group who responded to treatment and the ones who did not respond to treatment with oral ibuprofen

Variables	Group	Frequency	Mean	Standard Deviation	P Value
Age (day)	Respond to treatment	15	23.40	2.32	0.15
	Not respond to treatment	15	25.20	2.38	
Weight (gr)	Respond to treatment	15	3276.7	332.12	0.05
	Not respond to treatment	5	2820	649.61	
PDA size (mm)	Respond to treatment	15	2.7	0.45	0.06
	Not respond to treatment	5	3.2	0.57	

DISCUSSION AND CONCLUSION

The present study indicated that applying ibuprofen in two courses in 20-28 day infants with PDA can close PDA in most infants of case group compared to control. While no spontaneous closure was observed in any of the control patients. In a study carried out by Amoozgar, the effect of oral ibuprofen was investigated on 51 term infants and there was a statistical significant different (P=0.029) between the level of closing PDA in treatment group (73.3%) and control group (42.9%). There was also a significant difference between the days of closing PDA in two groups (Amoozgar et al., 2010). The difference between this study and ours is that infants' ages at the beginning of our study were older than the study of Amoozgar. The treatment response was also in one course of treatment, while this response was observed after two treatment courses in our study. This can be due to the beginning of treatment at the lower age. Otherwise infants in two studies had similar weights. Takami et al. (2007) in a study on 41 infants with PDA whose birth weights were above 2500 g concluded that intravenous indomethacin is effective in closing PDA of term infants. The difference between this study and ours was using intravenous indomethacin. But, the age of treatment beginning was almost the same as our study (average of 23 days) (Takami et al., 2007). Some studies also showed the effectiveness of ibuprofen to close PDA in their studies; but the difference of these studies with present results was lower weights and prematurity of infants. Ibuprofen has also been shown as prophylaxis in premature infants (Cherif et al., 2008 and Pourarian et al., 2008). For example, Sangtawesin et al. (2006) proved that incidence of signed PDA in ibuprofen group was less than placebo grouping. The prematurity of infants and prophylaxis medication were the difference of this study with present findings (Sangtawesin et al., 2006). Overmeire (2003) also indicated that ibuprofen is effective in PDA treatment and as prophylaxis in premature infants. Ibuprofen complications like increasing BUN serum and creatinine level, oliguria, thrombocytopenia and gastrointestinal complications were not observed in case group (Overmeire, 2003) . In the studies of Pourarian et al. (2008), Amoozgar et al. (2010) and Rajaei (2006) no complication was observed due to applying. In another study that ibuprofen and indomethacin effects was compared for PDA treatment in premature infants, reported that in ibuprofen group creatinine clearance level and urine volume were higher and BUN serum and creatinine level were lower (Su et al., 2003). In study of Aranda and Thomas (2006), the comparison of intravenous ibuprofen and placebo showed that intravenous ibuprofen was safer and more effective in PDA treatment and there was no significant difference between mortality of the two groups in, intraventricular hemorrhage, necrotizing enterocolitis, pulmonary function, retinopathy and pulmonary dysplasia. Unlike our study, this one used intravenous ibuprofen but, it didn't report any complications either (Aranda and Thomas, 2006). According to previous findings in spite of the successful closure of PDA with oral ibuprofen in premature neonates, caution should be advised in premature babies, who are critically ill such as being hemodynamically instable and who are intolerant feeding for the reason of increasing risk of bowel ischemia and necrotizing enter colitis (Wong and Ramli et al., 2010) . Cherif et al. (2008) indicated that applying oral ibuprofen can be at least equally successful as intravenous ibuprofen in PDA closure and complications of suspension ibuprofen

was lower. The limitations of our study can be its small sample size and not following patients for a long time. Although prescribing oral ibuprofen for PDA closure is not recommended in reference books, similar studies reported its effectiveness in first days after birth of term infants. Our study also indicates the effectiveness of oral ibuprofen in closing PDA after two treatment courses. It seems that as the age of term infants increase, higher doses of ibuprofen with longer course of treatment is needed. Complementary studies with greater sample size, higher doses and longer treatment course of ibuprofen as well as long term following of patients to check improvement of clinical symptoms and long term drug complications is recommended. It is concluded that two courses of treatment by oral ibuprofen seems effective with no complications in closing PDA of full-term infants' age 20-28 days.

Competing interests

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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