· Original Article in English ·

Comparison of oral ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants

Saed Hossein FAKHRAEE[1], *Zohreh BADIEE*[2], *Saied MOJTAHEDZADEH*[3], *Mohammad KAZEMIAN*[1], *Roya KELISHADI*[2]

1. *Division of Neonatology, Department of Pediatrics, Shahid Beheshti University of Medical Sciences, Tehran, Iran*; 2. *Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran*; 3. *Department of Pediatric Cardiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Abstract: **Objective** Intravenous indomethacin is the conventional treatment for patent ductus arteriosus (PDA) in preterm infants; however its use is associated with various side effects such as oliguria, gastrointestinal bleeding and reduction of cerebral perfusion. Intravenous ibuprofen has recently been used to treat PDA in preterm infants without reducing cerebral blood flow or affecting intestinal or renal hemodynamics. Intravenous forms of indomethacin and ibuprofen are not available in Iran. This study aimed to examine and compare the efficacy and safety of oral ibuprofen and oral indomethacin for the treatment of PDA in preterm infants. **Methods** Thirty-six infants (gestational age less than 34 weeks) who had echocardiographically confirmed PDA were enrolled in this study. The patients were randomly administered with three oral doses of either indomethacin (0.2 mg/kg, at an interval of 24 hrs) or ibuprofen (a first dose of 10 mg/kg, followed at an interval of 24 hrs by two doses of 5 mg/kg each) ($n = 18$ each group). The rate of ductal closure, side effects, complications, and the infants' clinical course were recorded. **Results** The ductus was closed in all of 18 patients (100%) in the ibuprofen group and in 15 (83.3%) patients in the indomethacin group ($P > 0.05$). There were no significant differences in the levels of serum blood urea nitrogen and creatinine between the two groups before and after treatment. Necrotizing enterocolitis (NEC) occurred in 3 patients in the indomethacin group and none in the ibuprofen group ($P < 0.05$). The survival rate at 1 month after treatment was 94% (17/18) in both groups. One infant in the ibuprofen group died from sepsis and one in the indomethacin group died as a result of NEC. **Conclusions** Oral ibuprofen is as effective as oral indomethacin for the treatment of PDA in preterm infants. Oral ibuprofen therapy is associated with a lower incidence of NEC. [**Chin J Contemp Pediatr**, **2007**, **9** (**5**):**399 – 403**]

Key words: Ibuprofen; Indomethacin; Oral; Patent ductus arteriosus; Preterm infants

口服消炎痛和布洛芬治疗早产儿动脉导管未闭的比较

Saed Hossein FAKHRAEE, Zohreh BADIEE, Saied MOJTAHEDZADEH, Mohammad KAZEMIAN, Roya KELISHADI. Shahid Beheshti 大学医学院新生儿科,德黑兰,伊朗

[**摘　要**] **目的**　静脉注射消炎痛是早产儿动脉导管未闭的常规治疗方法,但治疗过程中常出现一些副作用,如少尿、消化道出血、脑血流灌注减少。近年来,静脉注射布洛芬已用于治疗早产儿动脉导管未闭。布洛芬治疗不会减少脑血流灌注,也不会影响胃肠道和肾脏的血流动力学。伊朗目前尚无消炎痛和布洛芬的静脉制剂供应。该研究旨在比较这两种药的口服制剂治疗早产儿动脉导管未闭的疗效和安全性。**方法**　36 例胎龄小于 34 周经超声心动图确诊患有动脉导管未闭的早产儿被随机分为两组,每组 18 人。一组给予消炎痛口服,每次 0.2 mg/kg,24 h 给药 1 次,共 3 次。另一组给予布洛芬口服,共 3 次,间隔时间为 24 h,首剂为 10 mg/kg,随后两次各 5 mg/kg。用药后观察导管闭合率、副作用、并发症及临床过程。**结果**　用药后布洛芬组 18 例患儿动脉导管都闭合(100%),而消炎痛组 18 例中有 15 例患儿动脉导管闭合(83.3%)($P > 0.05$)。两组疗效差异统计学无显著性意义。治疗前后两组的血清尿素氮和肌酐含量差异也无显著性意义。消炎痛组发生了 3 例(16.6%)坏死性小肠结肠炎,布洛芬组则无,差异有显著性意义($P < 0.05$)。治疗 1 个月后两组成活率均为 94%(17/18)。消炎痛组 1 例死于坏死性小肠结肠炎,布洛芬组 1 例死于败血症。**结论**　口服布洛芬治疗早产儿动脉导管未闭和口服消炎痛治疗一样有效,而且坏死性小肠结肠炎的发生率较口服消炎痛治疗低。[**中国当代儿科杂志,2007,9(5):399 – 403**]

[**关　键　词**] 布洛芬;消炎痛;口服;动脉导管未闭;早产儿

[**中图分类号**] R722　[**文献标识码**] A　[**文章编号**] 1008 – 8830(2007)05 – 0399 – 05

[Received] February 25, 2007; [Revised] May 25, 2007

[Biography] Saed Hossein FAKHRAEE (Male), MD., Professor, Specializing in neonatology. Faculty of Shahid Beheshti University, Tehran, Iran. Email: Fakhraee@yahoo.com

Patent ductus arteriosus (PDA) is a common problem in the preterm infants especially in those with respiratory distress syndrome (RDS). Delayed ductal closure is inversely related to gestational age at birth, with incidence varying from 20% in preterm infants greater than 32 weeks gestation up to 60% in those less than 28 weeks gestation[1]. Substantial left to right shunting through the ductus may increase the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia and death [2]. Intravenous indomethacin is the conventional pharmacologic treatment for promoting closure of a patent ductus [3]. However, the concern remains regarding the safety of indomethacin which affects renal, gastrointestinal and cerebral perfusion and might lead to complications such as transient or permanent renal dysfunction, NEC, gastrointestinal hemorrhage and reduced cerebral intracellular oxygenation [4,5]. It was reported that intravenous ibuprofen may close the ductus in animals without affecting basal cerebral blood flow and intestinal or renal hemodynamics during positive pressure ventilation and had different effects on regional circulation from indomethacin[6-8]. Some early clinical studies suggest that ibuprofen is efficient at closing the duct and has less renal and cerebral side effects [2,3,5,9]. In Iran the intravenous forms of these drugs are not available and oral indomethacin is being conventionally used for medical treatment of PDA. If oral indomethacin and ibuprofen could be shown to be as efficacious and safe as the intravenous form, then the oral form would afford several important advantages: 1) oral ibuprofen and indomethacin is available in developing countries; 2) oral administration is extremely simple; 3) the oral form of these drugs is less expensive than the intravenous one. This study examined and compared the efficacy and safety of oral ibuprofen and indomethacin for the treatment of PDA in preterm infants by a prospective study.

Methods

Patients

A total of 36 preterm infants who were admitted at the neonatal intensive care unit of the Mofid Hospital, Tehran, Iran, between June 2003 and June 2004 were recruited prospectively. The study was approved by the medical ethics committee of the hospital and the written parental consents were also obtained. The 36 preterm infants met the following criteria: 1) gestational age <34 weeks, age ≤ 14 days; 2) platelet count $\geq 100\ 000/\mu L$, serum creatinin concentration ≤ 1.6 mg/dL, absence of clinical manifestations of abnormal clotting function, absence of 3-4 grade IVH according to the classification reported by Papile[2]; 3) color Doppler echocardiographic evidence of significant PDA. The exclusion criteria included major congenital anomalies, hydrops fetalis, urine output below 1 mL/kg of body weight per hour during the preceding 12 hours, bleeding tendency as revealed by hematuria, blood in the endotracheal aspirate, gastric aspirate, or stools, and oozing from puncture sites, and hyperbilirubinemia necessitating exchange transfusion [3,10].

Study design

The enrolled patients were randomly received either oral ibuprofen ($n = 18$) or oral indomethacin ($n = 18$). The patients from the ibuprofen group received oral ibuprofen suspension (Hakim. Co., Iran) at a first dose of 10 mg/kg, followed at an interval of 24 hours by two doses of 5 mg/kg each [3,10]. The patients from the indomethacin group received three doses of oral indomethacin at an interval of 24 hours (Loghman. Co., Iran, 0.2 mg/kg) [3,10]. If echocardiography demonstrated a significant PDA after 24 hours of administration of the third dose of each drug, the second course of treatment with the same treatment program as first course initiated. If the second treatment course failed to close the ductus, the third treatment course started.

Echocardiography

The color Doppler echocardiography (Sono 1000, Hewlett-Packard, Andover, Mass, USA) with 5.0 and 7.5 MHZ transducers was performed in all infants before drug administration and 24 hours after the third dose of the drug by a pediatric cardiologist who was blinded to the infants' treatment program. The internal ductal diameter, the maximal shunt velocity, left- atrium-to aortic-root ratio, and the degree of shunting were recorded. A definite diagnosis of PDA was made by echocardiography: left to right shunt with ductal size greater than 1.5 mm and the left- atrial-to aortic-root ratio >1.6 or sever diastolic backflow in the pulmonary trunk and in the aorta [3].

Side effects and complications monitoring

Serum creatinin and blood urea nitrogen (BUN) were measured before and 24, 48 and 72 hours after initiation of ibuprofen or indomethacin treatment. Urine was collected in adhesive urine bags and oliguria was defined as urine output ≤ 1 mL/kg hourly during a 24-hour collection period. NEC was diagnosed by a finding of pneumatosis intestinalis, hepatobiliary gas or free intraperitoneal air on radiography [11]. A tendency to bleed was defined according to the exclusion criteria used in the study. Cranial ultrasound scans were per-

formed for the assessment of IVH (grades 1 to 4) before drug administration and 24 hours after the third dose of drug.

Concomitant treatment

Fluid intake began at 70 to 80 mL/kg daily and increased by 10 to 20 mL/kg daily to a maximum of 150 mL/kg daily, adjusted according to body weight. Hypotension was treated with fluid replacement. Dopamine was used in the cases who the fluid treatment failed. Furosemide was not used during the first week of life.

Statistical analysis

Data were stored in a computer database and analyzed by SPSS software version 11.5 (SPSS, Chicago). Values are expressed as mean ± standard deviation. The significance of comparisons between mean values was evaluated by student's t test. Frequencies in various groups were compared by chi-square test.

Results

Population characteristics

The mean gestational age and birth weight of the ibuprofen and the indomethacin groups were 31.5 ± 1.4 (29-34) weeks, 1 658.3 ± 386.6 (1 100-2 400) g and 30.9 ± 2.0 (29-34) weeks, 1 522.1 ± 357.7 (900-2 100) g, respectively ($P > 0.05$). There were no significant differences between the two groups in baseline clinical characteristics (Table 1).

Table 1 Baseline clinical characteristics of the infants

Group	Birth weight (g) ($\bar{x} \pm s$)	Gestational age (week) ($\bar{x} \pm s$)	IVH (number of case)			
			No IVH	Grade 1	Grade 2	Grade 3
Indomethacin ($n=18$)	1 522.1 ± 357.7	30.9 ± 2.0	9	3	6	0
Ibuprofen ($n=18$)	1 658.3 ± 386.6	31.5 ± 1.4	8	7	3	0

PDA was diagnosed on the 3.5 ± 0.5 days of life in the ibuprofen group and on the 3.1 ± 0.6 days of life in the indomethacin group ($P = 0.88$).

Therapeutic effects and outcome

The ductus was closed in all of 18 patients (100%) in the ibuprofen group and in 15 (83.3%) patients in the indomethacin group ($P = 0.07$). There was no significant difference in the efficiency between the two treatments. One patient in the ibuprofen group and 3 patients in the indomethacin group required second course of treatment. One patient in the ibuprofen group and 3 patients in the indomethacin group required third course of treatment. There were no significant differences in serum creatinin and BUN values between the ibuprofen and the indomethacin groups (Table 2). The survival rate 1 month after treatment was 94% (17/18) in both groups. One infant in the ibuprofen group died from sepsis and one infant in the indomethacin group died as a result of NEC. There were no statistically significant relationship between the outcomes and the characteristics of PDA including the size and shunt speed of the PDA.

Table 2 Maximal serum BUN and creatinin values

($n=18$, $\bar{x} \pm s$, mg/dL)

Group	BUN	Creatinin
Indomethacin	30.72 ± 17.61	1.02 ± 0.38
Ibuprofen	25.88 ± 14.88	0.85 ± 0.33

The clinical outcomes of the infants are shown in Table 3. There were no significant differences in the incidence of IVH between the two groups. The incidence of NEC was significantly lower in the ibuprofen group ($P = 0.03$).

Table 3 Outcome of the two group patients (number of case)

Group	Death within 15 days	NEC	Progress of IVH during treatment		
			from grade 0 to grade 1	from grade 1 to grade 2	from grade 2 to grade 3
Indomethacin ($n=18$)	1	3	4	3	0
Ibuprofen ($n=18$)	1	0	3	2	0

Discussion

PDA is a challenging problem to neonatologists and cardiologists. Intravenous indomethacin is the conventional pharmacologic treatment for promoting closure of a patent ductus arteriosus in premature infants [3]. Intravenous ibuprofen has been shown to be as effective as indomethacin in PDA closure [3,6]. If treatment with oral form of indomethacin and ibuprofen is both effective and safe, then it would have the advantages of more widespread availability, simpler administration and decreased cost. This study showed both oral ibuprofen and oral indomethacin are effective and safe in PDA closure.

Vasodilator prostaglandins (PGS), PGE2 and PGI2, play a significant role in maintaining ductus patency during fetal and neonatal lives [12]. However possible side effects may occur during indomethacin therapy, including renal dysfunction, decreased platelet aggregation, increased risk of NEC, gastric perforation, and gastrointestinal hemorrhage [4,5]. Some studies suggest that intravenous ibuprofen is efficient at closing the duct and has less cerebral and renal side effects in neonates [13-14], and its prophylactic use within the first few hours after birth has been advocated recently [15-16]. Because of unavailability of intravenous indomethacin and ibuprofen in Iran, oral indomethacin was used for closure of PDA in our center. This study examined and compared the efficacy and side effects of oral preparations of the two prostaglandin synthetase inhibitors, ibuprofen and indomethacin.

On the basis of the findings from this study, it appears that oral ibuprofen is as effective as oral indomethacin in promoting ductal closure in preterm infants. The rate of ductal closure in the oral indomethacin group was similar to that in the patients receiving intravenous indomethacin [17], while the rate of ductal closure (100%) in the oral ibuprofen group was higher than that reported by Van Overmiere in 2000 (70%) [3] and in 1997 (75%) [9], where ibuprofen was administered intravenously. It was thought that relatively lower gestational age and postnatal age of patients in the Van Overmiere's studies resulted in the relatively lower rate of ductal closure. The results from this study were similar to those from Heyman's report [18] in which the closure rate was 95.5% by oral administration of ibuprofen and from Aly's report [19] in which the closure rate was 83% by oral administration of ibuprofen. Many previous studies have shown that the infants treated with intravenous ibuprofen had higher creatinin clearance -urine volume and lower serum creatinin and BUN values than the infants treaded with intravenous indomethacin [3,10], but this study found that there were no significant differences in creatinin and BUN values between the indomethacin and the ibuprofen groups, which was similar to the findings reported by Aly [19]. In this study oliguria was not observed in any of the patients. NEC was developed in significantly higher proportion of the infants who received indomethacin than of those who received ibuprofen. This was similar to the findings reported by Van Overmeire [3]. In an experimental model of bowel ischemia in rats, the rats treated with ibuprofen had a significantly lower incidence of intestinal necrosis and it was suggested that ibuprofen may have a cytoprotective role in animals at risk for bowel ischemia [20]. Some experimental evidence suggests that there may be mechanisms unrelated to the inhibition of prostaglandins that partly explain the differences in the effects of indomethacin and ibuprofen on regional circulations [15, 21].

It was concluded that oral ibuprofen therapy is as efficacious as oral indomethacin for treatment of PDA in preterm infants. Oral ibuprofen therapy was associated with a significantly lower incidence of NEC. As the outcome of patients who received oral preparations was comparable with that of patients who received intravenous preparations, it may be an alternative to oral preparations in the areas where the intravenous form is not available or affordable. However because of the small sample size in this study, a sufficiently large multicenter trial is needed to evaluate the efficacy and safety of oral ibuprofen and indomethacin in preterm infants with PDA.

Acknowledgment

The authors are grateful to Dr. Mohammad HEIDARZADEH and Dr. Minoo FALLAHI for technical assistance.

[**References**]

[1] Wyllie J. Treatment of patent ductus arteriosus [J]. Semin Neonatol, 2003, 8(6): 425-432.

[2] Papile LA, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 g [J]. J Pediatr, 1978, 92(4): 529-534.

[3] Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus [J]. N Engl J Med, 2000, 343(10): 674-681.

[4] Yeh TF, Car I. Pharmacologic closure of parent ductus arteriosus [M]. //Yeh TF. Neonatal Therapeutics. 2nd ed. St Louis: Mosby Year Book, 1991, 123-138.

[5] Patel J, Roberts I, Azzopardi D, Hamilton P, Edwards AD. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus [J]. Pediatr Res, 2000, 47(1): 36-42.

[6] Coceani F, White E, Olley PM. Age dependent changes in the response of the lumb ductus arteriosus to oxygen and ibuprofen [J]. Can J Physiol Pharmacol, 1979, 57(8): 825-831.

[7] Malcolm DD, Segar JL, Robillard JE, Chemtob S. Indomethacin compromises hemodynamics during positive pressure ventilation, independently of prostanoids[J]. J App Physiol, 1993, 74(4): 1672-1678.

[8] Speziale MV, Allen RG, Henderson CR, Barrington KJ, Finer NN. Effects of ibuprofen and indomethacin on regional circulation in newborn piglets[J]. Biol Neonate, 1999, 76(4): 242-252.

[9] Van Overmeier B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen[J]. Arch Dis Child Fetal Neonatal Ed, 1997, 76(3): F179-184.

[10] Su PH, Chen JY, Su CM, Huang TC, Lee HS. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants[J]. Pediatr Int, 2003, 45(6): 665-670.

[11] Kligman RM, Fanarrof AA. Necrotizing enterocolitis[J]. N Engl J Med, 1984, 310(17): 1093-10103.

[12] Clyman RI, Narayanan M. Patent ductus arteiosus: a physiologic basis for current treatment practice[M]. //Hansen TN, Mclntosh N. Current Topics in Neonatology. Number 4. Philadelphia: WB Saunders, 2000, 72-91.

[13] Aranda JV, Varvarigou N, Beharry K, Modanlou H, Bardin C, Papageorgiou A. The effect of early intravenous ibuprofen on renal function in premature newborns[J]. Pediatr Res, 1994, 37(1): 361A.

[14] Gimeno Navarro A, Cano Sanchez A, Fernandez Gilino C, Carrasco Moreno JI, Izquierdo Macian I, Gutierrez Laso A, et al. Ibuprofen versus indomethacin in the treatment of patent ductus arteriosus in preterm infants[J]. An Pediatr (Barc), 2005, 63(3): 212-218.

[15] Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants[J]. JAMA, 1996, 275(7): 539-544.

[16] Dani C, Bertini G, Pezzati M, Poggi C, Guerrini P, Martano C, et al. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study[J]. Pediatrics, 2005, 115(6): 1529-1535.

[17] Van Overmeire B, Brus F, Van Acker KJ, Van der Auwera JC, Schasfoort M, Elzenga NJ, et al. Aspirin versus indomethacin treatment of patent ductus arteriosus in the preterm neonate with respiratory distress syndrome[J]. Pediatr Res, 1995, 38(6): 886-891.

[18] 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[J]. Pediatrics, 2003, 112(5): e354.

[19] Aly H, Lotfy W, Badrawi N, Ghawas M, Abdel-Meguid IE. Oral ibuprofen and ductus arteriosus in premature infants: A randomized pilot study[J]. Am J Perinatol, 2007, 24(5): 267-70[Epub ahead of print].

[20] Grosfeld JL, Kamman K, Gross K, Cikrit D, Ross D, Wolfe M, et al. Comparative effects of indomethacin, prostaglandin E1, and ibuprofen on bowel ischmia[J]. J Pediatr Surg, 1983, 18(6): 738-742.

[21] Chemotob S, Beharry K, Barna T, Varma DR, Aranda JV. Differences in the effects in the newborn piglet of various nonsteroidal anti-inflammatory drugs on cerebral blood flow but not on cerebrovascular prostaglandins[J]. Pdeiatr Res, 1991, 30(1): 106-111.

(Edited by DENG Fang-Ming)