A Comparison of Oral Ibuprofen and Intravenous Indomethacin for Closure of Patent Ductus Arteriosus in Preterm Infants

URAIWAN CHOTIGEAT, MD*,
KESANAT JIRAPAPA, MD**,
THANARAT LAYANGKOOL, MD***

Abstract

Background : Indomethacin is widely accepted as the treatment for patent ductus arteriosus (PDA) in preterm infants but it has various side effects. Ibuprofen is the alternative treatment and believed to be less likely to induce side effects.

Objective : To compare efficacy and side effects of ibuprofen *versus* indomethacin treatment for symptomatic patent ductus arteriosus (PDA) in preterm infants.

Method : The authors studied 30 infants (gestational age $\leq$ 35 weeks, aged $\leq$ 10 days) who were diagnosed as having symptomatic PDA confirmed by echocardiogram. The infants were randomly assigned to receive three intravenous doses of indomethacin given at 12 -hour intervals or three doses of ibuprofen given at 24-hour intervals, starting within ten days of life. The demographic data, rate of clinical closure, need for additional treatment, side effects, complications and the infants' clinical course were recorded within 28 days.

Results : The rate of ductal closure was similar with the two treatment regimes. Ductal closure occurred in 7 of 15 infants given ibuprofen (46.67%) and 10 of 15 infants given indomethacin (66.67%). (Relative risk 0.669; 95% confidence interval, 0.328 to 1.364; p = 0.462) The number of infants who needed a second pharmacologic treatment was not significantly different between the two groups. (6 cases in the ibuprofen group, 5 cases in the indomethacin group) but surgical ligation was performed in two cases in the indomethacin group. There was a significant difference in using the diuretic drug (furosemide) in the indomethacin group (11 cases), compared to the ibuprofen group (3 cases), (p = 0.009). More cases of necrotizing enterocolitis were seen in the indomethacin group (66.67% compared to 40% in the ibuprofen group) but there was no statistically significant difference.

Conclusion : Ibuprofen has the same efficiency as indomethacin for the treatment of symptomatic patent ductus arteriosus in preterm infants and less likely to induce necrotizing enterocolitis and renal toxicity than indomethacin.

Key word : Patent Ductus Arteriosus, Closure, Ibuprofen, Indomethacin

CHOTIGEAT U, JIRAPAPA K, LAYANGKOOL T
J Med Assoc Thai 2003; 86 (Suppl 3): S563-S569

* Neonatal Unit,
** Pediatric Department,
*** Cardiological Unit, Queen Sirikit National Institute of Child Health, Bangkok 10400, Thailand.

Patent ductus arteriosus is often found in premature infants with respiratory distress syndrome. Intravenous indomethacin is the conventional pharmacologic treatment for promoting closure of a patent ductus in premature infants. Indomethacin affects renal, gastrointestinal and cerebral perfusion and may lead to complications such as renal dysfunction[1-3], necrotizing enterocolitis, gastrointestinal hemorrhage [4], and reduced cerebral intracellular oxygenation[5, 6]. Ibuprofen has been shown to close the patent ductus in animal studies[7] without affecting the cerebral, renal and intestinal hemodynamics[8]. Furthermore, it has been shown that its effect on regional circulation differs from indomethacin [1,9-10]. Ibuprofen has been shown to be effective in closure of patent ductus arteriosus in premature[11-13] infants without reducing mesenteric, renal[14] and cerebral[15] blood flow. In Thailand, there have only been a few small clinical trials conducted regarding the use of ibuprofen in PDA. Hence the authors conducted this trial to compare the efficacy of oral ibuprofen with that of intravenous indomethacin in inducing closure of patent ductus arteriosus in premature infants and compare the side effects betweeen the two groups.

PATIENT AND METHOD

Neonates admitted to the newborn unit were eligible for enrollment if they met the following inclusion criteria: 1) gestational age < 34 weeks, 2) respiratory distress with additional oxygen requirements above 30 per cent fractional inspired oxygenation, 3) aged < 10 days, 4) clinical and laboratory confirmation of PDA including at least three of five criterias (heart murmur, bounding pulse, wide pulse pressure > 25 mmHg, increased perihilar vasculature on the chest X-ray and color Doppler echocardiography). Exclusion criterias were congenital anomalies incompatible with life, recent intraventricular hemorrhage within 24 hours, urine output below 1 ml per kilogram of body weight per hour during the preceding 8 hours, a serum creatinine concentration of 1.6 mg per deciliter or higher, a serum urea nitrogen concentration greater than 40 mg per deciliter, a platelet count of 60,000 per cubic millimeter or less, a tendency to bleed, necrotizing enterocolitis and hyperbilirubinemia necessitating exchange transfusion. The parents of all the patients gave their informed written consent.

The infants were assigned to the treatment group by random number. Clinical care was performed by physicians who did not take part in the study. The study was conducted from January 1, 2001 to May 31, 2002. When the ductus arteriosus was still patent after the first randomly assigned treatment in both groups who were receiving mechanical ventilator. Indomethacin (three doses of 0.2 mg per kilogram at 12-hour interval) was given as a nonrandomized

rescue treatment. If this therapy failed to promote closure and the patient continued to receive mechanical ventilation or there was a contraindication to the second pharmacologic treatment, surgical ligation of the dustus was performed.

Echocardiography

Color Doppler echocardiography was performed by pediatric cardiologists in all infants. The purpose was to evaluate patency of the ductus arteriosus and shunting at the time of inclusion and within 24 hours after the last dose of the study drug was given. The second evaluation was performed within 7 days after the second course of treatment.

Clinical course and outcome

Biological data, demographic information and clinical outcomes including clinical presentation of PDA, diuretic drugs, inotropic drugs and respiratory support were prospectively recorded on the data sheets especially designed for this study. Gestational age, Apgar score, birth weight, age at treatment, daily fluid intake, urine production, and body weight were also recorded. Complete blood count, blood for urea nitrogen, and creatinine were monitored daily. Cranial ultrasound were performed before and at the end of the first week after treatment. Infants were assessed for intraventricular hemorrhage (grade 1 to 4) according to standard classification systems[16]. The outcome of the surviving patients was evaluated on the basis of clinical symptoms and the need for respiratory support (days during which mechanical ventilation and supplemental oxygen were needed). Primary outcome were defined[17] successful (no symptoms and no PDA on the echocardiogram), complete clinical closure (no symptom but echocardiogram showed PDA), partial response (clinical improvement after treatment) and no response (persistent symptomatic PDA). Bronchopulmonary dysplasia was defined by the need for supplemental oxygen after 28 days of life, in association with typical radiologic findings. Necrotizing enterocolitis was diagnosed when the clinical signs and radiologic findings generally accepted as characteristics of this condition were present[18].

Statistical analysis

The *t*-test, Mann-Whitney U test, and chi-square test or Fisher's exact test were used to compare continuous normal distributed data, nonparametric

Table 1. Characteristics of the infants before the study.

Characteristics	Indomethacin group (n = 15)	%	Ibuprofen group (n = 15)	%	P-value
Maternal factors					
Antepartum hemorrhage	5	33.33	1	6.67	NS
PROM	4	26.67	4	26.67	NS
Diabetic mother	1	6.67	0		NS
Preeclampsia	1	6.67	0		NS
Antenatal corticosteroid	3	20	3	20	NS
Multipara	4	26.67	3	20	NS
Neonatal factors					
Outborn	3	20	5	33.33	NS
Male	7	46.67	8	53.33	NS
Normal delivery	7	46.67	9	60	NS
Vacuum extraction	1	6.67	0		NS
Breech extraction	2	13.33	2	13.33	NS
Cesarean section	5	33.33	4	26.67	NS
Asphyxia	1	6.67	0		NS
RDS	12	80	7	46.67	NS
Gestational age (week)*	29.86 ± 2.92		30.8 ± 2.30		NS
Birth weight (gram)*	1,434 ± 421		1,412 ± 354		NS
Age at start of treatment (day)*	3.53 ± 1.59		6 ± 2.44		0.0029
PDA (milimeter)*	2.26 ± 0.59		1.86 ± 0.91		NS

NS = non-significant, PROM = premature rupture of membrane, * = X ± SD

continuous data and categorical data respectively. All reported p-values < 0.05 were considered statistically significant.

RESULTS

Thirty cases were studied, 15 in each group. There was no significant difference between the two groups in maternal factors and neonatal factors except the age at the start of treatment ($p < 0.05$) as shown in Table 1. The rate of closure of the patent ductus arteriosus was similar in the indomethacin and in the ibuprofen groups as was the need for rescue treatment (Table 2). Surgical ligation was done in only two cases in the indomethacin group, due to failure of closure by medication. Survival at one month was similar in both groups. There was no significant difference in the number of infants with the rate of survival to discharge, bronchopulmonary dysplasia, extension of IVH during treatment, necrotizing enterocolitis, retinopathy of prematurity, sepsis and death as shown in Table 3. Concerning renal complications, there was decreased urine output and increased serum creatinine in the indomethacin group after treatment but there was no significant difference between the two groups as shown in Table 4. There were more cases using a diuretic drug in the indomethacin group than in the ibuprofen group, (11 cases in the indomethacin group and 3 cases in the ibuprofen group) ($p < 0.05$). The need for respiratory support before and after treatment was similar in both groups as shown in Table 5. Seven patients in this study died between day 14 and day 28 after treatment.

DISCUSSION

According to the present study, ibuprofen was as effective as indomethacin in promoting ductal closure in premature infants. The rate of closure was similar in both groups, 7 of 15 cases in the ibuprofen group and 10 of 15 cases in the indomethacin groups (relative risk 0.669, 95% CI 0.328 to 1.364, $p = 0.462$). The infants needing a second course of drug were not different in both groups (5 cases in the indomethacin group and 6 cases in the ibuprofen group). The efficacy in ductal closure depends on age of the infant, in the present study the patients in the indomethacin group were younger than the ibuprofen group and still the authors did not find any statistically significant difference in ductal closure. Earlier smaller studies suggested that ibuprofen might be effective in the prevention and early treatment of patent ductus arteriosus in human neonates[11,16,17]. Ibuprofen has been shown to constrict the ductus arteriosus effectively in lambs[7]. In a preliminary study, when ibuprofen

Table 2. Outcome of infants according to treatment group.

Outcome of treatment	Drug				P-value
	Ibuprofen (n)	%	Indomethacin (n)	%	
Successful	6	40	9	60	NS
Complete clinical closure	1	6.67	1	6.67	NS
Partial response	3	20	3	20	NS
Non response	5	33.33	2	13.33	NS

Table 3. Outcome variable according to treatment group.

Outcome of treatment	Drug				P-value
	Ibuprofen (n)	%	Indomethacin (n)	%	
Extension of IVH during treatment	3	20	1	6.67	NS
Necrotizing enterocolitis	6	40	10	66.67	NS
Bronchopulmonary dysplasia	6	40	7	46.67	NS
Retinopathy of prematurity	3	25	4	33.33	NS
Sepsis	7	46.67	7	46.67	NS
Death within 28 days	3	20	2	13.33	NS

Table 4. Renal complication according to treatment group.

Outcome of treatment	Drug		P-value
	Ibuprofen	Indomethacin	
Urine output (ml/kg/hour)*			
24-hour after treatment	2.13 ± 1.18	2 ± 1.30	NS
48-hour after treatment	1.86 ± 0.74	1.8 ± 0.67	NS
72-hour after treatment	2.26 ± 0.96	2.06 ± 1.09	NS
Serum creatinine (mg/dl)*			
Before treatment	0.94 ± 0.30	0.96 ± 0.17	NS
24-48-hour	1.02 ± 0.29	1.02 ± 0.27	NS
At 72-hour after treatment	0.89 ± 0.19	1.06 ± 0.25	NS

* X ± SD

Table 5. Respiratory parameters in the ibuprofen and indomethacin groups before, after treatment and 14 days, 28 days after treatment.

Type of respirator and oxygen	Before	%	After 24-hour	%	14 days after treatment	%	28 days after treatment	%
Ibuprofen group								
HFOV or IPPV, $FiO_2 \geq 0.6$	2	13.33	1	6.67	0		0	
IPPV $FiO_2 \geq 0.3 < 0.6$	5	33.33	2	13.33	1	7.14	0	
IPPV $FiO_2 < 0.3$	4	26.67	6	40.00	6	42.86	1	8.33
CPAP, other additional O_2	1	6.67	3	20.00	3	21.43	4	33.33
Room air	3	20.00	3	20.00	4	28.57	7	58.33
Indomethacin group								
HFOV or IPPV, $FiO_2 \geq 0.6$	4	26.67	1	6.67	0		0	
IPPV $FiO_2 \geq 0.3 < 0.6$	2	13.33	0		0		2	15.38
IPPV $FiO_2 < 0.3$	6	40.00	9	60.00	6	42.86	3	23.08
CPAP, other additional O_2	3	20.00	5	33.33	4	28.57	1	7.69
Room air	0		0		4	28.57	7	53.85

HFOV = High frequency oscillatory ventilation,
IPPV = Intermittent positive-pressure ventilation, CPAP = continuous positive airway pressure

was administered within three hours after birth, it reduced the subsequent incidence of patent ductus arteriosus[12]. Van Overmeire B et al[13] found ibuprofen to be as effective as indomethacin in closing the ductus arteriosus on the third day of life and they observed that urine production was less affected by ibuprofen. In the present study, the urine production was not less than 1 ml per kilogram per hour in either group and increase in serum creatinine was not statistically significantly difference between both groups. Diuretic use was found to be more significantly different in the indomethacin group than the ibuprofen group because of the tendency of decrease in urine production in the indomethacin group after 48 hours of treatment. Necrotizing enterocolitis was found in the indomethacin group more than in the ibuprofen group. In piglets, ibuprofen did not affect intestinal and renal hemodynamics[8] and had no significant effects on gastrointestinal vascular resistance[10]. In preterm infants, ibuprofen did not significantly reduce mesenteric blood flow-velocity[14]. The other outcome variables such as retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia, sepsis and need for respiratory support were not significantly different between both groups.

In summary, the presented data indicates that oral ibuprofen is as effective as intravenous indomethacin in promoting ductal closure in premature infants. Ibuprofen is associated with fewer renal and gastrointestinal side effects.

(Received for publication on May 14, 2003)

REFERENCES

1. Feigen LP, King LW, Ray I, Beckett W, Kadowitzz PI. Differential effects of ibuprofen and indomethacin in the regional of the dog. J Pharmacol Exp Ther 1981; 219: 679-84.
2. Bekerur MV, Yeh TF, MillerK, Glasser RJ, Pildes RS. Indomethacin and its effects on renal function and urinary kallikrein excretion in premature infants with patent ductus arteriosus. Pediatrics 1981; 68: 99-102.
3. Van Bel F, Guit GL, Schhipper J, van de Bor M, Baan J. Indomethacin induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. J Pediatr 1991; 118: 621-6.
4. Rennie IM, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. Arch Dis Child 1986; 61: 233-8.
5. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral hemodynamics in very preterm infants. Lancet 1990; 335: 1491-5.
6. McCormick DC, Edwards AD, Brown GC, et al. Effect of indomethacin on cerebral oxidized cytochrome oxidase in preterm infants. Pediatr Res 1993; 33: 603-8.
7. Coceani F, White E, Bodach E, Olley PM. Age dependent changes in the response of the lamb ductus arteriosus to oxygen and ibuprofen. Can J Physiol Pharmacol 1979; 57: 825-31.
8. Malcolm DD, Segar JL, Robilard JE, Chemtob S. Indomethacin compromises hemodynamics during positive pressure ventilation independently prostanoids. J Appl Physiol 1993; 74: 1672-8.
9. Grosfeld JL, Kamman K, Gross K, et al. Comparative effects of indomethacin, prostaglandin E1, and ibuprofen on bowel ischemia. J Pediatr Surg 1983; 18: 738-42.
10. Spezial MV, Allen RG, Henderson CR, Barrington KJ, Finer NN. Effects of ibuprofen and indomethacin on regional circulation in newborn piglets. Biol Neonate 1999; 76: 242-52.
11. Patel J, Marks KA, Roberts I, Azzopardi D, Edwards AD. Ibuprofen treatment of patent ductus arteriosus. Lancet 1995; 346: 255.
12. Varvarigou A, Bardin CL, Bcharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA 1996; 275: 539-44.
13. Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child 1997; 76: F179-F184.
14. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cranciulli D, Rubaaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infant with patent ductus arteriosus. J Pediatr 1999; 135: 733-8.
15. Mosca F Bray M, Lattanzio M, Fumagalli M, Tosetto C. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. J Pediatr 1997; 131: 549-54.
16. Papile LA, Bourstein I, Bourstein R, Kloffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infant with birth weights less than 1,500 g. J Pediatr 1978; 92: 529-34.
17. Weiss H, Cooper B, Brook M, Schlucter M, Clyman R. Factors determining reopen of the ductus arteriosus after successful clinical closure with indomethacin. J Pediatr 1995; 127: 466-71.
18. Kliegman RM, Fanaroff AA. Necrotizing enterocolitis. N Eng J Med 1984; 310: 1093-103.

การศึกษาผลการรักษาโรคหัวใจ Patent ductus arteriosus ในทารกเกิดก่อนกำหนดด้วยยา Ibuprofen ชนิดรับประทานเปรียบเทียบกับยา Indomethacin ชนิดให้ทางหลอดเลือดดำ

อุไรวรรณ โชติเกียรติ, พบ,*
*เกศนาถ จิรัปปภา, พบ**, ธนะรัตน์ ลยางกูร, พบ****

ความเป็นมา : Indomethacin เป็นยามาตรฐานที่ใช้ในการรักษาปิด Patent ductus arteriosus (PDA) ในทารกเกิดก่อนกำหนด แต่พบว่ามีผลข้างเคียงมาก ต่างจาก Ibuprofen ซึ่งเชื่อว่า ให้ผลการรักษาใกล้เคียงกันและมีผลข้างเคียงน้อยกว่า

วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิภาพและผลข้างเคียงของยา Ibuprofen กับ Indomethacin ในการรักษาปิด PDA

วิธีการศึกษา : เป็นการศึกษาแบบ Randomized clinical trial ในผู้ป่วย 30 ราย ที่มี อายุครรภ์ ≤ 35 สัปดาห์ อายุหลังคลอด ≤ 10 วัน ที่ได้รับการวินิจฉัยว่าเป็น Symptomatic PDA และได้รับการตรวจสนับสนุนด้วย Echocardiogram โดยในกลุ่ม Indomethacin จะได้รับการบริหารยาทางหลอดเลือดดำ ทุก 12 ชั่วโมง จำนวน 3 ครั้ง ส่วนในกลุ่ม Ibuprofen จะได้ยารับประทานในขนาด 10 มก/กก/ครั้ง ทุก 24 ชั่วโมง จำนวน 3 ครั้ง ทำการบันทึกข้อมูลพื้นฐานของผู้ป่วยก่อนการรักษา อัตราการปิดของ PDA ยาอื่น ๆ ที่ผู้ป่วยได้รับและภาวะแทรกซ้อนที่เกิดขึ้นขณะทำการรักษาและหลังการรักษาภายใน 28 วัน

ผลการศึกษา : Ibuprofen มีประสิทธิภาพในการปิด PDA ได้ใกล้เคียงกับ Indomethacin คือ Ibuprofen สามารถปิด PDA ได้ 7 จาก 15 ราย คิดเป็นร้อยละ 46.67, Indomethacin สามารถปิด PDA ได้ 10 จาก 15 ราย คิดเป็นร้อยละ 66.67 (Relative risk = 0.669 ; 95% confidence interval, 0.328 to 1.364; p = 0.462) ผู้ป่วยที่ต้องรับการปิด PDA ด้วยยา ครั้งที่ 2 ไม่แตกต่างกัน คือในกลุ่ม Indomethacin 5 ราย เปรียบเทียบกับกลุ่ม Ibuprofen 6 ราย และให้การรักษาด้วยการผ่าตัดปิด PDA มี 2 รายซึ่งอยู่ในกลุ่ม Indomethacin ทั้งหมด ผู้ป่วยทั้ง 2 กลุ่มมีความแตกต่างกันในเรื่องของการได้รับยา Furosemide คือกลุ่ม Indomethacinมี 11 รายเปรียบเทียบกับกลุ่ม Ibuprofenมี 3 ราย (p = 0.009) และพบว่าอัตราการเกิด Necrotizing enterocolitis (NEC) ในกลุ่ม Indomethacin ค่อนข้างมากคือร้อยละ 66.67 เมื่อเปรียบเทียบกับกลุ่ม Ibuprofen คือร้อยละ 40 แต่ไม่มีความแตกต่างทางสถิติ

สรุปผลการศึกษา : Ibuprofen มีประสิทธิภาพใกล้เคียงกับ Indomethacin ในการรักษาปิด PDA ในทารกเกิดก่อนกำหนด โดยมี อัตราการเกิด NEC และมีภาวะแทรกซ้อนต่อไตน้อยกว่า

คำสำคัญ : หลอดเลือดเพเทนท์ ดักตัส, การปิด, ยาอินโดเมทาซิน, ยาไอบิวโปรเฟน

อุไรวรรณ โชติเกียรติ, เกศนาถ จิรัปปภา, ธนะรัตน์ ลยางกูร
จดหมายเหตุทางแพทย์ ฯ 2546; 86 (ฉบับพิเศษ 3): S563-S569

* หน่วยทารกแรกเกิด,
** กลุ่มงานกุมารเวชกรรม,
*** หน่วยโรคหัวใจ, สถาบันสุขภาพเด็กแห่งชาติมหาราชินี, กรุงเทพ ฯ 10400