Factors affecting successful closure of hemodynamically significant patent ductus arteriosus with indomethacin in extremely low birth weight infants

Chuan-Zhong Yang, Jiun Lee

Shenzhen, China and Singapore

Background: **The incidence of patent ductus arteriosus (PDA) is high in extremely low birth weight (ELBW) infants. Indomethacin has been widely used in the prophylaxis and treatment of hemodynamically significant PDA. This retrospective study was undertaken to identify factors such as birth weight, gestational age, gender, fetal growth retardation, ductal size, timing of the first dose of indomethacin and side effects of indomethacin, which may affect the successful closure of the PDA with indomethacin in ELBW infants.**

Methods: **A cohort of 139 ELBW infants who had received indomethacin treatment for PDA during a consecutive period of more than three years (September 2000 to December 2003) was retrospectively analyzed.**

Results: **Administration of indomethacin was associated with closure of PDA in 108 (77.7%) of 139 ELBW infants, and only 19.4% of infants required surgical ligation of the ductus eventually. There was no significant relationship between closure of PDA with gestational age, gender, fetal growth retardation, and ductal size. A higher birth weight and early use of indomethacin after birth could significantly increase the closure rate of PDA ($P<0.05$). Side effects of indomethacin such as transient oliguria and hyponatremia during indomethacin therapy did not affect PDA closure.**

Conclusions: **Indomethacin is effective for the treatment of PDA in ELBW infants. A higher rate of ductal closure is related to the increase of birth weight. PDA closure with indomethacin is age-related, and early administration of indomethacin could increase PDA closure and reduce the incidence of hyponatremia. There is no significant difference in major morbidities such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) after early treatment. Early screening for hemodynamically significant PDA in ELBW infants and early treatment with indomethacin are recommended.**

World J Pediatr 2008;4(2):91-96

Key words: **extremely low birth weight; indomethacin; patent ductus arteriosus; premature infants**

Author Affiliations: Department of Neonatology, South Medical University Affiliated Maternal & Child Healthcare Hospital of Shenzhen, Shenzhen 518028, China (Yang CZ); Department of Neonatology, National University Hospital, Yong Loo Lin School of Medicine, National University of Singapore, Republic of Singapore (Lee J)

Corresponding Author: Chuan-Zhong Yang, Department of Neonatology, South Medical University Affiliated Maternal & Child Healthcare Hospital of Shenzhen, Shenzhen 518028, China (Tel: 86-755-83360733; Fax: 86-755-83230651; Email: yangczgd@163.com)

Introduction

The incidence of patent ductus arteriosus (PDA) is high in infants with extremely low birth weight (ELBW, birth weight less than 1000 g). As a cyclooxygenase (COX) inhibitor that causes constriction of vessels, indomethacin has been used widely in the prophylaxis and treatment of hemodynamically significant PDA. It has been shown to be efficacious in premature infants (gestational age less than 37 weeks) with a closure rate of 70%-90%. However, the use of indomethacin is inadequately studied in ELBW infants with regard to the timing and duration of indomethacin and the relationship between PDA closure and factors such as birth weight, gestational age, gender and side effects.

This retrospective study aimed to identify the factors affecting successful closure of PDA with indomethacin in ELBW infants.

Methods

Subjects

Between September 2000 and December 2003,

we studied a cohort of 139 ELBW infants who had received indomethacin treatment for PDA at the NICU of KK Women's and Children's Hospital, Singapore. Exclusion criteria included the presence of major congenital anomalies. The study was approved by the Hospital's Ethics Committee. The infants enrolled had hemodynamically significant PDA documented by a cardiologist using echocardiography during the first 24 to 72 hours after birth or at any time if they manifested signs of PDA. The minimal diameter and the direction of shunting through the ductus were recorded. To document response, repeated echocardiography was performed between 48 to 72 hours after the last dose of a course of indomethacin. Additional scans were done when the infants were clinically suspected of having signs of a re-opened PDA or at the discretion of an attending physician. All the infants were managed according to the department protocol for ELBW infants.

Treatment schedule

Each infant received a conventional dose of indomethacin (Indocid I.V.; Merck, West Point, PA, USA) given at 0.2 mg/kg, 0.1 mg/kg, 0.1 mg/kg every 12 hours for 3 doses if the postnatal age was <48 hours; or 0.2 mg/kg every 12 hours for 3 doses if the postnatal age was >48 hours. The dose was given by infusion over half an hour. If the ductus failed to close or relapsed after the first course and was hemodynamically significant, a second course started after an interval of at least 48 hours from the last dose. The regimen of the second course was given at 0.2 mg/kg every 12 hours for 3 doses. Surgical ligation was conducted if both courses failed.

The administration of indomethacin was delayed for the following reasons: platelet count <60 000 per cubic millimeters, intraventricular hemorrhage within the past 12 hours, active bleeding, urine output <1 ml/kg per hour over the preceding 8 hours, and serum creatinine concentration >140 μmol/L.

Primary outcomes

The response to a course of indomethacin was defined echocardiographically as 1) *closed* if the ductus was closed (without relapse) and needed no further treatment, 2) *open* if the ductus was still open and hemodynamically significant, and 3) *relapsed* if the ductus relapsed (closed initially but subsequently re-opened) and was hemodynamically significant. Failure of response would indicate that the status of the ductus was either *open* or *relapsed* after treatment.

Secondary outcomes

These included the outcomes of each course of indomethacin, the need for a second course of indomethacin, the number of surgical ligations, and side effects. Anticipated side effects were oliguria (urine output <1 ml/kg body weight per hour for the preceding 24 hours), serum creatinine >140 μmol/L, serum sodium <130 mmol/L and <5 mmol/L of pretreatment value, brownish gastric aspirates needing treatment with ranitidine, fresh gastric bleeding, and focal gastrointestinal perforation. These ductal size were considered to be attributable to indomethacin if they occurred within a week of treatment.

Other variables recorded were gender, birth weight, gestational age, fetal growth retardation, size of the ductus before therapy, and timing of the first dose of indomethacin.

Statistical analysis

Normal distribution data were displayed as means ± SD. Abnormal distribution data were taken as median. The data were analyzed with commercial statistical software SPSS for Windows, version 11.0. The Chi-square test was used to analyze all variables. A value of $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 139 ELBW infants were included (Table 1). The mean postnatal age at which PDA was documented was 1.7±0.7 days. The mean diameter of the ductus before treatment was 2.0±0.7 mm (range: 0.8-3.9 mm). The mean age at the first dose of indomethacin was 44.2 ±24.7 hours (range: 8-226 hours). About 88.5% of the infants received a left-to-right shunt through the ductus.

Table 1. Baseline characteristics of ELBW infants with PDA (*n*=139)

Male sex, *n* (%)	77 (55.4)
Mean birth weight in g ± SD	807.3±139.8
Mean gestational age in week ± SD (range)	26.3±1.6 (23.1-31)
State of fetal growth, *n* (%)	
Small for gestational age	20 (14.4%)
Appropriate for gestational age	119 (85.6%)
Large for gestational age	0 (0%)
Median Apgar score at 1 min (range)	5 (1-8)
Median Apgar score at 5 min (range)	8 (1-9)
Prenatal steroid treatment, *n* (%)	119 (85.6)
Hyaline membrane disease (HMD), *n* (%)	120 (86.3)
HMD + Survanta, *n*	108
Bronchopulmonary dysplasia 28 day, *n* (%)	79 (56.8)
Intraventricular hemorrhage, *n* (%)	51 (36.7)
Grade 3 or 4, *n*	13
Periventricular leukomalacia, *n* (%)	4 (2.9)
Necrotizing enterocolitis, *n* (%)	17 (12.2)
Retinopathy of prematurity, *n* (%)	71 (51.1)
Mean length of hospital stay in day ± SD	102±60
Death, *n* (%)	14 (10.1)

In these infants, there were presence of heart murmur (55.6%), wide pulse pressure (37.3%, diastolic pressure less than half of systolic pressure), and hyperactive precordium (20.6%). In the 139 infants, altogether 193 courses of the treatment with indomethacin were completed. Fig. 1 shows the flow diagram of treatment with indomethacin. Side effects caused by indomethacin were hyponatremia and mild bleeding tendency (brownish or bloody gastric aspirates), which did not affect the continuity of treatment. Because of side effects such as oliguria, suspected necrotizing enterocolitis (NEC) or intraventricular hemorrhage (IVH), indomethacin administration was delayed at the discretion of an attending physician.

Treatment response

The response to indomethacin is shown in Table 2. One hundred and eight infants with PDA were successfully treated with one or more courses of indomethacin, giving a closure rate of 77.7%. Twenty-seven infants (19.4%) had their ductus ligated. The remaining 4 infants (2.9%) had open ductus despite one, two or three courses of indomethacin, and they died before further medical or surgical treatment was given. Ten infants whose ductus closed with indomethacin died later, thereby giving a mortality rate of 10.1% (14/139) for this cohort.

Factors affecting success of indomethacin treatment

The ELBW infants were grouped according to their birth weight, gestational age, gender, ductal diameter, timing of the first dose of indomethacin, and fetal growth retardation. The effect of factors affecting the closure rate after the first course and the final closure rate are shown in Table 3. Birth weight and

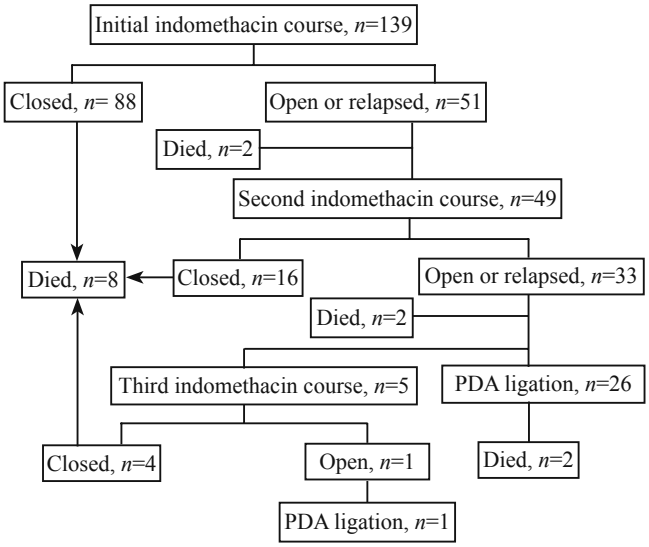

Fig. 1. Flow diagram of treatment of ELBW infants with PDA.

Table 2. Response to indomethacin

	First course		Second or third course		Final outcome	
	Number	%	Number	%	Number	%
Closed	88	63.3	20	37.0	108	77.7
Relapsed	19	13.7	4	7.4	-	-
Open	32	23.0	30	55.6	4	2.9
Required surgical ligation	-	-	-	-	27	19.4
Total	139	100	54	100	139	100

Table 3. Factors associated with successful ductal closure

		Number	First course			Final outcome		
			Closed	%	χ^2	Closed	%	χ^2
Birth weight (g)	≤800	63	31	49.2	9.87†	43	68.3	5.93*
	>800	76	57	75.0		65	85.5	
Gestational age (wk)	≤26	58	34	58.6	0.94	43	74.1	0.73
	>26	81	54	66.7		65	80.2	
Gender	Male	77	52	67.5	1.33	64	83.1	2.93
	Female	62	36	58.1		44	71.0	
Ductal diameter (mm)	≤2.0	80	48	60.0	0.89	63	78.8	0.12
	>2.0	59	40	67.8		45	76.3	
Age of first dose of indomethacin (h)	≤40	68	51	75.0	7.83*	58	85.3	4.43*
	>40	71	37	52.1		50	70.4	
State of fetal growth	SGA	20	15	75.0	1.38	18	90.0	2.04
	AGA	119	73	61.3		90	75.6	
Oliguria	Yes	23	16	69.6	0.46			
	No	116	72	62.1				
Hyponatremia	Yes	42	28	66.7	0.29			
	No	97	60	51.9				

*: $P<0.05$, †: $P<0.01$. SGA: small for gestational age; AGA: appropriate for gestational age.

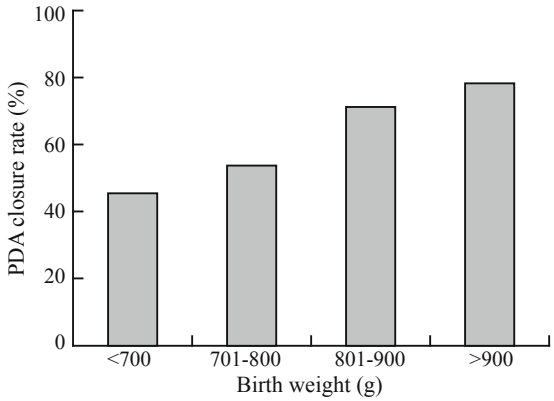

Fig. 2. Birth weight and its effect on PDA closure rate (P=0.014).

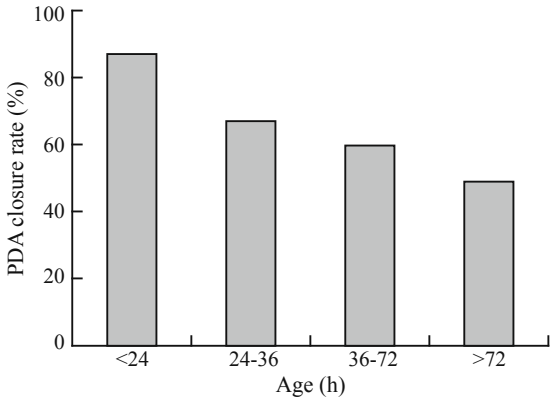

Fig. 3. Timing of the first dose of indomethacin and its effect on PDA closure rate (P=0.032).

Table 4. Effects of timing of first dose of indomethacin

Timing of first dose	Number	Ligation		Oliguria		Hyponatremia		BPD		IVH		NEC		ROP	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
≤40 h	68	8	11.8	11	16.2	15	22.1	41	60.3	29	42.6	11	16.2	33	48.5
>40 h	71	19	26.8	12	16.9	27	38.0	38	53.5	22	31	6	8.5	38	53.5
Total	139	27	19.4	23	16.5	42	30.2	79	56.8	51	36.7	17	12.2	71	51.1
χ^2		4.99*		0.01		4.20*		0.65		2.03		1.93		0.35	

*: P<0.05. BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity.

early administration of indomethacin were correlated significantly with the success of indomethacin treatment.

To further elucidate the effect of indomethacin on infants with varying birth weight, we stratified the birth weight and the age at the administration of indomethacin into four groups according to birth weight, namely ≤700 g, 701-800 g, 801-900 g, and >900 g. The age for the first dose of indomethacin was divided into within 24 hours, between 24-36 hours, between 36-72 hours, and more than 72 hours. Figs. 2 and 3 show the closure rates and effects of birth weight, and timing of the first dose of indomethacin. The closure rate was increased with the increasing birth weight and with the early administration of indomethacin in the first course of treatment (P<0.05).

Timing of the first dose and outcomes

The two groups of infants, divided by the timing of the first dose (≤40 and >40 hours of age) showed that earlier administration of the first dose (≤40 hours of age) was significantly associated with the lower incidence of surgical ligation and hyponatremia (P<0.05) (Table 4). However, morbidities such as grades 3 or 4 IVH, NEC, bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) were not significantly different between the two groups (P>0.05).

Discussion

Indomethacin is effective for the treatment of patent ductus arteriosus.[1,2] In small premature infants, the closure rate was 70%-90%. However, about 13%-53% of cases relapsed or remained open after treatment with indomethacin and surgical ligation was required eventually.[3,4] In our study, the closure rate of PDA in ELBW infants with indomethacin was 77.7% and surgical ligation rate was 19.4%. Even in the ELBW infants, the ductus arteriosus responded well to indomethacin, a nonselective prostaglandin synthesis inhibitor. Moreover, the closure rate was 45.2% for infants who weighed less than 700 g at birth and 78.0% for those who weighed 900-999 g after one course of indomethacin.

PDA in small premature infants is often treated for decreasing morbidity, because a hemodynamically significant left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, respiratory distress syndrome, and death.[1,5,6] However, some studies[7,8] showed that prophylactic pharmacologic or surgical closure of PDA in small premature infants produced only short-term benefits like a decrease in later symptomatic PDA or a reduction in the duration of oxygen dependence. In an observational study,[9] a longer duration of indomethacin exposure was associated with less white matter injury in infants

delivered before 28 weeks' gestation. There is no good evidence that any of the strategies can result in a long-term benefit, in particular, the morbidities of BPD, IVH and disability-free survival.[10-13] Conventional dose of indomethacin has shown to be effective in closing PDA in premature infants, but it could result in more severe side-effects. Prolonged administration of low-dose indomethacin (0.1 mg/kg daily for 6 days) is equally, but not more, effective than the conventional dose. Also, there is a trend toward increased incidence of NEC.[14] Sperandio et al[15] reported recently that high-dose indomethacin resulted in an overall closure rate of 98.5% (single indomethacin doses up to 1 mg/kg) and comparing with the conventional-dose indomethacin therapy, there were no differences in the incidences of renal or electrolyte abnormalities, gastrointestinal bleeding, intraventricular hemorrhage, or periventricular leukomalacia. Early prophylactic use of indomethacin can reduce the incidence of clinically significant PDA in small premature infants from 56%-83% to 7%-20%,[3,16,17] but a significant proportion of the ductus close spontaneously in preterm infants. Reller et al[18] reported that the spontaneous closure rate of PDA on day 3 of life in healthy preterm infants of more than 30 weeks' gestation ranged from 81.3% to 87.5%, and nearly 27%-34% in infants of 27 weeks' gestation.[19,20] The incidence of PDA in ELBW infants was approximately 60.3% at our NICU (KKWCH Singapore) during the years 2000 to 2003. Thus, prophylactic indomethacin may result in about 40% of babies being treated unnecessarily. There has been a controversy as to whether or when the ductus arteriosus should be closed. In premature infants, left-to-right shunt through the ductus arteriosus may be a normal mechanism by which pulmonary blood flow is maintained during the initial transition from fetal to neonatal circulation. Therefore, very early treatment to close the ductus arteriosus by pharmacologic or surgical methods may be contraindicated in some settings.[21]

Gersony et al[1] reported that the closure rate of PDA with indomethacin may reach 80% to 86% in infants who weighed 1000-1750 g at birth; however, the rate was only 54% in infants <1000 g. Our study also demonstrated that the closure rate of PDA with indomethacin increased significantly when the birth weight increased. Many factors may influence the weight-dependent closure rate of PDA by indomethacin, such as the maturity of the contractile spiral smooth muscle fibers of the ductus arteriosus, the presence and concentration of prostaglandin receptors in the ductus, and the effect of the immature respiratory system in infants with lower birth weight. These factors all affect the closure of the ductus arteriosus.

Adverse side-effects might occur frequently during indomethacin treatment,[22-24] including hyponatremia, oliguria, active bleeding, and impaired renal function, which are transient and seem to have no long-term sequelae. Necrotizing enterocolitis (stage II and III), intraventricular hemorrhage, and focal gastrointestinal perforation are rarely found during therapy. These side-effects of indomethacin are due to the nonselective vasoconstrictive effect of the drug and the reduction of blood flow through various organs. The two common side-effects, hyponatremia and oliguria, are secondary to vasoconstriction of the renal vasculature. Does the presence of these side-effects correlate with successful closure of the ductus since their presence in an infant probably indicates that the vasoconstrictive effects of indomethacin are strong? Our study did not show such an association. We speculate that this might attribute to the variable vasoconstrictive effects of indomethacin in different organs. In our study, early administration of indomethacin significantly reduced the incidence of hyponatremia but not oliguria.

Interestingly, we found that the timing of the first dose of indomethacin was significantly associated with the closure rate, and that early administration reduced the need for surgical ligation. Up to 85.2% of PDA would close if the first dose of indomethacin was administered within 24 hours after birth, and the rate decreased to 48.1% if it was started 72 hours or later after birth. The corresponding rates for surgical ligation were 3.7% and 25.9% respectively. Schmidt et al[10] found that in premature infants weighing <1000 g at birth, the incidence of severe periventricular and intraventricular hemorrhage ranged from 13% in infants with persistent patency of the ductus down to 9% in those whose PDA was closed earlier. Therefore, early administration of indomethacin in ELBW infants with significant PDA not only resulted in a higher incidence of ductal closure and a lower incidence of surgical ligation, but also produced short-term benefits when a shunting through the ductus was stopped.

In summary, indomethacin is effective in treating PDA in ELBW infants. The rate of ductal closure is related to the birth weight of the infants. There was also an age-related mechanism for PDA closure with indomethacin. Early administration of indomethacin can increase the closure rate of PDA and reduce the incidence of some side effects. However, there is no significant difference in major morbidities such as BPD, IVH, NEC and ROP after early treatment with indomethacin. Early screening for hemodynamically significant PDA in ELBW infants and early treatment with indomethacin are recommended.

Acknowledgements

We are grateful to Drs Quek B H, Lim Sok Bee, Khoo PC, Ho Nai Kiong and others at the Department of Document Management of KK Women's and Children's Hospital, Singapore for their assistance in this study. Special thanks also to Dr Zhu Xiaoyu of Shenzhen Maternity & Child Healthcare Hospital, China for reviewing the manuscript.

Funding: None.
Ethical approval: This study was approved by the Ethics Committee of KK Women's and Children's Hospital, Singapore.
Competing interest: None declared.
Contributors: Yang CZ proposed the study and wrote the first draft. Lee J is the guarantor.

References

1 Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. J Pediatr 1983;102:895-906.
2 Van Overmeire B, Chemtob S. The pharmacologic closure of the patent ductus arteriosus. Semin Fetal Neonatal Med 2005;10:177-184.
3 Krueger E, Mellander M, Bratton D, Cotton R. Prevention of symptomatic patent ductus arteriosus with a single dose of indomethacin. J Pediatr 1987;111:749-754.
4 Hammerman C, Glaser J, Schimmel MS, Ferber B, Kaplan M, Eidelman AI. Continuous versus multiple rapid infusions of indomethacin: effects on cerebral blood flow velocity. Pediatrics 1995;95:244-248.
5 Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 1978;93:647-651.
6 Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics 2007;119:1165-1174.
7 Lemmers PM, Toet MC, van Bel F. Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants. Pediatrics 2008;121:142-147.
8 Cordero L, Nankervis CA, Delooze D, Giannone PJ. Indomethacin prophylaxis or expectant treatment of patent ductus arteriosus in extremely low birth weight infants? J Perinatol 2007;27:158-163.
9 Miller SP, Mayer EE, Clyman RI, Glidden DV, Hamrick SE, Barkovich AJ. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks' gestation at birth. Pediatrics 2006;117:1626-1631.
10 Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966-1972.
11 Hanigan WC, Kennedy G, Roemisch F, Anderson R, Cusack T, Powers W. Administration of indomethacin for the prevention of periventricular-intraventricular hemorrhage in high-risk neonates. J Pediatr 1988;112:941-947.
12 Alfaleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B. Trial of Indomethacin Prophylaxis in Preterms Investigators. Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. Pediatrics 2008;121:e233-e238.
13 Ment LR, Peterson BS, Meltzer JA, Vohr B, Allan W, Katz KH, et al. A functional magnetic resonance imaging study of the long-term influences of early indomethacin exposure on language processing in the brains of prematurely born children. Pediatrics 2006;118:961-970.
14 Lee J, Rajadurai VS, Tan KW, Wong KY, Wong EH, Leong JY. Randomized trial of prolonged low-dose versus conventional-dose indomethacin for treating patent ductus arteriosus in very low birth weight infants. Pediatrics 2003;112:345-350.
15 Sperandio M, Beedgen B, Feneberg R, Huppertz C, Brüssau J, Pöschl J, et al. Effectiveness and side effects of an escalating, stepwise approach to indomethacin treatment for symptomatic patent ductus arteriosus in premature infants below 33 weeks of gestation. Pediatrics 2005;116:1361-1366.
16 Mahony L, Carnero V, Brett C, Heymann MA, Clyman RI. Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birth-weight infants. N Engl J Med 1982;306:506-510.
17 Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2003;88:F464-466.
18 Reller MD, Ziegler ML, Rice MJ, Solin RC, McDonald RW. Duration of ductal shunting in healthy preterm infants: an echocardiographic color flow Doppler study. J Pediatr 1988;112:441-446.
19 Narayanan M, Cooper B, Weiss H, Clyman RI. Prophylactic indomethacin: factors determining permanent ductus arteriosus closure. J Pediatr 2000;36:330-337.
20 Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics 2006;117:1113-1121.
21 Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? Curr Opin Pediatr 2004;16:146-151.
22 O'Donovan DJ, Baetiong A, Adams K, Chen A, Smith EO, Adams JM, et al. Necrotizing enterocolitis and gastrointestinal complications after indomethacin therapy and surgical ligation in premature infants with patent ductus arteriosus. J Perinatol 2003;23:286-290.
23 Pietz J, Achanti B, Lilien L, Stepka EC, Mehta SK. Prevention of necrotizing enterocolitis in preterm infants: a 20-year experience. Pediatrics 2007;119:e164-e170.
24 Zanardo V, Vedovato S, Lago P, Piva D, Faggian D, Chiozza L. Effects of ibuprofen and indomethacin on urinary antidiuretic hormone excretion in preterm infants treated for patent ductus arteriosus. Fetal Diagn Ther 2005;20:534-539.

Received August 21, 2007
Accepted after revision March 31, 2008