

# Comparison of Intravenous and Enteral Indomethacin Administration for Closure of Patent Ductus Arteriosus in Extremely-low-birth-weight Infants

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**Background:** The objective of this retrospective cohort study was to compare the patent ductus arteriosus (PDA) closure rate with different routes (intravenous and enteral) of indomethacin treatment and neonatal outcomes.

**Methods:** Infants with a birthweight <1,000 g born between July 1997 and June 2007 at Taipei Veterans General Hospital and who received indomethacin treatment for PDA were included in the study. Outcome measures were ductal closure rate and neonatal outcomes.

**Results:** Of 41 extremely-low-birth-weight infants with PDA, 3 infants had spontaneous closure and 3 died before treatment. Of the remaining 35 infants, 13 received enteral ethanol solution of indomethacin and 22 received the intravenous (IV) form. The total closure rates of the IV and enteral groups were 81.8% and 76.9%, respectively. There were no significant differences in the incidence of impaired renal function, necrotizing enterocolitis, chronic lung disease or severe retinopathy of prematurity between the 2 groups.

**Conclusion:** Our results suggest that ethanol-based indomethacin is an effective alternative to IV indomethacin for the pharmacological closure of PDA in extremely-low-birth-weight infants. [*J Chin Med Assoc* 2010;73(1):15–20]

**Key Words:** enteral route, indomethacin, patent ductus arteriosus, preterm

## Introduction

Persistent patent ductus arteriosus (PDA) is frequently encountered in preterm infants. A variety of morbidities such as necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia arise because of failure of closure of the ductus arteriosus (DA).<sup>1</sup> Therefore, closure of the PDA is crucial in the care of prematurity, especially for extremely-low-birth-weight (ELBW) neonates (birth body weight <1,000 g) who are prone to long-term sequelae if the clinical course is complicated by PDA.

Indomethacin has been used since the early 1970s for this purpose, and intravenous (IV) indomethacin is a standard medical treatment, with effectiveness up to 70–80%.<sup>2–4</sup> However, if the IV form is not available, oral indomethacin is a potential alternative. Several previous studies have reported a poor response to oral indomethacin due to marked variability in the serum concentrations of indomethacin.<sup>5,6</sup> In contrast, Mrongovius et al reported that both the rates of permanent closure and transient closure were similar in either the IV route or oral route and the closure rate was independent from serum concentrations.<sup>7</sup> Scanlon



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showed that an 85% closure rate was achieved with an ethanol-based oral solution.<sup>8</sup> It is not clear whether using a base-aqueous solution or ethanol makes any difference. Therefore, we compared the effectiveness of oral ethanol-based indomethacin and IV indomethacin for PDA closure in ELBW infants.

## Methods

### *Study infants and design*

This was a retrospective chart review study. The study subjects included ELBW infants who were treated with indomethacin due to hemodynamic significant PDA. All these babies were born between July 1997 and June 2007 at Taipei Veterans General Hospital, Taiwan. Hemodynamically significant PDA was defined as the presence of any of the following signs: systolic or continuous murmur together with widening of pulse pressure or active precordial heave, cardiomegaly and increased pulmonary vascularity on chest radiography, and failure to wean from mechanical ventilation. ELBW infants with other congenital diseases such as congenital heart disease other than PDA and congenital renal disease were excluded from the study.

Before initiation of indomethacin treatment, serum creatinine levels, platelet count, total bilirubin and electrolytes were assessed. Therapy was given if the platelet count was  $> 50,000/\mu\text{L}$ , serum creatinine levels were  $< 1.5 \text{ mg/dL}$ , or urine output was  $> 1 \text{ mL/kg}$  per hour in the preceding 8 hours. During the treatment, when urine output declined below  $1 \text{ mL/kg}$  per hour, furosemide  $0.5\text{--}1.0 \text{ mg/kg}$  was given. After treatment, serum creatinine was assessed again, and fluid and electrolyte administration was adjusted according to the daily variation of body weight and serum electrolytes. In case of adverse events such as intraventricular hemorrhage grade III or higher, gastrointestinal bleeding, or perforation and NEC, indomethacin was withheld until clinical status improved. Cranial ultrasonography was performed before and after every treatment course.

### *Diagnosis of PDA and follow-up*

The diagnosis of PDA was confirmed by echocardiography with the demonstration of left-to-right blood flow through the open duct. The ductal size was measured with a 2-dimensional image through the parasternal short-axis view. The size and ejection fraction of the left ventricular chamber was also measured by cardiography. Color and pulsed wave spectral Doppler scanning was applied to assess the direction and the velocity of ductal flow. After every treatment

course, echocardiography was repeated to confirm the closure of ductus, which was defined as a ductal diameter  $< 1 \text{ mm}$  or a tiny blood jet. If echocardiography indicated ductus closure, daily assessment of heart murmur was performed.

### *Indomethacin treatment regimen*

The choice of either the IV route or oral route depended on the policy of in-charge attending physicians. In the enteral group, indomethacin was prepared by dissolving a 25-mg indomethacin capsule with beer to a final concentration of  $1 \text{ mg/mL}$ . IV regimen of indomethacin ( $1 \text{ mg/mL}$ , Indocid PDA; Merck Sharp & Dohme, Hertfordshire, UK) was diluted in distilled water to a final concentration of  $0.1 \text{ mg/mL}$  and infused over 30 minutes. Every course included 3 doses at a dosage of  $0.2 \text{ mg/kg}$ . The same dose was repeated 12 hours and 24 hours later if the urine amount was not less than  $1 \text{ mL/kg}$  per hour; however, if the urine volume was less, the interval was prolonged. Echocardiography was conducted 24–36 hours after completion of the course. In treatment failure cases, another course of treatment was administered through the same route. The treatment was delayed when any of the following conditions were present: unstable hemodynamic status; progressive, active bleeding diathesis; urine amount  $< 1 \text{ mL/kg/hr}$ ; serum creatinine level  $> 1.5 \text{ mg/dL}$ ; significant hyperbilirubinemia near exchange transfusion level or NEC. Surgical ligation was attempted if a total of 3 courses failed to close the PDA.

### *Data collection*

The following information was collected: the response to the 1<sup>st</sup> course of indomethacin (closed or open), the need for a 2<sup>nd</sup> or 3<sup>rd</sup> course, the cases of surgical ligations, and the side effects of indomethacin. Anticipated adverse effects were oliguria (urine output  $< 1 \text{ mL/kg}$  per hour for the following 8 hours), post-treatment serum creatinine levels  $> 1.5 \text{ mg/dL}$ , serum sodium  $< 130 \text{ mmol/L}$  or a decrease in serum sodium of more than  $5 \text{ mmol/L}$  when compared with pretreatment values, coffee ground aspirate, and fresh blood from the gastric tube. These side effects were attributed to indomethacin if they occurred during the treatment course or within 48 hours after treatment.

Potential confounding factors such as daily fluid intake, the setting of mechanical ventilation, surfactant use, antenatal steroids and culture-proven sepsis, were examined in the study. Various clinical outcomes such as days on oxygen supplement or mechanical ventilation, chronic lung disease (CLD), retinopathy of prematurity (ROP), intraventricular hemorrhage,

cystic periventricular leukomalacia (PVL), and NEC were recorded. PVL was defined as periventricular hyperchogenicity that progressed to cyst formation.

### Statistical analysis

Numeric data expressed as the mean with standard deviation or median with range were compared by Student's *t* test. Fisher's exact test was used for the comparison of non-numeric data. The Mann-Whitney test was used for non-parametric data. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed with SPSS version 15 (SPSS Inc., Chicago, IL, USA).

## Results

In total, there were 144 ELBW infants born between July 1997 and June 2007 and 72 cases survived; 41 ELBW infants had PDA and 29 of these infants survived (28.5%/40.1% of PDA in this total/survival group). Spontaneous closure without indomethacin treatment occurred in 3 patients and 3 patients died before treatment administration. The gestational ages and body weights at birth of these 3 infants with spontaneous closure were 25, 29, 27 weeks and 698, 924,

770 g, respectively. These infants did not receive indomethacin treatment because of their stable condition without ventilator support at the age of PDA diagnosis, and they had PDA closure just with fluid restriction. The remaining 35 infants were treated with indomethacin. Thirteen infants received oral ethanol-based solution and 22 infants received the IV form. There were 9 mortality cases all due to sepsis. There were no significant differences in clinical characteristics between the enteral and IV groups (Table 1).

The courses and responses to indomethacin therapy are shown in Table 2. Both the total closure rate and the response rates to the 1<sup>st</sup> treatment course were higher in the IV group than in the enteral group, but this was not significantly different. In the IV group, 2 infants received surgical ligation at the postnatal ages of 32 and 38 days after 3 treatment courses, and extubation was successful on the 2<sup>nd</sup> day after operation. In the enteral group, 4 cases did not receive the full treatment courses despite their persistent PDA; 3 of them received 2 courses and 1 case received 1 course only because of severe oliguria and sepsis. The infant with 1 course had intermittent mandatory ventilation for 6 days and then died. The other 3 infants were ventilator-dependent for 40, 50 and 56 days, and they had PDA closure before discharge ( $p = 0.0437$ ). Surgical

**Table 1.** Clinical characteristics of the study population\*

	Enteral group (n = 13)	IV group (n = 22)	p
GA (wk)	26 ± 2.3	27 ± 2.5	0.11
BBW (g)	833.7 ± 110.3	807.4 ± 146.8	0.58
Sex			0.41
Male	3	8	
Female	10	14	
Twin/triple pregnancy	5 (33.3)	8 (36.4)	0.73
Apgar score			
1-min	3 (1–7)	4 (1–7)	0.73
5-min	6 (5–8)	6 (1–9)	0.47
RDS			
I/II	7 (46.7)	11 (50)	0.82
II/III	8 (53.3)	11 (50)	0.82
Surfactant	10 (66.7)	17 (77.2)	0.32
Ductal size (cm)	0.25 ± 0.12	0.18 ± 0.08	0.10
Age at diagnosis (d)	9 (1–28)	5 (2–32)	0.73
Age at therapy (d)	11 (3–28)	7 (2–57)	0.96
Antenatal steroid	1 (6.7)	4 (18.2)	0.39

\*Data presented as mean ± standard deviation or n or n (%) or median (range). IV = intravenous; GA = gestational age; BBW = birth body weight; RDS = respiratory distress syndrome.

**Table 2.** Responses to indomethacin therapy by treatment group\*

	Enteral group (n = 13)	IV group (n = 22)	p
Closure	10 (76.9)	18 (81.8)	0.72
1 <sup>st</sup> course	7 (46.7)	13 (59.1)	0.76
2 <sup>nd</sup> course	1 (61.5) <sup>†</sup>	2 (68.2) <sup>†</sup>	0.69
3 <sup>rd</sup> course	2	3	
Ligation	0	2	0.52
Closed after conservative treatment	3	0	0.04
Mortality	2	7	0.43

\*Data presented as n (%) or n; <sup>†</sup>cumulative percentage. IV = intravenous.

**Table 3.** Adverse events during indomethacin therapy by treatment group\*

	Enteral group (n = 13)	IV group (n = 22)	p
Urine < 1 mL/kg/hr	2 (13.3)	6 (27.2)	0.35
Serum Cr > 1.5 mg/dL	4 (26.6)	3 (13.6)	0.29
GI hemorrhage	4 (26.6)	12 (54.5)	0.13
Necrotizing enterocolitis	3 (20)	4 (18.2)	0.51
Hyponatremia	3 (20)	3 (13.6)	0.44

\*Data presented as n (%). IV = intravenous; Cr = creatinine; GI = gastrointestinal.

**Table 4.** Neonatal outcomes by treatment group\*

	Enteral group (n = 13)	IV group (n = 22)	p
O <sub>2</sub> supplement (d)	41.2 ± 26.3	38.6 ± 28.6	0.79
CPAP (d)	27.8 ± 26.4	18.7 ± 14.4	0.21
IMV (d)	24.1 ± 27.5	20.4 ± 22.8	0.68
CLD at 36 wk gestation	7 (53.8)	7 (31.8)	0.53
ROP (stage III/IV)	2 (15.4)	1 (4.5)	0.67
IVH	6 (46.2)	7 (31.8)	0.64
PVL	3 (23.1)	2 (9.1)	0.35
Sepsis	4 (30.8)	9 (40.9)	0.58
NEC	3 (23.1)	5 (22.7)	0.86
Full feeding (d)	49.6 ± 37.8	36.4 ± 37.1	0.33

\*Data presented as mean ± standard deviation or n (%). IV = intravenous; CPAP = continuous positive airway pressure; IMV = intermittent mandatory ventilation; CLD = chronic lung disease; ROP = retinopathy of prematurity; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; NEC = necrotizing enterocolitis.

ligation was not attempted in these 3 cases because of unstable condition.

The occurrence rate of oliguria and upper gastrointestinal hemorrhage was higher in the IV than in the enteral group, but this was not statistically significant. However, the incidence of impaired renal function, such as elevated creatinine level, electrolyte imbalance or NEC, was similar in both groups (Table 3). Enteral patients had a longer dependence on continuous positive airway pressure (CPAP), a higher rate of CLD at a gestational age of 36 weeks, and a higher incidence of

ROP and PVL (Table 4), but none of these differences were statistically significant.

## Discussion

The effect of indomethacin on PDA closure appears to be related to drug concentration, drug exposure time<sup>9</sup> and host constitution. IV indomethacin is a well-accepted medical treatment for PDA closure;<sup>10</sup> however, the effects of the enteral form of indomethacin

are still controversial, possibly because of its high variability of pharmacodynamics in preterm babies. To our knowledge, there are very few studies that have compared the effectiveness of the IV and enteral forms of indomethacin for PDA closure in ELBW infants. Cooke and Pickering reported 5 cases of treatment failure in 7 very-low-birth-weight infants who had an oral aqueous solution.<sup>5</sup> Earlier pharmacokinetic studies by Bhat et al<sup>11</sup> and Evans et al<sup>12</sup> reported that the absorption of oral indomethacin in preterm neonates with PDA was low and erratic. However, later clinical studies reported a 70% closure rate with an aqueous solution.<sup>13</sup> The greater effectiveness of an ethanol-based solution has been demonstrated by Scanlon who found an 85% closure rate.<sup>8</sup> A possible factor that might influence the outcome is the preparation solution of the enteral indomethacin. Previous studies have shown a large interindividual variability in plasma concentrations of indomethacin with an aqueous solution, and the *in vitro* bioavailability was approximately 20%.<sup>6,11,12</sup> Scanlon demonstrated that diluting indomethacin in water would consistently underdose, and the percent variance from the mean was almost triple that for ethanol.<sup>8</sup> Recently, a pharmacokinetic study reported that a saline-ethanol-dextrose suspension achieved a 98.6% absorption rate in preterm infants; this finding provided evidence that preterm infants could be switched between the IV and orogastric routes.<sup>14</sup> In this study, the enteral method used ethanol-based indomethacin, and the closure rate was 76.9% compared with 81.8% using the IV form; there was no significant difference between the 2 routes of administration.

The incidence of oliguria and impaired renal function was similar in both groups. This finding may be explained from the pharmacokinetic standpoint since some studies have reported that no definite relationship exists between drug concentration and PDA closure<sup>7,15-17</sup> as well as kidney function.<sup>7</sup> Previous reports have documented the increased incidence of CLD due to persistent PDA,<sup>18,19</sup> as well as CLD, severe ROP and PVL among infants exposed to indomethacin.<sup>20</sup> In this study, the enteral group had a longer dependence on CPAP and a trend for an increased incidence of CLD, severe ROP and PVL. However, because there was an insufficient number of cases, these differences were not statistically significant. The causal relationship between these findings requires further investigation.

Surgical ligation should be considered if medical therapy has failed or the patient's status is not suitable for indomethacin therapy. Keller and Clyman suggested that additional indomethacin treatment is unlikely to produce ductus closure in premature infants if there is persistent Doppler evidence of ductal flow within

24 hours after an initial short course, and earlier surgical ligation is suggested.<sup>21</sup> A recent study questioned the long-term safety of more than 2 courses of indomethacin in preterm infants.<sup>22</sup> However, a survey of Neonatal Fellowship Program Directors in the United States reported that multiple courses of indomethacin (up to 3 courses) are commonly used for persistent PDA.<sup>23</sup> There is still debate on whether surgical ligation or multiple courses of indomethacin should be the preferred treatment if the PDA fails to close after the initial course. In our study, 2 patients in the IV group received surgical ligation due to failure of extubation and persistent dyspnea after 3 full courses of indomethacin. Both of the patients were extubated on the 2<sup>nd</sup> day after surgery and were soon independent from oxygen and the ventilator. Four patients in the enteral group did not undergo surgical ligation after medical therapy failure due to sepsis. Except for 1 case who died before PDA closure, the other 3 cases were extubated soon after sepsis resolved and had spontaneous PDA closure after infection control; however, they had a much longer dependence on CPAP with a ventilator and oxygen. It remains a challenge for the clinician to determine what is the best time point for surgery or whether to just give conservative therapy.

There were some limitations in this study. Because of the retrospective design, there was a latent shortage of homogeneity in patient data, and the case numbers in both groups were insufficient. Although this was a retrospective study, the findings were from a single unit over a 10-year period. There were no major changes in clinical practice during this study period.

This study showed that the outcome of treatment with an enteral preparation of ethanol-based indomethacin was comparable to that of the IV preparation. This finding suggests that ethanol-based indomethacin is an effective alternative to IV indomethacin for the pharmacological closure of PDA in ELBW infants.

## References

1. Clyman RI. Patent ductus arteriosus in premature infant. In: Taucusch WH, Ballard RA, eds. *Avery's Diseases of the Newborn*, 8<sup>th</sup> edition. Philadelphia: WB Saunders, 2004:816-23.
2. Narayanan M, Clyman R. Pharmacologic closure of patent ductus arteriosus in the neonate. *NeoReviews* 2003;4:e215-22.
3. Gerysony 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;102:895-905.
4. Rudd P, Motanez P, Hallidie-Smith K, Silverman M. Indomethacin treatment for patent ductus arteriosus in very low birth-weight infants: double blind trial. *Arch Dis Child* 1983;58:267-70.

5. Cooke RW, Pickering D. Poor response to oral indomethacin therapy for persistent ductus arteriosus in very low birthweight infants. *Br Heart J* 1974;41:301-3.
6. Sharma PK, Garg SK, Narang A. A preliminary study on pharmacokinetics of oral indomethacin in premature infants in north India. *Indian J Med Res* 2003;117:164-9.
7. Mrongovius R, Imbeck H, Wille L, Muller H, Seyberth HW. Variability of serum indomethacin concentrations after oral and intravenous administration to preterm infants. *Eur J Pediatr* 1982;138:151-3.
8. Scanlon JW. Oral aqueous suspension of indomethacin should be abandoned. *Pediatrics* 1982;69:507.
9. Lewis IG, Harvey DP, Maxwell GM. Indomethacin therapy of patent ductus in preterm infants controlled by plasma levels. *Aust Paediatr J* 1985;21:181-3.
10. Stevenson DK, Wright LL, Lemons JA, Oh W, Korones SB, Papile LA, Bauer CR, et al. Very-low-birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. *Am J Obstet Gynecol* 1988;2:328-36.
11. Bhat R, Vidyasagar D, Fisher E, Hastreiter A, Ramirez JL, Burns L, Evans M. Pharmacokinetics of oral and intravenous indomethacin in preterm infants. *Dev Pharmacol Ther* 1980;1:101-10.
12. Evans M, Bhat R, Vidyasagar D, Patel M, Hastreiter A. A comparison of oral and intravenous indomethacin disposition in the premature infant with patent ductus arteriosus. *Pediatr Pharmacol* 1981;1:251-8.
13. So LY, Fok TF, Sung RY, Ho JK. Preterm infants with patent ductus arteriosus: treatment with an enteral preparation of indomethacin. *Trop Paediatr* 1992;12:403-8.
14. Al-Za'abi MA, Donovan T, Tudehope D, Woodgate P, Collie L, Charles B. Orogastric and intravenous indomethacin administration to very premature neonates with patent ductus arteriosus: population pharmacokinetics, absolute bioavailability, and treatment outcome. *Ther Drug Monit* 2007;29:807-14.
15. Alpert BS, Lewins MJ, Rowland DW, Grant MJ, Olley PM, Soldin SJ, Swyer PR, et al. Plasma indomethacin levels in preterm newborn infants with symptomatic patent ductus arteriosus—clinical and echocardiographic assessment of response. *J Pediatr* 1979;95:578-82.
16. Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. Pharmacokinetics of indomethacin in the neonate. Relation of plasma indomethacin levels to response of the ductus arteriosus. *N Engl J Med* 1981;305:67-72.
17. Petersen S, Christensen NG, Jensen KM, Ryssing E. Serum indomethacin concentrations after intravenous administration to preterm infants with patent ductus arteriosus. *Acta Paediatr Scand* 1981;70:729-33.
18. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. *J Pediatr* 2007;150:216-9.
19. 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;93:647-51.
20. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr* 2007;150:229-34.
21. Keller RL, Clyman RI. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. *Pediatrics* 2003;112:583-7.
22. Sangem M, Asthana S, Amin S. Multiple courses of indomethacin and neonatal outcomes in premature infants. *Pediatr Cardiol* 2008;29:878-84.
23. Amin SB, Handley C, Carter-Pokras O. Indomethacin use for the management of patent ductus arteriosus in preterms: a web-based survey of practice attitudes among neonatal fellowship program directors in the United States. *Pediatr Cardiol* 2007;28:193-200.