Indomethacin Prophylaxis for Patent Ductus Arteriosus (PDA) in Infants with a Birth Weight of Less Than 1250 Grams

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Abstract

Background : Very low birth weight (VLBW, less than 1500 g) and extremely low birth weight infants (ELBW, less than 1000 g) are the premature infants that are most likely to develop symptomatic PDA. Intravenous indomethacin has proven effective in prevention of PDA in many prospective trials. This strategy will be a useful adjunctive therapy for premature infants in Thailand.

Objective : To answer the following questions:

1. Will multiple doses of intravenous indomethacin, given to VLBW infants within the first day of life, effectively prevent the occurrence of symptomatic PDA? Are there any side effects or complications?
2. Will this strategy be more beneficial in ELBW?

Methods and subjects : The study included thirty VLBW infants born at Ramathibodi Hospital, with birth weights ranging from 630 to 1230 g. They were randomized into 2 groups of 15 infants each. One group received 3 doses of intravenous indomethacin at the dosage of 0.2 mg/kg initially and then 0.1 mg/kg every 12 hours for 2 more doses; the second group received a placebo. The study was performed by a double blind control.

Results : Sixteen infants developed symptomatic PDA, 4 in the indomethacin group and 12 in the placebo group. The decrease in incidence of PDA is statistically significant. But when the data was analyzed separately for the VLBW and ELBW groups. The effects were only significantly different in ELBW but not yet significant in the VLBW group. There was a statistically significant difference in the incidence of severe intraventricular hemorrhage (IVH) (grade 3 or higher) in the ELBW infants.

Conclusion : Intravenous indomethacin therapy given to VLBW infants with a birth weight of less than 1250 g decreased incidence of symptomatic PDA with no significant permanent side effects. The effect was markedly noticable in ELBW infants. Incidence of severe IVH was also markedly decreased in the ELBW infants who received indomethacin.

Key word : PDA, Indomethacin Prophylaxis, Premature Infant

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Patent ductus arteriosus (PDA) is one of the most common complications that affects premature newborn infants. PDA increases morbidity and prolongs hospital stay, therefore, increasing the cost of caring for VLBW infants[1]. The lack of skilled personnel to surgically treat PDA also complicates the situation and creates more difficulty in caring for premature infants in many hospitals in Thailand. Indomethacin is the only pharmacologic agent which is effective in closure of PDA in premature infants[1-4]. Many studies prove that intravenous indomethacin given to premature infants in the first day of life can decrease incidence of symptomatic PDA[5-9]. Those studies however, reported no decrease in incidence of bronchopulmonary dysplasia (BPD) or markedly decrease in hospital stay. Those studies were done in countries where surgical ligation of PDA is available. This investigation is therefore performed to investigate the efficacy of intravenous indomethacin in the prevention of symptomatic PDA and other possible benefits including BPD, IVH etc. in premature infants with a birth weight of less than 1250 g who have the highest risk of symptomatic PDA.

POPULATION AND STUDY PROTOCOLS

The study was performed in a prospective, randomized double blind placebo controlled trial in premature infants born at Ramathibodi Hospital during April 1, 1994 to May 31, 1995 who had birth weights of less than 1250 g.

The inclusion criteria included:

(1) randomization of the patients in the first 24 hours of life,

(2) platelet count > 60,000/μl,

(3) plasma creatinine < 2 mg/dl and BUN < 30 mg/dl,

(4) no bleeding diathesis and

(5) urine output during 8 hours prior to the randomization > 0.5 ml/kg/h.

The exclusion criteria included :

(1) major congenital anomalies and

(2) suspicion of developing necrotizing enterocolitis (NEC).

METHODS

All premature infants who fitted the criteria were examined for gestational age by Ballard score. Blood tests were done for complete blood count, platelet count, BUN and creatinine. The infants then were randomized to placebo or indomethacin groups by using previously prepared sealed envelopes. The randomization was done separately for infants with birth weight of less than 1000 g and between 1000-1250 g in order to ensure equal patients being randomized into both groups in each birth weight group. The infants either received intravenous indomethacin, 0.2 mg/kg initially then 0.1 mg/kg every 12 hours twice, or saline placebo which appeared identical. All the caretakers, attending neonatologists, and nurses were all unaware of the treatment that the baby had received.

PDA was diagnosed according to clinical criteria including active precordium, bounding pulses, continuous or systolic ejection murmur at left upper parasternal border, hepatosplenomegaly and radiologic diagnosis of cardiomegaly. All suspected infants had a 2D echocardiogram to confirm the diagnosis of PDA by pediatric cardiologists.

Three doses of intravenous indomethacin 0.2 mg/kg/dose were given every 8 hours to all infants with PDA, if there were no contraindications.

PDA was diagnosed as successfully closed by indomethacin if the previous heart murmur, bounding pulse or active precordium disappeared or closure was confirmed by 2D echocardiogram.

The following data were collected from all infants enrolled: hospital number, sex, gestational age, birth weight, Apgar score, numbers of days on mechanical ventilation, hospital stays, discharge weight.

PDA data included incidence, age at diagnosis, rate of PDA closure by therapeutic indomethacin or surgery, failure and reopening rate, daily fluid intake and output.

Complications included respiratory distress syndrome (RDS), apnea of prematurity, hyperbilirubinemia, IVH, retinopathy of prematurity (ROP), BPD, NEC, renal failure, sepsis and death.

Statistics

Student's *t* test was used for comparison of continuous variables. Chi- square and Fisher's exact tests were used for proportional variables.

RESULTS

There were 32 premature infants born in Ramathibodi Hospital during the study period who fitted the inclusion criteria. Two infants were ex-

cluded because they died before being randomized. The remaining 30 infants received all 3 doses of the studied medications.

Twelve infants with birth weights of less than 1000 g were randomized into 2 groups of 6 each. The remaining 18 infants with birth weights between 1000-1250 g were also randomized into 2 groups of 9 each. There were no statistically significant differences between the treatment and placebo groups regarding sex, birth weight, gestational age, mode of delivery, Apgar score, platelet count, blood urea nitrogen and creatinine. There were significant differences in the number of infants receiving surfactant replacement (Exosurf®) in both groups (10 in indomethacin and 3 in placebo groups) (Table 1). There were 4/15 infants in indomethacin and 12/15 infants in the control group who developed symptomatic PDA. Intravenous indomethacin significantly reduced the incidence of PDA in the studied infants ($p < 0.05$).

The total amount of fluid intake and output in the first week of life in all infants was not significantly different but urine output of the indomethacin group on day 1 and 3 was significantly lower than the placebo group.

Indomethacin when given to the infants with birth weights of less than 1000 g within the first 24 hours of life significantly decreased the incidence of PDA (1/6 in indomethacin and 6/6 in placebo groups). However, in the infants with birth weights of 1000 to 1250 g, the incidence of PDA was not statistically or significantly different (3/9 in indomethacin and 6/9 in placebo groups).

When indomethacin was used for therapeutic purposes in infants with birth weights of less than 1000 g who developed PDA, PDA was successfully closed in 3 out of 6 infants in the placebo group but none in the indomethacin group. In larger infants, PDA closure was 4/6 in the placebo and 3/3 in indomethacin groups. Six infants had surgical ligation of PDA, 5 in the placebo group and 1 in the indomethacin group (Table 2, 3).

Incidence of severe IVH (grade 3 or higher) was statistically significantly less in the indomethacin group (1/6) compared to the placebo group (5/6) in infants with birth weights of less than 1000 g. Otherwise all other parameters were not significantly different.

Table 1. Clinical characteristics of population.

	Placebo (n = 15)	Indomethacin (n = 15)	Significance
Gestational age (wk)	28.9 ± 1.8	29.1 ± 1.6	NS
Birth weight (g)	983 ± 183.4	981.7 ± 184.3	NS
Sex (M:F)	7 : 8	3 : 12	NS
Mode of delivery (Normal/Cesarian section)	12 : 3	11 : 4	NS
Appropriate for GA : Small for GA	10 : 5	5 : 10	NS
Apgar score at 5 min	9.4 ± 1.4	8.8 ± 2.1	NS
Exosurf administration (yes : no)	3 : 12	10 : 5	$p < 0.05$
Laboratory findings:			
Hematocrit (%)	44.50 ± 7.87	45.35 ± 5.94	NS
Platelet count (per μl)	261,420 ± 143	235,466 ± 83	NS
Pretreatment serum creatinine (mg/dl)	0.84 ± 0.26	1.02 ± 0.33	NS

Table 2. Clinical course of population.

	Birthweight < 1000 g		Birthweight 1000-1250 g	
	No PDA	PDA	No PDA	PDA
Placebo	0	6	3	6
Indomethacin	5	1	6	3
P value	< 0.05	< 0.05	NS	NS

Table 3. Complication in study population.

	Placebo n = 15 (%)	Indomethacin n = 15 (%)	Significance
RDS	3 (20)	4 (27)	NS
Hyperbilirubinemia	8 (54)	6 (40)	NS
Apnea of prematurity	11 (74)	8 (53)	NS
ROP	4 (27)	3 (20)	NS
Pneumonia	3 (20)	4 (27)	NS
BPD	7 (47)	5 (33)	NS
Sepsis	5 (33)	1 (6)	NS
IVH	7 (47)	5 (33)	NS
Acute renal failure	3 (20)	2 (13)	NS
Transient tachypnea of the newborn	0 (0)	1 (6)	NS
Hypoglycemia	2 (13)	0 (0)	NS
CPIP	0 (0)	1 (6)	NS
Anemia	2 (13)	2 (13)	NS
Hypocalcemia	1 (6)	0 (0)	NS
NEC	1 (6)	0 (0)	NS
Death	1 (6)	0 (0)	NS

* CPIP = chronic pulmonary insufficiency of prematurity

DISCUSSION

Our study has shown that prophylactic use of intravenous indomethacin is effective in preventing symptomatic PDA in VLBW infants with birth weights of less than 1250 g and markedly so in the ELBW infants. The study also showed that severe IVH in the ELBW infants also decreased which was also found in many other studies[5-10] and the Cochrane collaboration review. Ment et al [9] however had found no significant difference in the incidence of IVH in their prospective trials. We decided to use three doses of indomethacin to investigate any benefits or complications related to multiple doses of indomethacin prophylaxis without increased cost.

There were no serious complications except for a decrease in urine output on day 1 and day 3 but there was no permanent damage to the kidneys. Another difference was that the indomethacin group had more subjects that received Exosurf than the placebo group. The effects of surfactant replacement in premature newborn infants were a rapid improvement of pulmonary function, decreased pulmonary vascular resistance and decreased pulmonary blood pressure. These effects increase the chance of left to right shunt *via* PDA. In surfactant replacement trials, the incidence of PDA was significantly higher in the treatment group compared to the placebo group. The indomethacin group in our study should have had a higher incidence of PDA. Therefore, the effect of indomethacin prophylaxis was more dramatic.

At our institution, surgical ligation of PDA in premature infants is readily available which is an exception for Thailand. The effect of low incidence of PDA in our institution may not contribute to the decreased incidence of chronic lung disease, length of hospital stay and mortality. However, in most of the other hospitals in Thailand where surgical ligation of PDA in premature infants is virtually impossible, the decrease in incidence of PDA may be helpful in caring for preterm infants.

Intravenous indomethacin is not available now in Thailand due to cessation of production from the European manufacturer. The only distributor now is in the United States and the cost is expensive. The ideal situation for Thailand would be a reliable source of oral indomethacin. We are now in the process of producing a good solvent of indomethacin that is stable, safe and delivers a reliable amount of the drug. When we do have the oral form, multicenter trials using oral indomethacin prophylaxis should be done.

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การป้องกันการเกิด symptomatic PDA ด้วยยาอินโดเมธาซินในทารกเกิดก่อนกำหนดที่มีน้ำหนักแรกเกิดน้อยมาก

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ข้อมูลเบื้องต้น : ทารกแรกเกิดน้ำหนักตัวน้อย (VLBW, น้อยกว่า 1,500 กรัม) และน้อยมาก (ELBW, น้อยกว่า 1,000 กรัม) เป็นทารกแรกเกิดกลุ่มที่มีความเสี่ยงสูงในการที่จะมีปัญหาของ PDA ที่มีอาการทางคลินิก การใช้ยาอินโดเมธาซินในการป้องกัน PDA ที่มีอาการทางคลินิกเป็นที่นิยมใช้กันแพร่หลาย แต่การศึกษาในทารกแรกเกิดในประเทศไทยยังไม่มีการศึกษาประสิทธิภาพของยานี้ในทารกแรกเกิดน้ำหนักตัวน้อยกว่า 1250 กรัม

จุดประสงค์ :

1. การใช้ยาอินโดเมธาซินชนิดฉีด 3 ครั้งในทารกแรกเกิด VLBW ภายใน 24 ชั่วโมงแรกของชีวิต จะช่วยลดความเสี่ยงของการเกิด PDA ที่มีอาการทางคลินิกได้หรือไม่ มีผลข้างเคียงหรือไม่
2. การป้องกันดังกล่าวมีผลดีมากขึ้นในกลุ่มทารกแรกเกิด ELBW หรือไม่

วิธีการศึกษา : ทารกแรกเกิดน้ำหนักตัวน้อยและน้อยมาก 30 ราย ที่เกิดในโรงพยาบาลรามาธิบดี ที่มีน้ำหนักตัวแรกเกิด 630–1230 กรัม ถูกแบ่งเป็น 2 กลุ่ม กลุ่มละ 15 ราย โดยกลุ่มแรกจะได้ยาอินโดเมธาซินชนิดฉีด 0.2 มก./กก. ภายใน 24 ชั่วโมงแรกของชีวิต ตามด้วย 0.1 มก./กก. อีก 2 ครั้ง ห่างกัน 12 ชั่วโมง อีกกลุ่มหนึ่งจะได้รับยาหลอก

ผลการศึกษา : ทารกแรกเกิดกลุ่มศึกษามี PDA เปิด 16 ราย ในกลุ่มอินโดเมธาซินพบ 4 ราย และในกลุ่มยาหลอกพบ 12 ราย ซึ่งการลดลงของอุบัติการของ PDA มีนัยสำคัญทางสถิติ แต่เมื่อดูข้อมูลแยกเป็นกลุ่ม VLBW และ ELBW กลุ่ม ELBW นั้น อุบัติการของ PDA ลดลงอย่างมีนัยสำคัญ ส่วนในกลุ่ม VLBW อุบัติการลดลงแต่ไม่มีนัยสำคัญ อัตราการเกิดภาวะ intraventricular hemorrhage (IVH) เกรด 3 ลดลงอย่างมีนัยสำคัญในกลุ่ม ELBW

สรุปผลการศึกษา : การใช้ยาอินโดเมธาซินชนิดฉีดในทารก VLBW และ ELBW ในวันแรกของชีวิต สามารถลดอุบัติการการเกิด PDA ได้ โดยมีผลข้างเคียงน้อย และไม่มีผลข้างเคียงถาวร อุบัติการของ IVH ชนิดรุนแรงในกลุ่ม ELBW ลดลง อย่างมีนัยสำคัญ

คำสำคัญ : PDA, ทารกแรกเกิดก่อนกำหนด, ยาอินโดเมธาซิน

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