Prophylaxis of Symptomatic Patent Ductus Arteriosus with Oral Ibuprofen in Very Low Birth Weight Infants

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Background: *Patent ductus arteriosus (PDA) is a common cause of mortality and morbidity among very low birth weight infants. Oral ibuprofen suspension has been shown to have the same efficacy and safety as intravenous indomethacin in the prevention and treatment of symptomatic PDA. With lower dosage, the prevalence of side effects may decrease without changes in efficacy.*
Objective: *To evaluate the efficacy and side effects of low dose ibuprofen suspension for prevention of symptomatic PDA in very low birth weight infants.*
Patients and Method: *A prospective, double blind, randomized controlled trial was conducted on premature neonates with gestational ages between 28-32 weeks, birth weight 1500 grams or less, at the Neonatal Unit, Queen Sirikit National Institute of Child Health (QSNICH) during October 2005 to October 2006. Only infants who had PDA on echocardiogram were included in the study. Three doses of ibuprofen suspension or placebo were randomly given at the dosage of 10, 5, 5 mg/kg every 24 hours. Daily physical examination, serial laboratory evaluation and echocardiogram were used to evaluate symptomatic PDA, complications and side effects.*
Results: *Sixty-two infants were recruited in the study and randomly assigned into the study and control group. The gestational age and birthweight of the 2 groups were similar. The prevalence of symptomatic PDA was less in the ibuprofen group than in placebo group (9.86% vs. 35.48%; p = 0.015). There were no differences in the prevalence of complications and adverse effects between the two groups.*
Conclusion: *Prophylactic oral ibuprofen suspension at lower dosage results in less symptomatic PDA without significant side-effects.*

Keywords: *Oral ibuprofen, Patent ductus arteriosus, Very low birth weight infants*

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Patent ductus arteriosus (PDA) is a common problem in very low birth weight infants resulting in increased mortality and morbidity[1-7] . Ibuprofen has the same efficacy in the closure of PDA as indomethacin with less renal, gastrointestinal and cerebral adverse affects. Patients treated with ibuprofen needed less surgical ligation than patients treated with indomethacin[8-13]. In the previous study carried out at QSNICH, three doses of oral ibuprofen (10 mg/kg/dose) given at the interval of 24 hours reduced the prevalence of symptomatic PDA by 95.45% without significant side effects[14]. Heyman conducted a study with the use of lower dosage of oral ibuprofen (10, 5, 5 mg/kg/dose) for the prevention of symptomatic PDA and the prevalence of ductal closure at 72 hours of life was 95.5%. With lower dosage, the prevalence of some side effects such as gastrointestinal bleeding may decrease without changes in efficacy.

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Objectives

1. To evaluate the efficacy of ibuprofen in the prevention of symptomatic PDA during the first week of life in very low birth weight infants.

2. To evaluate the safety of ibuprofen suspension.

Material and Method

Very low birth weight premature neonates with PDA, birth weight of 1500 grams or less, admitted at the Neonatal Unit, Queen Sirikit National Institute of Child Health between October 2005 to October 2006 were recruited in the study.

Patients with the following criteria were excluded from the study:

1. Congenital heart disease (other than PDA)
2. Symptomatic PDA
3. Maternal prenatal infection
4. Maternal drug abuse
5. Maternal non-steroidal anti-inflammatory drug use
6. Hydrops fetalis
7. Unstable clinical conditions
8. Other major congenital anomalies
9. Persistent pulmonary hypertension
10. Serum creatinine $\geq$ 1.5 mg/dL and or BUN $\geq$ 30 mg/dL
11. Platelet count $\leq$ 75,000 cells/mm^3
12. Abnormal coagulogram

An informed consent was obtained from the parents before recruitment. Patients were evaluated for PDA by color Doppler echocardiogram (GE Ving Med Color Display Monitor, System 5, Transducer FPA 7.5 MHZ; GE Ultrasound) performed by the single pediatric cardiologist who was blind to the treatment being given. Patients whose ductus arteriosus was completely closed were excluded. Patients were then randomly assigned into the study and control group by block randomization. Sample size was calculated with confidence interval 0.05, power 0.8, and 10% estimated drop out rate according to the previous study[16].

The patients in the study group were given 3 doses of oral ibuprofen suspension (Junifen®, Boots Company, Thailand) Reg.No.1A 163/45 , Lot.No.716 B, Mfg. Date: Feb 2005, Exp. Date: Feb 2008 at a dosage of 10 mg/kg for first dose within 24 hours of life and 5 mg/kg for the second and third doses after 24 and 48 hours. The drug was given via the orogastric tube, followed by 0.5 ml of distilled water. Patients with any significant adverse drug reactions which required treatment were excluded from the study.

The patients in the control group were given 3 doses of orange starch suspension as placebo. Placebo was administered with the same method and time schedule as oral ibuprofen suspension in the study group. The external appearance of placebo was like ibuprofen suspension and could not be differentiated by naked eyes.

The medical personnel who took care of the patients were blind to the group assignment. All medical and nursing care was performed without any interference from the study team.

Clinical evaluation was performed daily by the study team until 28th day of life. Complete blood count, BUN, creatinine, electrolyte and coagulogram were evaluated 24 hours after the fully course of drug administration. An echocardiogram was performed before each dose of ibuprofen administration and on the 7th, 14th and 28th day of life.

Symptomatic PDA was defined as echocardiographic and clinical evidence of hemodynamically significant PDA.

Echocardiographic evidence of hemodynamically significant PDA is defined as any of the following[15]:

1. Diastolic turbulence flow in pulmonary artery (left to right or bidirectional shunt)
2. Left atrium/aortic root diameter ratio > 1.4
3. Ductal size > 1.5 mm

Clinical evidence of hemodynamically significant PDA is defined as any of the followings[15]:

1. Bounding pulses
2. Pulse pressure > 35 mmHg
3. Hyperactive precordium
4. Tachycardia (heart rate > 170 beats/minute)
5. Hepatomegaly
6. Cardiothoracic ratio > 0.6 from chest X-ray
7. Increased pulmonary vasculature in chest X-ray

If during the course of the study, symptomatic PDA did occur, standard treatment with intravenous indomethacin was given. Surgical ligation was performed in cases of medication failure.

Statistic analysis

1. Continuous data (such as weight, gestational age, various treatment modalities, IVH, and age at start of treatment) were presented as mean $\pm$ standard deviation. The mean differences were tested with independent t-test.

2. Categorial variables (such as sex, antenatal steroid therapy, number of PDA cases) were analyzed

with the percentage in each variable and the mean difference in each variable compared by Chi-square or Fisher's Exact test. Changes in serum creatinine concentrations were compared using t-test.

3. Number needed to treat was calculated.

Results

There were 100 patients admitted during the study period. Only 62 cases were recruited in the study. Thirty-eight cases were excluded due to closed ductus arteriosus (5 cases), symptomatic PDA at the first evaluation (2 cases), congenital heart disease other than PDA (4 cases), maternal prenatal infection (12 cases), abnormal serum BUN/creatinine/coagulogram/platelet count (9 cases), chromosome abnormality (1 cases), anomaly of the central nervous system (1 cases), hydrops fetalis (1 cases) and no informed consent (3 cases). The enrolled 62 cases were randomly assigned to the study and control group. The demographic data, clinical characteristics (Table 1), daily fluid intake and urine output in the first 7 days of life (Table 2) were not statistically different between the groups.

The mean size of PDA in the study and control groups on the first echocardiogram was 1.72 ± 0.75 and 1.83 ± 0.50 mm, respectively. They were not statistically different (p = 0.519).

The prevalence of symptomatic PDA in the study group was lower than the control group. (3/31 =

Table 1. Demographic data of the neonates

Characteristics	Ibuprofen (n = 31)	Placebo (n = 31)	p-value
Gestational age in weeks			
(mean ± SD)	29.32 ± 1.94	29.29 ± 2.16	0.951
(range)	26-32	26-32	
Birth weight; grams			
(mean ± SD)	1156.90 ± 263.6	1162.90 ± 261.0	0.929
(range)	765-1500	690-1500	
Sex (Male : Female)	14:17 (1:1.2)	17:14 (1.2:1)	0.612
Apgar score at 1 min (mean ± SD)	6.19 ± 2.30	6.23 ± 2.56	0.959
at 5 min (mean ± SD)	8.16 ± 1.29	8.03 ± 2.03	0.766
Mode of delivery			
vagina (n)	15	12	0.609
cesarean section(n)	13	18	0.310
breech (n)	3	1	0.612
Age of drug administration; hours (mean ± SD)	18.14 ± 6.03	20.09 ± 5.67	0.194
Surfactant therapy (n; %)	9 (29.03)	8 (25.80)	0.780
Antenatal steroid (n; %)	21 (67.74)	19 (61.29)	0.603
Ventilator assistant (n; %)	29 (93.55)	27 (87.10)	0.399

Table 2. Daily fluid intake and urine output in the first week (mean ± SD)

Day	Fluid intake (cc/kg/day)			Urine output (cc/kg/day)		
	Ibuprofen (n = 31)	Placebo (n = 31)	p-value	Ibuprofen (n = 31)	Placebo (n = 31)	p-value
1	77.33 ± 11.02	72.88 ± 12.06	0.135	2.34 ± 0.75	2.186 ± 0.98	0.503
2	86.47 ± 12.12	84.04 ± 11.86	0.428	3.06 ± 1.18	3.24 ± 1.36	0.584
3	96.35 ± 23.20	95.59 ± 18.19	0.886	2.84 ± 0.91	2.76 ± 1.01	0.747
4	116.76 ± 18.11	110.32 ± 20.20	0.191	2.81 ± 0.97	2.64 ± 0.78	0.444
5	129.65 ± 17.82	130.26 ± 22.82	0.909	2.74 ± 0.99	2.73 ± 1.17	0.956
6	139.49 ± 17.92	145.19 ± 22.36	0.275	2.97 ± 1.01	3.01 ± 1.28	0.870
7	147.02 ± 18.33	147.25 ± 20.93	0.964	2.96 ± 1.18	3.10 ± 1.18	0.647

9.68% vs. 11/31 = 35.48 %; p = 0.015). Oral ibuprofen administration reduced the prevalence of symptomatic PDA by 90.32%.

Of the 3 cases with symptomatic PDA in the study group, 2 were successfully treated with indomethacin and there was 1 case who needed surgical PDA ligation after failure with indomethacin treatment. In the control group, 11 cases with symptomatic PDA underwent indomethacin treatment. Ten out of 11 had ductal closure after single course of indomethacin while the last case had ductal closure after 4 courses of indomethacin because of parental refusal for surgical ligation.

The rate of ductal closure of the study and control group was not different. (p = 0.054) on the 3rd day of life after complete course of ibuprofen/ placebo administration (Table 3).

However, when comparing the groups with birth-weight 1200 gm or less, the rate of ductal closure was higher in the ibuprofen group than in the placebo

Table 3. Primary outcomes: efficacy of ibuprofen

Patent ductus arteriosus	Ibuprofen (n = 31)	Placebo (n = 31)	p-value
PDA size (mm, mean ± SD)	1.72 ± 0.75	1.83 ± 0.50	0.519
Closed on day 3; n/N (%)	25/31 (80.65)	18/31 (58.07)	0.054
≤ 1200 g; n/n (%)	14/17 (82.35)	6/17 (35.29)	0.005*
1201 -1500 g; n/n (%)	11/14 (78.57)	12/14 (85.71)	0.5
Symptomatic PDA	3/31 (9.68)	11/31 (35.48)	0.015*

Table 4. Comparision of secondary outcomes of ibuprofen and placebo groups

Outcomes	Ibuprofen (n = 31)	Placebo (n = 31)	p-value
Respiratory system			
PPHN; n/N (%)	0/31 (0)	0/31 (0)	1.000
BPD;* n/N (%)	8/30 (26.67)	13/28 (46.43)	0.124
Ventilator day; (mean ± SD)	12.78 ± 18.53	14.42 ± 17.66	0.725
Days of oxygen therapy; (mean ± SD)	8.55 ± 13.11	12.62 ± 15.92	0.293
Renal function			
Serum BUN (mean ± SD) mg/dL			
Day 0	13.08 ± 5.40	13.12 ± 5.97	0.980
Day 3	19.74 ± 11.05	23.22 ± 15.35	0.309
Serum Cr (mean ± SD) mg/dL			
Day 0	0.77 ± 0.15	0.78 ± 0.19	0.860
Day 3	0.85 ± 0.22	0.81 ± 0.21	0.403
Gastrointestinal system			
Days of start feeding; (mean ± SD)	5.48 ± 2.76	6.54 ± 5.00	0.054
Days of full feeding; (mean ± SD)	25.23 ± 15.11	23.21 ± 13.69	0.596
Local GI bleeding; n/N (%)	13/31 (41.94)	6/31 (19.35)	0.054
NEC ≥ stage II; n/N (%)	0/31 (0)	1/31 (3.23)	0.325
Intraventricular hemorrhage; n/N (%)			
Total IVH	10/30 (33.33)	10/28 (35.71)	0.852
grade 1	4/30 (13.33)	8/28 (28.57)	0.201
grade 2-3	6/30(20)	2/28 (7.14)	0.260
Retinopathy of prematurity; n/N (%)			
Total ROP	4/30 (13.33)	6/28 (21.43)	0.424
stage 1	3/30 (10)	3/28 (10.71)	1.000
stage 2	1/30 (3.33)	3/28 (10.71)	0.344
Length of hospital stay; days (mean ± SD)	57.37 ± 27.24	54.07 ± 31.07	0.663
Death; n/N (%)	2/31 (6.45)	3/31 (9.68)	0.647

Table 5. Coagulogram and platelet count before and after prophylactic treatment

Laboratory (mean ± SD)	Day 0			Day 3		
	Ibuprofen (n = 31)	Placebo (n = 31)	p-value	Ibuprofen (n = 31)	Placebo (n = 31)	p-value
PT (sec)	17.30 ±1.97	17.02 ± 1.76	0.552	16.52 ± 2.63	15.79 ± 1.97	0.240
INR	1.53 ± 0.18	1.49 ± 0.194	0.458	1.43 ± 0.26	1.39 ± 0.19	0.466
PTT (sec)	47.42 ± 9.26	7.27 ± 8.78	0.945	48.07 ± 16.44	42.78 ± 8.92	0.132
TT (sec)	6.85 ± 2.59	7.49 ± 2.16	0.362	8.66 ± 10.21	7.00 ± 1.87	0.402
Platelet/mm^3	215,616 ± 59,626	217,945 ± 57,588	0.876	81,203 ± 86,337	69,451 ± 71,372	0.561

group (p = 0.005).

Two cases (one in each group) had re-opening of PDA after 7 days of life which was not statistically significant different (p = 0.817).

Five cases died during the study period, 2 in the study group and 3 in the control group. The causes of death were Klebsiella septicemia in 3 cases, clinical sepsis in 1 case and bronchopulmonary dysplasia (BPD) in 1 case.

There were no statistical differences in days of mechanical ventilation, hours of oxygen therapy, bronchopulmonary dysplasia (BPD), feeding problems, necrotizing enterocolitis (NEC), gastrointestinal bleeding, bleeding disorder, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), length of hospital stay and mortality rate between the groups. (Table 4, 5).

Discussion

The most effective dosage of oral ibuprofen suspension for the prevention and treatment of symptomatic PDA in low birth-weight infants is still unknown. Conventional dosage of 10 mg/kg/dose at 24 hour-interval has been proposed by expert opinions from the dosage used in older children for antipyretics and anti-inflammatory effects. The pharmacokinetics and pharmacodynamic data of oral ibuprofen in low birth-weight infants are limited. Sharma[16] studied the pharmacokinetics of ibuprofen in premature infants and found that there was a large interindividual variability with peak plasma concentrations (Cmax; 137.9 ± 14.0 ng/ml), elimination half-life (t1/2 el; 21.4 ± 1.7 h) and area under the plasma concentrations time curve (AUC0-infinity;4172 ± 303 ng.h/ml). Variables like birth weight, and sex did not have any significant effect on ibuprofen pharmacokinetics. However, the plasma half life of ibuprofen was significantly ($p < 0.01$) larger in older infants (gestational age > 30 wk) in comparison to younger ones (gestational age ≤ 30 wk)[16]. Previous study of the ibuprofen pharmacokinetics at QSNICH revealed nearly the same Cmax (31.73 mcg/ml) but longer t_{max} (45 min) and $t_{1/2}$ (28.42 hrs)[14]. The study suggested that lower dosage may be as effectively as the conventional dosage in the closure of PDA in low birth-weight infants.

Oral ibuprofen at the dosage of 10 mg/kg first dose followed by 5 mg/kg as the second and third doses has first been shown by Heyman[17] to close the ductus arteriosus by 95.50% and have absolutely prevented symptomatic PDA. The result of the present study is comparative with Heyman's study of 80.65% ductal closure rate at 72 hours of life and 90.32% efficacy of prevention of symptomatic PDA. The number needed to treat was 4.3. Ductal closure rate was higher in patients with birth-weight under 1000 grams in whom the number needed to treat was 2.2.

Aly compared oral ibuprofen (at the dosage of 10, 5, 5 mg/kg/dose every 24 hours) with intravenous indomethacin in the treatment of symptomatic PDA of prematurity and found that there is no significant difference (83% in oral ibuprofen and 78% in indomethacin; p = 0.75)[18]. Cherif studied the efficacy of oral ibuprofen and found that 95% had ductal closure with good toleration[19].

In the present study, there were no differences in mortality and morbidity between the groups. A lot of confounders affecting mortality and morbidity of premature infants are well known. Although the number of symptomatic PDA decreased significantly, the number needed to treat for decreasing mortality and morbidity may be much more than the total number in this study. The result of this study goes along with previous studies which revealed less side effects of oral ibuprofen[13,14,17-19].

Conclusion

Prophylactic oral ibuprofen suspension at lower dosage was effective in the prophylaxis of

symptomatic PDA without significant adverse affects in very low birth-weight premature infants.

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การป้องกันการเกิด อาการของ patent ductus arteriosus ด้วยการให้รับประทานยา ibuprofen ในทารกที่มีน้ำหนักตัวน้อยมาก

วราภรณ์ แสงทวีสิน, ชัยสิทธิ์ แสงทวีสิน, วัชรี เลิศสุทธิวงศ์, วิบูลย์ กาญจนพัฒนกุล, มิรา โครานา, จินตกานต์ เกษมศรี ณ อยุธยา

ภูมิหลัง: *Patent ductus arteriosus เป็นสาเหตุหนึ่งของการเกิดความพิการและการตายในทารกคลอดก่อนกำหนดที่มีน้ำหนักน้อยกว่า 1,500 กรัม ยาไอบูโพรเฟนชนิดรับประทานสามารถใช้ในการป้องกัน และรักษา symptomatic PDA เช่นเดียวกับยา Indomethacin การให้ขนาดยาน้อยช่วยลดอาการผลข้างเคียงโดยยังคงประสิทธิภาพเหมือนเดิม*

วัตถุประสงค์:

1. เพื่อศึกษาประสิทธิภาพของการใช้ยาน้ำแขวนตะกอนไอบูโพรเฟนเพื่อป้องกัน symptomatic PDA ในทารกน้ำหนัก $\leq$ 1,500 กรัม

2. เพื่อศึกษาอาการไม่พึงประสงค์ของยาน้ำแขวนตะกอนไอบูโพรเฟน

ผู้ป่วยและวิธีการ: *Prospective, double blind, randomized, controlled trial ทารกก่อนกำหนดที่มีอายุครรภ์ 28-32 สัปดาห์ น้ำหนักแรกเกิด $\leq$ 1,500 กรัม ที่ มี PDA โดยการตรวจ echocardiogram ที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินีในระหว่าง ตุลาคม พ.ศ. 2548 ะ ตุลาคม พ.ศ. 2549 ทารกในกลุ่มศึกษาจะได้รับยาจริง กลุ่มควบคุมจะได้รับยา หลอก 3 ครั้ง ด้วยขนาด 10, 5, 5 มิลลิกรัม/กิโลกรัม ห่างกันทุก 24 ชั่วโมง การประเมินอาการทางคลินิกของทารกจนถึงอายุ 28 วัน*

ผลการศึกษา: *ทารกในกลุ่มศึกษาและกลุ่มควบคุม กลุ่มละ 31 ราย ไม่มีความแตกต่างในด้านข้อมูลระบาดวิทยา อุบัติการณ์ของ symptomatic PDA ในกลุ่มศึกษาน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (9.86 % vs 35.48 %, p = 0.015) อาการไม่พึงประสงค์ในทารกสองกลุ่มไม่แตกต่างกัน*

สรุป: *การให้ยากินไอบูโพรเฟนสามารถลดอุบัติการณ์ของ symptomatic PDA โดยไม่เกิดภาวะแทรกซ้อนที่สำคัญ*