Oral Ibuprofen and Indomethacin for Treatment of Patent Ductus Arteriosus in Premature Infants : A Randomized Trial at Ramathibodi Hospital

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Abstract

Background : Ibuprofen given intravenously to premature newborn infants is a proven treatment for patent ductus arteriosus (PDA). The efficacy of ibuprofen is comparable to indomethacin in many clinical trials with fewer renal side effects. However, the intravenous form of ibuprofen is not available in Thailand, whereas, the oral suspension form is widely used for antipyretic treatment in children. Therefore, the authors investigated the possibilities of using oral ibuprofen for the treatment of PDA in premature newborn infants.

Objective : To assess whether oral ibuprofen at 10 mg/kg/dose daily for 3 days was as effective as indomethacin to treat symptomatic PDA in premature infants and to compare the side effects of oral ibuprofen to indomethacin.

Subjects and Method : Eighteen premature infants with gestational ages less than 34 weeks born at Ramathibodi Hospital who developed symptomatic PDA were randomly assigned to receive three doses of either indomethacin (oral or intravenous administration 0.2 mg/kg/dose for three doses given at 12 hourly intervals or oral ibuprofen (10 mg/kg/dose for three doses given at 24 hourly intervals). The rates of ductal closure, infants' clinical courses, side effects and complications were recorded.

Results : Birth weight, gestational age, gender, age onset and number of infants who had respiratory distress syndrome were similar in both groups, PDA was closed in 7 of 9 infants given ibuprofen (78%) and in 8 of 9 infants given indomethacin (89%) ($p>0.05$). The mean plasma concentration of ibuprofen was 28.05 μg/ml at 1 hour after the third dose. Neonates in the ibuprofen group had more urine output. However, the increment of serum BUN and creatinine were not significantly different in both groups. There were no significant differences in duration of ventilator support as well

as number of patients with bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis and death in both groups.

Conclusion : Oral ibuprofen therapy is as effective as indomethacin for the treatment of PDA in premature infants and seems to have fewer renal side effects.

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

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Patent ductus arteriosus (PDA) in premature infants may lead to an increased risk of intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) (1-4). Indomethacin is the conventional medication for the treatment of PDA(5-8). However, its use is associated with many side effects especially impaired renal function. Intravenous ibuprofen, another prostaglandin synthesis inhibitor, at the dose of 10 mg/kg and then 5 mg/kg for 2 doses daily was used for the successful closure of PDA in premature infants (9-12). However, the intravenous form of ibuprofen is not available in Thailand, whereas, the oral form has been widely used for antipyretic treatment in children. In a previous study in our hospital (unpublished data), oral ibuprofen was used for prophylaxis of PDA and the serum drug levels were measured. At the dose of 10 mg/kg/day, the serum level of ibuprofen was approximately 20 per cent of what the baby would achieve with the intravenous form but oral ibuprofen was still successful in preventing PDA in those premature infants. Therefore, the authors chose the same dosing schedule of oral ibuprofen that had been used previously to compare oral ibuprofen and indomethacin with regard to the efficacy and side effects on renal function for the treatment of PDA in premature infants.

PATIENTS AND METHOD

The study was performed in a prospective, randomized controlled trial in premature infants born at Ramathibodi Hospital from April 1, 2000 to August 31, 2001 who developed symptomatic PDA during their hospital stay.

Criteria for diagnosis of symptomatic PDA(3,13)

1. Systolic murmur at left upper parasternal border.
2. Continuous murmur at left upper parasternal border.
3. Active precordium.
4. Bounding pulse, wide pulse pressure (pulse pressure >35 mmHg).
5. Tachycardia (heart rate >170/min).
6. Hepatomegaly.
7. Chest X-ray with cardiomegaly (CT ratio >0.6) or increased pulmonary vasculature.

Any infant with more than 3 of the above criteria was diagnosed with symptomatic PDA.

Exclusion criteria

1. Congenital anomalies or chromosomal abnormalities.
2. Congenital heart diseases or persistent pulmonary hypertension.
3. Moribund infant.
4. Congenital infection or intrauterine infection.
5. Mother had received NSAID during pregnancy.
6. The infant had contraindications for using an non-steroidal anti-inflammatory drug (NSAID)

which included intraventricular hemorrhage, clinical bleeding tendency (hematuria, bleeding in the gastric tube, stool occult blood positive), thrombocytopenia (platelet <60,000/μl) and oliguria (urine output <1 ml/kg/h).

Data collection

After the infant was diagnosed as having symptomatic PDA, informed consent was obtained from the infant's parents or legal guardians. The infant was randomized into either the indomethacin or ibuprofen group by randomly choosing a sealed envelop.

Indomethacin group

The infant received oral or intravenous indomethacin at 0.2 mg/kg every 12 hours for 3 doses.

Ibuprofen group

The infant received oral ibuprofen at 10 mg/kg daily for 3 consecutive days.

Clinical and laboratory findings were recorded as follows:

1. Demographic data including birth weight, sex, gestational age, Apgar score, maternal use of dexamethasone, age at diagnosis of PDA and receiving treatment and days on mechanical ventilation.

2. Vital signs and clinical symptoms of PDA were recorded before and after the medication for 7 days.

3. Fluid intake/output were recorded daily from the beginning of the medication until 3 days after discontinuation of the medication.

4. CBC and platelet counts before the start of the medication.

5. Serum BUN and creatinine before the first dose and after the third dose.

6. Serum ibuprofen level 1 hour after the third dose.

7. Related outcome variables: BPD, IVH, NEC, death.

PDA ligation was considered by the team of neonatologists if the infants in the ibuprofen group still had signs or symptoms of PDA after the third dose and also were not responding after the rescue course of standard indomethacin treatment.

Statistical analysis

Student *t*-test, ANOVA and Mann-Whitney U test were used for continuous data and Fisher's exact test for categorical data.

According to the sample size analysis, the authors chose α error = 0.05, β error = 0.2 (95% CI, power 80%) and expected significant difference at 30 per cent. The calculated sample size was 68 if it was presumed that the effectiveness of indomethacin treatment was 94 per cent (the authors' unpublished data).

RESULTS

During the period from June 1, 2000 to August 31, 2001, there were 174 premature newborn infants born at less than 34 weeks of gestational age but only 30 (17%) developed symptomatic PDA. There were 21 infants enrolled in the study but 3 were excluded (2 with VSD and 1 with pulmonic stenosis). Only 18 infants remained in the study, 9

Table 1. Demographic data of the studied population.

Characteristics	Ibuprofen group (n = 9)	Indomethacin group (n = 9)
Sex (F : M)	1 : 8	3 : 6
Birth weight (g)	1,446.7 ± 38.5	1,431.7 ± 530.5
Gestational age (weeks)	30.1 ± 2.7	30.4 ± 2.6
Age at onset of PDA (days)	3.0 ± 1.1	3.3 ± 2.3
Age at treatment for PDA (days)	3.0 ± 1.1	3.4 ± 2.2
Fluid intake (ml/kg/h)	72.3 ± 18.7	78.8 ± 34.9
Number of patients with		
Apgar score at 1 min < 3	2	1
Maternal dexamethasone of 1 dose	4	3
Maternal dexamethasone of 2 doses	3	1
Respiratory distress syndrome	8	6
Surfactant therapy	2	5

Table 2. Serum BUN and creatinine (Cr) (mean ± SD) of infants, before and after treatment.

Group (n)	Serum BUN (mg/dl)		Serum Cr (mg/dl)	
	Before	After	Before	After
Ibuprofen (9)	22.8 ± 10.8*	19.6 ± 9.3*	0.9 ± 0.4*	0.8 ± 0.3*
Indomethacin (9)	16.6 ± 9.0*	22.0 ± 11.1*	0.9 ± 0.3*	1.1 ± 0.3*

* $p > 0.05$ (before *vs* after, ibuprofen *vs* indomethacin)

Table 3. Fluid intake in both groups from day 1 to day 4.

Fluid intake (ml/kg/day)	Ibuprofen group (n = 9)	Indomethacin group (n = 9)
Before treatment	72.3 ± 18.7	78.8 ± 38.9
Day 1	80.4 ± 18.2	76.6 ± 26.8
Day 2	87.2 ± 18.5	93.7 ± 27.2
Day 3	103.0 ± 16.2	100.3 ± 23.6
Day 4	119.4 ± 25.30	126.1 ± 35.1

infants in each group. In the indomethacin group, 6 received the oral form and 3 the intravenous form.

Comparison between the efficacy of ibuprofen and indomethacin, revealed that 7 of 9 (78%) patients in the ibuprofen group and 8 of 9 (89%) patients in the indomethacin group had successful closure of PDA after treatment. There was no significant difference in the efficacy between these two treatments ($p>0.05$).

Comparison between the ibuprofen and indomethacin groups, revealed that the incidence of respiratory distress syndrome (RDS), surfactant treatment, fluid intake and other demographic data including birth weight, sex, age at diagnosis of PDA and age at the onset of treatment were not significantly different (Table 1).

Median serum ibuprofen levels were 25.62 and 17.03 μg/ml in the responders and non-responders, respectively. There were no significant differences in blood levels between the infants with and without response.

Infants in the ibuprofen group had decreased serum BUN and creatinine after the treatment course but those in the indomethacin group had mildly elevated serum BUN and creatinine. However, serum BUN and creatinine in both groups were not significantly different before and after the course of treatment (Table 2).

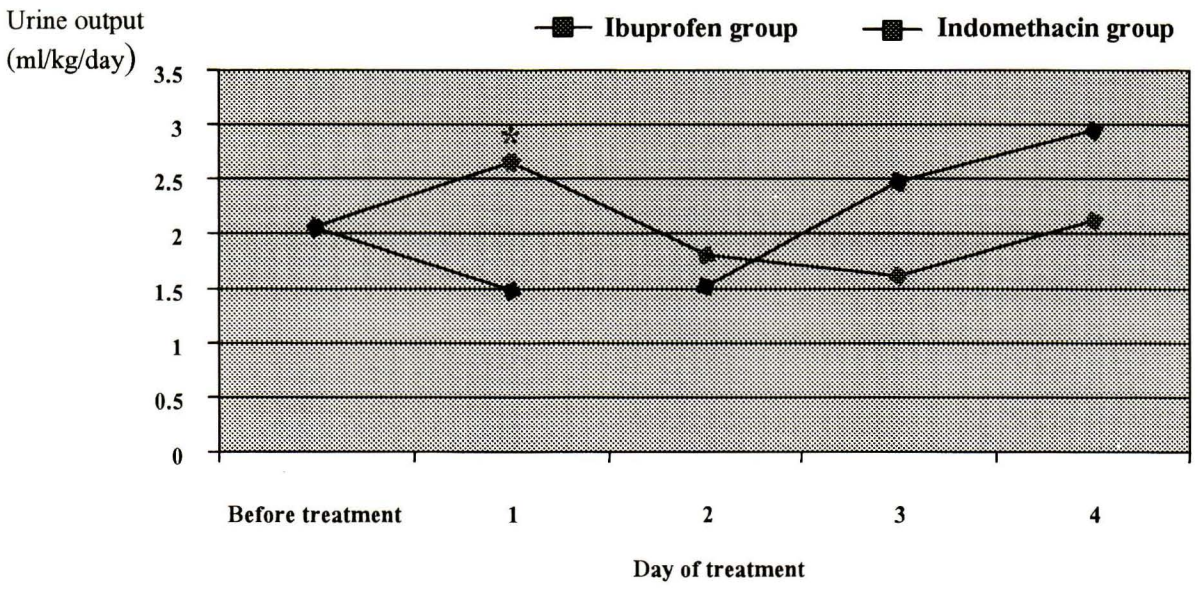
Infants in both groups received an equal amount of fluid from day 1 to 4 (Table 3) but the urine output of infants in the ibuprofen group was not reduced as much as that of the indomethacin group after the first day of treatment and was significantly different ($p=0.01$) but not on day 2, 3 or 4 (Fig. 1).

The means ± SD of days of mechanical ventilator support in the ibuprofen and indomethacin groups were similar at 36.1 ± 32.3 and 36.8 ± 22.1, respectively. Late clinical sequelae and morbidities of infants in both groups including BPD, IVH and NEC were not significantly different (Table 4).

DISCUSSION

The present study suggests that treatment with oral ibuprofen is as effective as indomethacin for symptomatic PDA in the premature newborn with comparable long- term outcomes but with fewer renal side effects. Unfortunately, during the period of the present investigation, the number of patients was unexpectedly small. The authors have continued to perform multicenter trials to pursue the answer to this question and the preliminary data remain encouraging.

The dosage used in the present study was based on a previous study in which the authors used oral ibuprofen at 10 mg/kg daily 3 doses for prophylaxis of PDA in premature very low birth weight infants and the mean serum level of ibuprofen in that group of infants was 21 μg/ml compared to 113 μg/ml in the intravenous ibuprofen group (10 mg initially and 5 mg/kg daily for 2 doses)[14]. Although the serum levels were different, the primary outcome (closure of PDA) remained the same in both groups. In the present study, the mean serum level of ibuprofen of the infants was 28 μg/ml and those of infants who responded and did not respond was not significantly different. This was not surprising since in the author' previous study using indomethacin, it was also found



* p value = 0.01

Fig. 1. Urine output of both groups from day 1 to day 4.

Table 4. The number of patients with secondary outcome variables in both groups.

Outcome	Ibuprofen group (n = 9)	Indomethacin group (n = 9)
Bronchopulmonary dysplasia	6	6
Intraventicular hemorrhage	4	3
Necrotizing enterocolitis	1	3
Death	1	1

that there were no significant difference of mean serum levels of indomethacin in the infants who responded and who did not respond.

The authors conclude that oral ibuprofen at the dose of 10 mg/kg daily for 3 days is as effective as indomethacin with fewer renal side effects and comparable morbidities. However, the number of patients was small and further study in a greater number of patients is necessary to assure the safety and efficacy of this drug in Thailand. Higher doses of oral ibuprofen should be investigated if effectiveness of this dose is too low since in the persent study, the serum levels were well below those of the intravenous form.

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ประสิทธิภาพของยา Ibuprofen ชนิดรับประทาน และยา Indomethacin ในการรักษา Patent Ductus Arteriosus (PDA) ในทารกเกิดก่อนกำหนด

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มีการศึกษาในต่างประเทศพบว่า การให้ ibuprofen ชนิดฉีดเข้าหลอดเลือดดำสามารถปิด PDA ได้ และพบว่าไม่มีผลเสียต่อการทำงานของไต แต่เนื่องจากยา ibuprofen ชนิดฉีดเข้าหลอดเลือดดำ ยังไม่มีจำหน่ายในประเทศไทย ดังนั้นผู้วิจัยจึงสนใจศึกษาการใช้ ibuprofen ชนิดรับประทานเพื่อรักษา PDA ในทารกเกิดก่อนกำหนด

วัตถุประสงค์ : ศึกษาผลการให้ ibuprofen ชนิดรับประทานในการรักษา PDA ในทารกเกิดก่อนกำหนด เปรียบเทียบการให้ indomethacin ชนิดฉีดหรือชนิดรับประทาน และศึกษาผลข้างเคียงของการให้ ibuprofen ชนิดรับประทานต่อการทำงานของไต

วิธีการศึกษา : รูปแบบงานวิจัยเป็น Prospective randomized parallel study ของทารกเกิดก่อนกำหนดที่เกิดในโรงพยาบาลรามาธิบดีที่มีอายุครรภ์น้อยกว่า 34 สัปดาห์ และได้รับการวินิจฉัยว่าเป็น PDA จำนวน 18 ราย แบ่งเป็นกลุ่มที่ได้รับยา ibuprofen 9 ราย (10 mg/kg/dose 3 ครั้ง ห่างกัน 24 ชั่วโมง) และกลุ่มที่ได้รับยา indomethacin 9 ราย (0.2 mg/kg/dose 3 ครั้ง ห่างกัน 12 ชั่วโมง) บันทึกข้อมูลทั่วไปของผู้ป่วย อาการแสดงทางคลินิก ปริมาณปัสสาวะ ตรวจ serum BUN, creatinine ก่อนและหลังได้รับยา

ผลการศึกษา : ทารกทั้ง 2 กลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในเรื่องข้อมูลพื้นฐานทั่วไป จากการศึกษานี้พบว่า ibuprofen สามารถใช้ในการรักษา PDA ได้ผลร้อยละ 78 indomethacin ใช้ในการรักษา PDA ได้ผลร้อยละ 89 ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญสถิติ ระดับยา ibuprofen เฉลี่ยหลังให้ยาครั้งที่ 3 ประมาณ 1 ชั่วโมง เท่ากับ 28.1 ไมโครกรัม/มล และพบว่าทารกกลุ่มที่ได้ indomethacin มีปริมาณปัสสาวะลดลงในวันแรกหลังให้ยามากกว่าทารกกลุ่ม ibuprofen อย่างมีนัยสำคัญทางสถิติ ส่วนจำนวนของทารกที่มีภาวะ bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis และเสียชีวิตไม่แตกต่างกัน

สรุปผลการศึกษา : การให้ ibuprofen ชนิดรับประทาน สามารถใช้ในการรักษา symptomatic PDA ในทารกแรกเกิดก่อนกำหนดได้ผลเทียบเท่ากับการรักษาด้วย indomethacin โดยมีผลลดปริมาณปัสสาวะน้อยกว่า

คำสำคัญ : อิบูโพรเฟน, อินโดเมธาซิน, การรักษาพีดีเอ, ทารกเกิดก่อนกำหนด

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