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Original Article

EFFECTIVENESS AND SAFETY OF HIGH DOSE ORAL IBUPROFEN VERSUS STANDARD DOSE FOR TREATMENT OF PRETERM INFANTS WITH PATENT DUCTUS ARTERIOSUS

YAOWARET MEKKHAYAI[a], CHULEEGONE SORNSUVIT[b], KANCHANA PREEDISRIPIPAT[c], SORAWIT PONGPITTAYUT[c]

[a]Department of Pharmacy, Chiangrai Prachanukroh Hospital, [b]Faculty of Pharmacy, Chiang Mai University, [c]Department of Pediatrics, Chiangrai Prachanukroh Hospital

Email:

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ABSTRACT

Objective: The objective of this research compares effectiveness and safety of high-dose oral ibuprofen and standard dose for treatment symptomatic PDA.

Methods: A retrospective cohort study was carried out in 126 preterm infants with patent ductus arteriosus (PDA) who received oral ibuprofen and hospitalized in neonatal intensive care unit and sick newborn ward during January 2010-December 2014, preterm infants with PDA was assigned to high dose (10-10-10 mg/kg/day) oral ibuprofen group and standard dose group (10-5-5 mg/kg/day), 63 patients within in each group.

Results: Baseline characteristics were no significant difference between two groups. The closure rate of the ductus arteriosus of the high dose group was significantly higher (82.5%) than in standard dose group (66.7%) (p=0.04). So, lower rate of re-open and PDA ligation. However, ductus arteriosus closure rate at discharge was not significantly different. There was no significant difference between two groups in adverse drug reaction.

Conclusion: The results obtained for this study show the high dose of oral ibuprofen is more effectiveness than the standard dose for closing PDA in preterm infants without increasing the adverse drug reaction rate.

Keywords: Preterm, Oral ibuprofen, Patent ductus arteriosus.

INTRODUCTION

Patent Ductus Arteriosus (PDA) is the most common cardiovascular abnormality in preterm neonates with the reported incidence as high as 77% in Texas [1-2] and 26.9% in newborns aged less than 33 w gestation in Thailand [3]. Neonates with PDA have higher respiratory failure rates, lower survival rates, and increased risk of intracranial hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC)[3-5].

Ibuprofen is a nonselective non steroidal anti-inflammatory drug that induces the closure of the PDA by inhibiting cyclo-oxygenase. Now PDA can be treated with oral ibuprofen (10-5-5 mg/kg/day). However many studies [6-12] found the higher failure rate in this dose and suggest that the failure of pharmacologic treatment for PDA closure might be due to inadequacy of 10-5-5 mg/kg/day. Moreover, Desfrere *et al.* [10] and Hirt *et al.* [11] show that the closure rate of PDA was related to the cumulative dose of ibuprofen administrated. In addition, Dani *et al.* [12] found high-dose ibuprofen (20-10-10 mg/kg/day) is more effective than the standard dose (10-5-5 mg/kg/day) without increasing the adverse effect rate [12].

In case of Chiangrai Prachanukroh hospital, the present has two regimens of oral ibuprofen for PDA management, 10-5-5 mg/kg/day and 10-10-10 mg/kg/day that follow Varaporn S [13] whom demonstrated the recommended dose regimen of oral ibuprofen is 10-10-10 mg/kg/day in Thai neonates whom with gestational age less than 32 w. This present found ibuprofen suspension could reduce the symptomatic PDA without any significant side effects.

The author preformed a retrospective cohort study to compare efficacy and safety of high dose and standard dose oral ibuprofen for closure of PDA in preterm infants which would be help pediatrician to be appropriate determine the dose of oral ibuprofen for PDA treatment.

METERIALS AND METHODS

The present study was a retrospective cohort study that approved by the internal ethical committee of research in human subject Chiangrai Prachanukroh Hospital, on 24 March 2015 and reference number is CR 0032.102/9212.

All preterm infants which hospitalized in newborn critical care unit and sick newborn ward during January 2010 to December 2014 were recruited in the present study. The criteria for enrollment were gestational age less than 37 w, clinical and/or echocardiography evidence of PDA by neonatologist and received three doses of oral ibuprofen either according to the standard regimen (an initial dose of 10 mg/kg, followed by two doses of five mg/kg each, after 24 and 48 h) or per a high-dose regimen (an initial dose of 10 mg/kg and after 24 and 48 h) via an orogastric tube.

The exclusion criteria were major congenital anomalies; persistent pulmonary hypertension, diagnosed by clinical and/or echocardiography when the presence of a right-to-left shunt and incomplete patient's data.

Clinical data and demographic information were collected by reviewing medical records of the enrolled patients.

Statistical analysis

The authors calculated that a sample size of at least 63 infants in each group was necessary for a power of 0.80 and p-value of 0.05. The baseline characteristics of the two groups were described in terms of mean values and SD, median value and range, or rate and percentage. The independent sample t-test, Mann-Whitney U test and Chi-square test or Fisher's exact test was used to compare continuous normally distributed data, nonparametric continuous data, and categorical data, respectively.

Multiple binary logistic regressions was performed to assess the predictive factors as the closure rate of PDA after the first oral ibuprofen course, the factors the authors analyzed were: the average postnatal age at first time of oral ibuprofen, received amikacin and meropenem during used oral ibuprofen and history of prenatal steroid, and assignment to the standard or high-dose oral ibuprofen regimen group. Effect estimates are expressed as adjusted odd ratio.

RESULTS

Subject demographic and baseline characteristics

A retrospective cohort study was carried out in 126 preterm infants with patent ductus arteriosus (PDA) who received oral

ibuprofen and hospitalized in neonatal intensive care unit and sick newborn ward during January 2010-December 2014. The author divided preterm infants into two groups to receive either the standard dose regimen (10-5-5 mg/kg/day; n=63) or the high-dose regimen (10-10-10 mg/kg/day; n=63). There were no significant differences in baseline characteristics, including gestational age, birth weight, gender, delivery method, APGAR scores, fluid intake at day of life 1-7 and on first day received oral ibuprofen. However, there was significant higher average postnatal age at first day of oral ibuprofen in the high-dose group than in standard dose group (p=0.00), history of prenatal steroid in standard dose group (49.2%) is higher than in high-dose group (30.2%) (p=0.03) and lower number of preterm infants in the standard dose group received amikacin and meropenem during used oral ibuprofen than in high-dose group (p=0.02). The baseline characteristic data were shown in table 1.

Table 1: Baseline characteristics of infants in the standard dose and high dose groups of oral ibuprofen in preterm infants with PDA

Baseline characteristics	Standard dose group (n=63)	High dose group (n=63)	p-value[d]
Gestational age (week)a	30.6±2.9	30.4±2.7	0.81
Birth weight (gram) a	1520.1±727.3	1417.7±384.1	0.32
Delivery method[a]			
Normal delivery	53 (84.1)	48 (76.2)	0.26
Vacuum extractor	1 (1.6)	0 (0)	1
Cesarean section	9 (14.3)	15 (23.8)	0.17
Sex[a]			
Male	36 (57.1)	33 (52.4)	0.59
Female	27 (42.9)	30 (47.6)	0.59
APGAR score (score)[b]			
0 min	6.5±2.1	6.6±2.4	0.81
5 min	7.7±1.2	7.6±2.0	0.71
10 min	8.1±1.1	8.0±1.9	0.87
Comorbidity[a]			
Respiratory distress	59 (93.7)	56 (88.9)	0.34
Birth asphyxia	0 (0)	5 (7.9)	0.05
Pneumonia	2 (3.2)	1 (1.6)	1.00
Sepsis	2 (3.2)	1 (1.6)	1.00
Fluid intake (ml/kg/day)[b]			
DOL 1	69.1±13.8	69.2±10.1	0.96
DOL 2	70.8±14.7	71.1±11.7	0.88
DOL 3	85.5±17.7	83.4±14.9	0.74
DOL 4	98.1±21.6	97.0±17.1	0.76
DOL 5	114.2±20.2	110.6±17.4	0.29
DOL 6	125.5±20.4	122.6±19.6	0.41
DOL 7	135.3±19.3	129.2±20.3	0.09
Co-medication[a]			
Ampicillin+gentamicin	25 (39.7)	15 (23.8)	0.05
Ampicillin+cefotaxime	18 (28.6)	12 (19.0)	0.21
Ceftazidime+amikacin	8 (12.7)	14 (22.2)	0.16
Meropenem+amikacin	7 (11.1)	17 (27.0)	0.02
Dexamethasone	4 (6.3)	1 (1.6)	0.36[e]
Others[c]	21 (45.7)	25 (54.3)	0.46[e]
Diagnosis of PDA[a]			
Clinical	39 (61.9)	28 (44.4)	0.05
Echocardiography	0	0	N/A
Clinical and echo[f]	24 (38.1)	35 (55.6)	0.05
Hospital stay (day)[b]	50.9±26.6	51.62±29.9	0.90

[a]mean±SD, [b] rate (%), [c] others: vancomycin and/or cefoperazone and sulbactam and/or piperacillin and tazobactam and/or furosemide, [d] Chi-square test, [e] Fisher's exact test, [f] echocardiography and DOL: day of life.

Day of life

Multiple logistic regression analysis used to demonstrate the relation between those factor and PDA closure rate. The author found that prenatal steroid (adjusted OR ratio 1.5; 95% CI: 0.6-3.5), co-medication during on oral ibuprofen: meropenem and amikacin (adjusted OR 0.6; 95% CI: 0.2-2.0) and postnatal age at first day received oral ibuprofen (adjusted OR 1.0; 95% CI: 1.0-1.0) were not related with the PDA closure rate (table 2).

Efficacy

After the first course of oral ibuprofen, the PDA closed in 42 (66.7%) of the patients assigned to the standard dose oral ibuprofen group versus 52 (82.5%) of those enrolled in the high dose oral ibuprofen group (p=0.04). The reopening of ductus arteriosus after first course was 16 (25.4%) of standard dose and 8 (12.7%) (p=0.07) of the high-dose group.

The second course started when failure to closure DA after complete the first course which was closed in five and eight patients of the standard and high group, respectively. Surgical closure of PDA was needed in four patients in standard dose group and in one patient in the high-dose group. At the time of discharge, 57 patients in standard dose group and 54 patients in high dose group were with PDA (table 3).

Table 2: Baseline characteristic and PDA closure rate

Baseline characteristic	Adjusted OR (95% CI)	p-value
Prenatal steroids	1.5 (0.6–3.5)	0.30
Comedication: meropenem and amikacin	0.6 (0.2-2.0)	0.48
Postnatal age at 1st oral ibuprofen	1.0 (1.0-1.0)	0.07

Table 3: Efficacy of treatment for the standard dose and high dose groups of oral ibuprofen in preterm infants with PDA

	Standard dose group (n=63)	High dose group (n=63)	p-value[a]
	Rate (%)		
PDA occurrence	First course of oral ibuprofen		
Closure	42 (66.7)	52 (82.5)	0.04
Patent	21 (33.3)	11 (17.5)	
Reopen	16 (25.4)	8 (12.7)	0.07
	Second course of oral ibuprofen		
Closure	5 (55.6)	8 (53.3)	0.32[b]
Patent	4 (44.4)	7 (46.7)	
Surgical closure	4 (6.3)	1 (1.6)	0.42[b]
PDA at discharge	57 (90.4)	54 (85.7)	0.58[b]

[a] Chi square test,[b] Fisher's exact

Table 4: Adverse drug reactions in standard dose and high dose groups of oral ibuprofen in preterm infants with PDA

Adverse drug reactions	Standard dose group (n=63)	High dose group (n=63)
Renal function		
Acute kidney injury (rate)[a]	2 (3.1)	1 (1.5)
Serum creatinine (mg/dl)[b]		
Before 3 doses oral ibuprofen	0.6±0.3	0.7±0.3
After 3 doses oral ibuprofen	0.6±0.5	0.6±0.4
Oliguria (rate)[a]	0	1 (1.5)
Urine output (ml/kg/h)[b]		
1st day on ibuprofen (Day1)	3.6±1.6	3.8±1.6
2nd day on ibuprofen (Day 2)	3.7±1.8	3.6±1.6
3rd day on ibuprofen (Day 3)	4.0±1.5	3.5±1.5
1st day after ibuprofen (Day 4)	4.4±1.8	3.9±1.9
2nd day after ibuprofen (Day 5)	4.4±2.2	4.0±1.7
3rdday after ibuprofen (Day 6)	4.3±2.1	3.9±1.9
4th day after ibuprofen (Day 7)	4.4±2.2	3.7±1.8
Bleeding disorder (rate)[a]	6 (9.5)	6 (9.5)
Respiratory tract	6 (9.5)	6 (9.5)
Upper GI bleeding	0	0
Thombocytopenia	0	0
Platelets (cell/mm3)[b]		
Before 3 doses oral ibuprofen	208 682±8289	247 000±16 242
After 3 doses oral ibuprofen	308 714±19 273	306 873±19 277
Necrotizing enterocolitis	0	0
Dead (rate)[a]	4 (57.1)	3 (42.9)

[a]mean±SD, [b] rate (%),

Safety

Adverse drug reaction was similar in standard dose group and high-dose group 8 (12.7%) versus 8 (12.7%). Bleeding disorder in respiratory tract was the most adverse drug reaction in this present but similar between two groups. Renal function, the change of serum creatinine increased 2-fold from baseline found in the standard dose group more than high-dose group 2 (3.1%) versus 1 (1.5%) and only one patient in the high-dose group developed oliguria. None of patients had necrotizing enterocolitis. (table 4).

DISCUSSION

The optimal dose of oral ibuprofen for closing PDA is unclear; this present was the first retrospective cohort study attempting to compare the effectiveness and safety between high dose and standard dose of oral ibuprofen in Chiangrai Prachanukroh Hospital, that did not have the standard treatment for PDA in preterm infants. Both oral ibuprofen regimen in this present are used in real practice due to standard dose is recommended in many suggestion [8-14] and high doses is recommended in Varaporn *et al.* [13], studied in Queen Sirikit National Institute of Child Health Ministry of Public Health, Thailand.

Many clinical parameters associated with ductus arteriosus closure in preterm infants either birth weight, gestational age, delivery method, APGAR score, total fluid at the first week of life, co-morbidity, prenatal steroid or postnatal age at the first day of received oral ibuprofen [2, 14-15]. In the present study, they were not significant difference between two groups, except prenatal steroids, received amikacin and meropenem and postnatal age at the first day of received oral ibuprofen. Prenatal steroids were also reported to decrease the nitric oxide productivity, vasodilator, sensitivity of a ductus arteriosus to prostaglandin and increase vascular contracted through a high calcium influx on smooth muscle leading to higher PDA closure rate [2]. However, infants in this present started oral ibuprofen at day of life 10, that take long time to infants to have steroids effect from maternal, thus prenatal steroids higher rate in the standard dose group may not relate PDA closure rate. The next difference factor was postnatal age, Hirt *et al.* [11] found important effect of postnatal age on ibuprofen. Ibuprofen clearance increase in the older age of neonate due to the maturity of renal development; which would increase the clearance of ibuprofen from the body resulting in lowering ibuprofen in blood. The lower level of ibuprofen in the blood stream could not enough to close PDA. These reasons explain that the older subjects were less successful on the DA closure rate by oral ibuprofen. Nevertheless, this present found higher postnatal age and higher closure rate in high dose group. The explanation was the high dose group even though higher rate clearance but an ibuprofen blood level is also high enough for closing PDA together with anatomical closure. The last factor that significant difference between two groups was the use of amikacin and meropenem during received oral ibuprofen. Reese *et al.* [16] studied vasodilator properties from medication that used in neonate and found that gentamicin and aminoglycoside had vasodilator properties because this medicine inhibit phospholiphase C and decrease calcium ion due to vascular dilate. On the other hand,

Reese *et al.* [16] studied in very high dose of gentamicin and aminoglycoside, 100-1000 fold in real practice; therefore this factor could not affect to PDA closure rate. Nevertheless when the multiple binary logistic regression was tested, all above difference factors were not significant related to PDA closure rate.

The effectiveness of this present is conform to the study of Desfrere *et al.* [10] whom found that high dose (15-7.5-7.5 mg/kg/day), higher PDA closure rate. Furthermore, Dani *et al.* [12], the latest study compare first course of high dose (20-10-10 mg/kg/day) and standard dose (10-5-5 mg/kg/day), found the high-dose ibuprofen regimen was more effective than the standard dose regimen in closing PDA in preterm infants<29 w of gestational without increasing adverse drug reaction rate. Moreover, this present found the reopen rate and PDA ligation rate in high-dose group were twofold and fourfold, respectively, lower than the standard dose. These shown the benefit of oral ibuprofen high dose. However, time duration from the first course to the second course was not specified, which might interfere the closing effect from anatomical closure. In other studies, closure rate in second course, PDA at discharge and long of hospital stay were not significant difference between two groups. The difference from other studies may be owing to, first, the increasing of postnatal age which resulting to the higher rate of anatomical closing PDA. Second, the final outcome (closing PDA) was evaluate using only clinical sign for diagnosis that can differ from physician to physician, which would affect to the closure rate. Third, the hospital policy of infant's bodyweight at discharge having a body weight at least 2000 grams and the chronic lung disease from the long use of oxygen resulting in older age of a patient at discharge. Thus, longer hospital stay, higher postnatal age at discharge, higher rate of PDA closure. Diagnoses by clinical sign were used more in the standard dose group than in the high-dose group, which may be because of in a diagnosis process by clinical sign with the wide PDA size is easy to detect. Thus, in the standard dose group, with younger postnatal age, wide PDA size usually found an obviously less and difficult to close by nature. However, they are significant between two groups.

Ibuprofen is non-steroid anti-inflammatory drugs (NSAIDs) [17] effects to several body organs especially gastrointestinal (GI), inhibition cyclo-oxygenase can decrease mucus secretion and thus, induced gastric ulcer and inhibition of thromboxane A2 production relates to gastric bleeding. In addition, the decreasing of PGI2 and PGE2, vasodilator at renal, controlling blood circulation inside of renal; effect to interstitial inflammatory and increase serum creatinine level. But safety details not a difference between two groups accordingly with Dani *et al.*[12], Desfrere *et al.* [10] and Hirt *et al.* [11].

The present study has several limitations. The major limitation is its retrospective design may be vulnerable to confounding errors and bias. Second, this study lacks some echocardiography data due to PDA size when diagnosis of PDA and PDA closure at a complete course of oral ibuprofen. Future study should be a prospective randomized study based on echocardiography and clinical data, study in all types of oral ibuprofen regimens in Chiangrai Prachanukroh hospital and should study in infants of gestational age between 28-32 w, aim to decrease confounding variable related to PDA closure from less or more gestational age.

CONCLUSION

In summary, the present data indicate that high dose of oral ibuprofen (10-10-10 mg/kg/day) is more effectiveness than the standard dose (10-5-5 mg/kg/day) for treatment of PDA in preterm infants without increasing adverse drug reactions.

CONFLICTS OF INTERESTS

All authors have none to declare

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