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ORIGINAL ARTICLE

Oral Ibuprofen versus Intravenous Indomethacin for Closure of Patent Ductus Arteriosus in Very Low Birth Weight Infants

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Key Words
oral ibuprofen;
indomethacin;
patent ductus arteriosus;
very low birth weight infants

Background: The purpose of this study is to compare the effects and complications of pharmacologic closure of patent ductus arteriosus (PDA) by intravenous indomethacin or oral ibuprofen in neonates weighing <1500 g at birth [very low birth weight (VLBW) infants].
Methods: This is a retrospective study of infants treated with intravenous indomethacin (0.2 mg/kg initially followed by two doses at 24-hour intervals) or oral ibuprofen (10 mg/kg initially followed an interval of 24 hours by two doses of 5 mg/kg) for symptomatic PDA in a neonatal intensive care unit at a medical center in Taiwan during the period of January 2005 to December 2010.
Results: A total of 88 infants received indomethacin and 52 received oral ibuprofen. Among the survivors, the closure rate without surgical ductal ligation was 70.5% (62/88) in the indomethacin group and 61.5% (32/52) in the ibuprofen group ($p = 0.342$). The incidence rates of oliguria and elevated serum creatinine were significantly lower in the ibuprofen group ($p = 0.002$ and $p = 0.022$, respectively). There was no significant difference in incidence of upper gastrointestinal hemorrhage or necrotizing enterocolitis between the ibuprofen and indomethacin groups (17.3% versus 23.9%; 3.8% versus 11.3%).
Conclusion: In infants with VLBW, oral ibuprofen is as effective as intravenous indomethacin for closure of PDA and is associated with significantly fewer cases of necrotizing enterocolitis among infants with birth body weights <1250 g and significantly lower rates of elevated creatinine levels among neonates with birth body weights ranging from 1000 to 1500 g.

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1. Introduction

The incidence of patent ductus arteriosus (PDA) in premature, very low birth weight (VLBW) infants (birth weight <1500 g) is approximately 30%.[1] The hemodynamic effects consist of disturbances in the diastolic flow of the pulmonary artery and the aorta and disturbances in the diastolic flow of the cerebral and mesenteric perfusion, which increase the risk for intraventricular hemorrhage (IVH) and gastrointestinal bleeding.[2] More than two thirds of infants with a birth weight below 1750 g require either medical or surgical closure of PDA.[3] Treatment options include medical therapy and surgical ligation.[4,5] Medical closure of PDA can be achieved with nonselective cyclooxygenase inhibitors, such as indomethacin and ibuprofen, which block the conversion of arachidonic acid to prostaglandins.[5,6] Treatment with indomethacin is associated with adverse events such as reduced renal, mesenteric, and cerebral perfusion.[7–9] Unlike indomethacin, ibuprofen has fewer effects on renal perfusion.[10–12]

In April 2006, intravenous ibuprofen was introduced as an alternative agent in the United States; however, its use was suspended in early 2010.[13] Intravenous ibuprofen is not available in most countries and is much more expensive than the oral form. Oral ibuprofen has been used for closure of PDA since early 2000.[14] The availability and lower cost of oral ibuprofen has led many physicians to use that regimen for closure of PDA.[15–19]Although oral ibuprofen is used widely, few randomized studies have compared its efficacy and safety with intravenous indomethacin, especially among infants in different VLBW categories.[18,20,21]

The purpose of this study was to compare the efficacy and complications of intravenous indomethacin with those of oral ibuprofen in closure of PDA among infants in different VLBW categories.

2. Materials and Methods

2.1. Patients

This retrospective study was conducted in the neonatal intensive care unit of the Changhua Christian Hospital of Changhua city in Taiwan during the period of January 2005 to December 2010. The inclusion criteria included a birth body weight <1500 g, a postnatal age between 48 and 96 hours, and echocardiographic evidence of left-to-right shunting across the ductus arteriosus with sign(s) of heart failure (respiratory distress, apnea, tachycardia, bounding pulse, and widened pulse pressure). Infants who died within 3 days after birth, those with echocardiographic evidence of right-to-left shunting, infants with major congenital anomalies, and those with IVH grade 3 or 4 were excluded.

2.2. Study design

Clinical data and information were collected from the medical records of the enrolled infants and included the response to intravenous indomethacin or oral ibuprofen (closed or failed), the need for surgical ligation, and adverse effects associated with indomethacin or ibuprofen. The endpoint for medical therapy of PDA closure and complication has been the end of the initial medical treatment. Adverse events included oliguria (urine output <1 mL/kg/hour), post-treatment (within 1 week after treatment) serum creatinine levels > 1.2 mg/dL, necrotizing enterocolitis (NEC), coffee-ground aspirate, or fresh blood aspirated through the gastric tube. These signs were considered to be adverse events of therapy if they occurred during the treatment course or within 48 hours after treatment. In clinical practice, if the patient was unsuitable for medical treatment or more serious complications occurred, they underwent surgical PDA ligation.

During the study period, routine echocardiographic screening of infants with birth weights <1500 g was performed between 48 and 96 hours after birth. Infants with respiratory distress, increased oxygen requirements, apnea, tachycardia, bounding pulse, widened pulse pressure, or evidence of renal dysfunction were considered to have symptomatic PDA.

Infants who received intravenous indomethacin were stratified into Group I. Intravenous indomethacin was given in three doses at 24-hour intervals depending on patient age (<48 hours of life, 0.2 mg/kg, 0.1 mg/kg, and 0.1 mg/kg; 2–7 days of life, 0.2 mg/kg; and > 7 days of life, 0.2 mg/kg, 0.25 mg/kg, and 0.25 mg/kg).

Infants who received oral ibuprofen were stratified into Group O. Oral ibuprofen (Idofen, standard, Taiwan; 1 mL equals 20 mg of ibuprofen, pH: 4.6) was given in three doses: 10 mg/kg, 5 mg/kg, and 5 mg/kg with a 24-hour interval between each dose. Ibuprofen was administered through an oral-gastric tube, followed by flushing with distilled water. Contraindications to either agent included serum creatinine > 1.7 mg/dL or platelet count <70,000/mm^3. The indication of PDA ligation included a contraindication to medical therapy, oliguria, gastrointestinal bleeding, and pulmonary hemorrhage.

2.3. Subgroup analysis

Infants in Group O and those in Group I were subdivided into three subgroups according to birth weight: <1000 g, 1000–1249 g, and 1250–1499 g.

2.4. Outcome

The primary outcome in our study was closure of PDA. Treatment failure in Group O was defined in patients that required intravenous indomethacin or surgical ligation after initial treatment with oral ibuprofen. Treatment failure in Group I was defined in patients that required surgical ligation or required conversion to oral therapy after initial treatment with intravenous indomethacin. Secondary outcomes included the development of oliguria (urine out put <1 mL/kg/hour), elevated serum creatinine (Cr > 1.2 mg/dL), NEC (any stage, radiographic signs include dilated bowel loops, paucity of gas, a "fixed loop," or pneumatosis intestinalis, according to Bell classification of NEC), or upper gastrointestinal bleeding (fresh blood and/or coffee-ground aspirate from the nasogastric tube).

2.5. Statistical analysis

Data were analyzed according to the intention-to-treat principle. Statistical analysis of data was performed using the Chi-square test, the Mann Whitney U test, or Fisher's exact test. Relative risk and 95% confidence intervals were estimated by Poisson regression with robust error variance. Continuous data, such as weight, gestational age, serum blood urea nitrogen and Cr levels, and urine output are presented as mean ± standard deviation. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (Version 15.0, SPSS, Chicago, IL, USA).

3. Results

During the period of January 2005 to December 2010, a total of 468 very low birth weight infants survived to the third day of hospitalization in the neonatal intensive care unit of the Changhwa Christian Hospital. Among them, 185 (39.5%) had Doppler-ultrasonographic evidence of PDA. Five infants were excluded, three for right-to-left shunting and two for severe IVH. PDA spontaneously closed without pharmacologic treatment after fluid restriction in 26 infants and 14 sick infants received surgical ligation without medical therapy. A total of 88 infants received intravenous indomethacin and 52 infants were treated with oral ibuprofen (Figure 1). The baseline characteristics were similar between both groups of neonates (Table 1).

3.1. Primary outcome

Closure of PDA was achieved in 32 (61.5%) of the infants in the oral ibuprofen group and in 62 (70.5%) of the infants in the intravenous indomethacin group ($p = 0.342$, Table 2). The subgroup analysis revealed that oral ibuprofen treatment was more effective at closing PDA in patients with higher birth body weights (closure rate: 71.4% in infants weighing 1250–1499 g; 69.2% for infants weighing 1000–1249 g; and 44.4% for infants weighing <1000 g); however, there was no significant difference in the rate of closure between the three subgroups (Table 2).

In Group I, failure to close the PDA with intravenous indomethacin occurred in three infants (3.4%), although closure was achieved after the regimen was switched to oral ibuprofen therapy. In Group I, 26.1% (23/88) of the infants required surgical PDA ligations after failure of medical therapy. Among them, oliguria occurred in 11 infants, UGI bleeding occurred in five, and NEC in three. In Group O, failure to close the PDA with oral ibuprofen occurred in 11 infants (21.2%) although the PDA was closed successfully in those neonates after the regimen was switched to intravenous indomethacin therapy. Nine infants (17.3%; 9/52) in Group O received surgical PDA ligation after failure of medical treatment (Figure 2). Among the nine infants, one infant developed oliguria, two infants developed UGI bleeding, and none developed NEC.

3.2. Secondary outcome

The incidence of elevated serum creatinine was significantly lower in Group O than in group I [$p = 0.022$, relative risk (RR) = 0.308, 95% confidence interval (CI): 0.112–0.844; (Table 3)]. The subgroup analysis revealed that serum creatinine levels were significantly lower among patients in Group O with birth body weights ranging from 1000 g to 1249 g ($p < 0.001$) and among those with weights ranging from 1250 to 1499 g ($p < 0.001$) than among their counterparts in Group I.

During the first week after treatment, oliguria developed in nine infants (9.6%) in Group O and in 33 infants (37.5%) in Group I ($p = 0.002$, RR = 0.256, 95% CI: 0.107–0.616; Table 3). Urine output (g/kg/hour) was significantly higher among infants in Group O on Days 3–7 of therapy (1.79 ± 0.61 vs. 1.44 ± 0.74, $p = 0.002$). The subgroup analysis revealed that urine output was significantly higher among infants with birth body weights > 1000 g than among infants in the other two body weight categories ($p = 0.035$).

The incidence rates of upper gastrointestinal hemorrhage and NEC were lower in Group O than in Group I (17.3% vs. 23.9%; 3.8% vs. 11.4%, Table 4); however, there was no significant difference in incidence of those two adverse events between the three birth body weight subgroups (Table 4).

There was no significant difference in incidence of NEC between infants in Group O and those in Group I; however, in the subgroup analysis, the incidence of NEC between infants in Group O and those in Group I was significantly lower in patients with birth body weights ranging from 1000 to 1249 g ($p < 0.001$) and in infants weighing > 1000 g ($p < 0.001$) than in neonates with a birth body weight ranging from 1250 to 1499 g (Table 4).

4. Discussion

Clinical studies have shown that intravenous ibuprofen is as effective as indomethacin for the treatment of PDA in preterm infants.[6,12] Intravenous ibuprofen is not available in most countries and is more expensive than the oral form. If oral ibuprofen were proved to be as efficient as intravenous indomethacin with no greater adverse effects, then its simple administration and lower cost would be important advantages.[22] Our study was designed with sufficient power for determining whether oral ibuprofen and intravenous indomethacin treatments are equally efficacious in PDA closure.

The incidence of PDA in VLBW infants in our study was approximately 30%, a rate that is similar to that reported previously.[1] The closure rate of PDA with intravenous indomethacin (70.5%) in our study was similar to that reported by Van Overmeire.[6] Our study indicated that PDA closure with oral ibuprofen in VLBW infants is at least as effective as closure with intravenous indomethacin.

Recent meta-analyses of studies that compared intravenous ibuprofen with indomethacin therapy for PDA closure in preterm infants revealed that intravenous ibuprofen and intravenous indomethacin are equally effective.[23–26] A recent Cochrane review of 20 studies

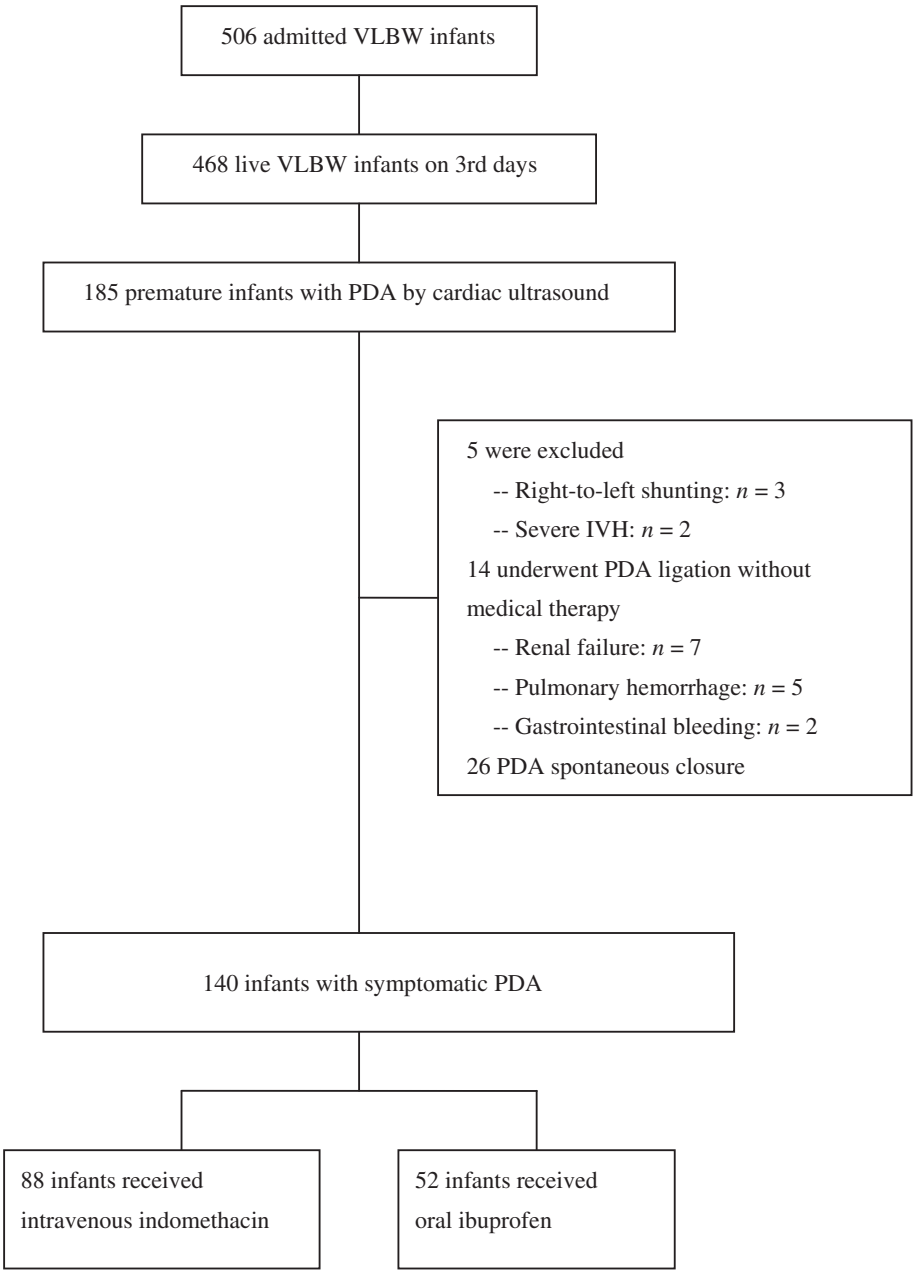

Figure 1 Infants enrolled in the study protocol.

Table 1 Baseline characteristics of the study infants.

Characteristic	Group O ($N = 52$)	Group I ($N = 88$)	p value
Gestational age, mean ± SD, wk	28.76 ± 2.28 (24–33.86)	28.93 ± 2.23 (23.57–33.86)	0.703
Birth weight, mean ± SD, g	1129.74 ± 240	1130.6 ± 222.5	0.902
<1000, *n* (%)	18 (34.6)	27 (30.7)	0.449
1000–1249, *n* (%)	13 (25)	31 (35.2)	0.46
1250–1499, *n* (%)	21 (40.4)	30 (34.1)	0.384
Sex			
Male, *n* (%)	29 (55.8)	43 (48.9)	0.43
Female, *n* (%)	23 (44.2)	45 (51.1)	0.43
Delivery by cesarean section, *n* (%)	36 (69.2)	56 (63.6)	0.5

Group O: treated with oral ibuprofen. Group I: treated with intravenous indomethacin. Data are presented as mean ± SD (range) or number (%).

Table 2 Oral ibuprofen and intravenous indomethacin for closure of PDA.

Variable	Group O ($N = 52$)	Group I ($N = 88$)	p value	Relative risk (95% confidence interval)
Closure of PDA, n (%)				
Overall	32 (61.5)	62 (70.5)	0.342	0.872 (0.69-1.15)
Birth weight, g				
<1000, n (%)	8/18 (44.4)	12/27 (44.4)	1.0	1.00 (0.51−1.95)
1000−1249, n (%)	9/13 (69.2)	25/31 (80.6)	0.456	0.858 (0.58−1.28)
1250−1499, n (%)	15/21 (71.4)	25/30 (83.3)	0.493	0.857 (0.65−1.24)

Group O: treated with oral ibuprofen. Group I: treated with intravenous indomethacin. Data are presented as mean ± SD (range) or number (percent). PDA = patent ductus arteriosus.

($n = 956$ infants) reported that ibuprofen (oral form, initial dose of 10 mg/kg followed by 5 mg/kg 24 and 48 hours later) was as effective as indomethacin (intravenous form, 0.2 mg/kg every 12 hours for three doses) in closing PDA and that ibuprofen reduces the risk of developing NEC and transient renal insufficiency.[26]

Oral ibuprofen for closure of PDA in premature infants was first used by Hariprasad[14] in 13 infants in 2000. Since then, a number of trials have been conducted to evaluate the efficacy of oral ibuprofen for closure of PDA.[17,18,21,27,28] The sample sizes in all of those studies, however, were relatively small. In a randomized controlled study, Fakhraee et al[19] found that PDA was successfully closed in all 18 premature infants (<34 weeks of gestation) who received oral ibuprofen and that closure of the PDA was achieved in 15 of 18 premature infants who had been given oral indomethacin ($p < 0.05$).

The results from a number of clinical trials have demonstrated that there is no significant difference in the rate of closure of PDA in preterm infants between oral ibuprofen and intravenous ibuprofen.[15−17,22,29] However, Chotigeat et al[20] and Supapannachart et al[21] found that oral ibuprofen was more effective than intravenous indomethacin at closing PDA. In nonrandomized open trials, oral ibuprofen was associated with a ductal arteriosus closure rate of 95% (38 of 40 infants) in a study by Cherif et al,[15] a closure rate of 95.4% (21 of 22 infants) in a study by Heyman et al,[27] and a closure rate of 84.6% (11 of 13 infants) in a study by Hariprasad et al.[14] Ohlsson et al[26] reviewed a total of 7 studies ($n = 189$ infants) and found that there was no significant difference in failure rate of PDA closure between infants who received oral ibuprofen and infants who were treated with intravenous indomethacin.

The endpoint of this study was the end of the initial medical treatment. In clinical practice, if the patient was unsuitable for medical treatment, surgical PDA ligation was performed. According to our study, the study group who received oral ibuprofen rarely required further surgical PDA ligations. This phenomenon would be related to lower complications from oral ibuprofen treatments.

Although a few studies have found that intravenous ibuprofen was associated with a higher rate of PDA closure than intravenous indomethacin among those VLBW infants with higher birth body weights,[30,31] our study, to the best of our knowledge, is the first study to compare the effectiveness of orally administered ibuprofen with that of intravenously administered indomethacin at closing PDA among preterm infants stratified by birth body weight. We found that the rate of closure of PDA tended to be higher among infants with a higher birth body weight in both treatment groups. There was no significant difference in closure rate between patients that received oral ibuprofen and those that received intravenous indomethacin in each

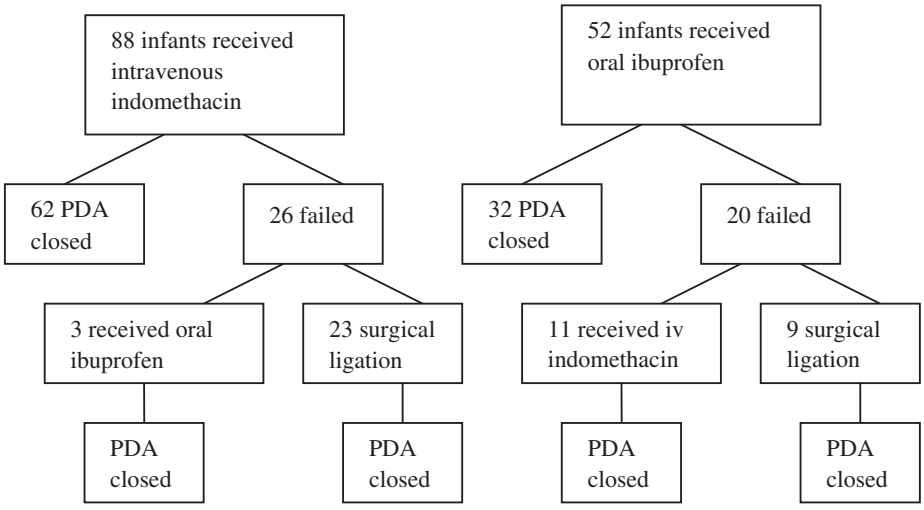

Figure 2 Flow chart of therapy.

Table 3 Incidence of elevated serum creatinine and oliguria.

Variable	Group O ($N = 52$)	Group I ($N = 88$)	p value	Relative risk (95% confidence interval)
Elevated serum creatinine, *n* (%)				
Overall	4 (7.7)	22 (25.0)	0.022	0.308 (0.11—0.84)
Birth weight, g				
<1000, *n* (%)	4/18 (22.2)	11/27 (40.7)	0.224	0.55 (0.21—1.45)
1000—1249 g, *n* (%)	0/13 (0)	9/31 (29.0)	<0.001	—
1250—1499 g, *n* (%)	0/21 (0)	2/30 (6.7)	<0.01	—
Oliguria, *n* (%)				
Overall	5 (9.6)	33 (37.5)	0.002	0.256 (0.107—0.616)
Birth weight, g				
<1000, *n* (%)	2/18 (11.1)	13/27 (48.1)	0.035	0.231 (0.059—0.903)
1000—1249, *n* (%)	2/13 (15.4)	10/31 (32.3)	0.291	0.477 (0.121—1.883)
1250—1499, *n* (%)	1/21 (4.8)	10/30 (33.3)	0.054	0.143 (0.02—1.033)

Group O: treated with oral ibuprofen. Group I: treated with intravenous indomethacin. Data are presented as mean ± SD (range) or number (percent).

subgroup (Table 2). This tendency of higher rate of PDA closure among preterm infants who received medical treatment with higher birth body weights may be meaningful in clinical practice. However, the relatively small number of patients in each subgroup limited the power of our study to detect significant differences. Large sample and prospective randomized studies are certainly needed to validate these findings.

Premature babies with immature organ systems are more susceptible to pharmacological interactions. Tiker et al[32] reported that oral ibuprofen therapy was associated with acute renal failure in extremely low birth weight (ELBW) infants. In our analysis, five infants developed oliguria and four infants had elevated serum Cr levels after oral ibuprofen therapy. The majority of those patients were ELBW infants. As can be seen from the above results, the lower body weight premature infants are more susceptible to pharmacologic complications. In our analysis, the incidence of associated renal complications such as oliguria or elevated serum Cr levels was lower in the oral ibuprofen group than in the intravenous indomethacin group. In addition, the incidence of oliguria was significantly lower in the extremely low birth weight subgroup that received oral ibuprofen. It appears that oral ibuprofen resulted in fewer renal adverse events than intravenously administered indomethacin. Chotigeat et al[20] and Supapannachart et al[21] also reported that oral ibuprofen resulted in fewer renal adverse events than oral or intravenously administered indomethacin. Clinicians should be vigilant for complications of acute renal failure in treatment of PDA closure by given oral ibuprofen, especially in ELBW infants. Even the incidence of associated renal complications was lower in the oral ibuprofen group than the intravenous indomethacin group for the treatment of PDA closure.

Upper gastrointestinal hemorrhage and NEC are common sequelae in preterm infants with PDA.[33] In our study, the incidence rates of gastrointestinal hemorrhage and NEC were lower among infants who received oral ibuprofen, although there was no significant difference in the development of those sequelae between patients that received

Table 4 Incidence of upper gastrointestinal bleeding and necrotizing enterocolitis after medical PDA therapy.

Variable	Group O ($N = 52$)	Group I ($N = 88$)	p value	Relative risk (95% confidence interval)
UGI bleeding, *n* (%)				
Overall	9 (17.3)	21(23.9)	0.37	0.725 (0.36-1.463)
Birth weight, g				
<1000, *n* (%)	3/18 (16.7)	6/27 (22.2)	0.652	0.75 (0.215—2.62)
1000—1249, *n* (%)	2/13 (15.4)	10/31 (32.3)	0.291	0.477 (0.121—1.883)
1250—1499, *n* (%)	4/21 (19.0)	5/30 (16.7)	0.826	1.143 (0.347—3.759)
Necrotizing enterocolitis, *n* (%)				
Overall	2 (3.8)	10 (11.4)	0.151	0.338 (0.077—1.485)
Birth weight, g				
<1000, *n* (%)	0/18 (0)	4/27 (14.8)	<0.001	—
1000—1249, *n* (%)	0/13 (0)	5/31 (16.1)	<0.001	—
1250—1499, *n* (%)	2/21 (9.5)	1/30 (3.3)	0.378	2.857 (0.277—29.51)

Group O: treated with oral ibuprofen. Group I: treated with intravenous indomethacin. Data are presented as mean ± SD (range) or number (%).

oral ibuprofen and infants that received intravenous indomethacin. None of the infants who received oral ibuprofen treatment in our study showed evidence of bowel perforation. The rate of NEC among our infants who received enteral ibuprofen was similar to that reported by Tulin et al,[22] but it was below the overall rate reported for intravenous ibuprofen [27/356 (8%)] in a recent meta-analysis of studies on preterm infants with HsPDA.[34] In our infants, the drug was given undiluted through a feeding tube in a very small volume followed by flushing with distilled water. The pH of the ibuprofen suspension used in our study was 4.6, which is not associated with gastrointestinal irritation. Toleration of the oral form of ibuprofen was better than that of intravenously administered indomethacin in terms of gastrointestinal complications such as intestinal perforation or bleeding and NEC.

There are limitations in applying the results of our study because of its retrospective design, power and sample size. Although the infants in our study were not randomized, the characteristics of the infants in the two groups were similar and there were no major changes in clinical practice during the 6-year study period. Despite these limitations, the final result still contributes valuable information on the feasibility of using oral ibuprofen in treatment of PDA closure in premature infants.

5. Conclusions

In VLBW infants, oral ibuprofen is as effective as intravenous indomethacin for closure of PDA and is associated with significantly fewer cases of necrotizing enterocolitis among infants with birth body weights $<$1250 g and significantly lower rates of elevated creatinine levels among neonates with birth body weights ranging from 1000 to 1500 g. Larger, prospective randomized studies are needed to clarify the efficacy and safety of oral ibuprofen with the efficacy and safety of other medical treatments for closure of PDA in infants with premature extremely low birth weight infants.

References

1. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. *Pediatrics* 2001;**107**:E1.
2. Weir FJ, Ohlsson A, Myhr TL, Fong K, Ryan ML. A patent ductus arteriosus is associated with reduced middle cerebral artery blood flow velocity. *Eur J Pediatr* 1999;**158**:484–7.
3. Gersony 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**:895–906.
4. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. *J Perinatol* 2006;**26**:14–8.
5. Van Overmeire B, Chemtob S. The pharmacologic closure of the patent ductus arteriosus. *Semin Fetal Neonatal Med* 2005;**10**:177–84.
6. Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;**343**:674–81.
7. Van Bel F, Guit GL, Schipper J, Van de Bor M, Baan J. Indomethacin induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. *J Pediatr* 1991;**118**:621–6.
8. Mardoum R, Bejar R, Merritt TA, Berry C. Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. *J Pediatr* 1991;**118**:112–5.
9. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in newborn: effects of patent ductus arteriosus and parenteral indomethacin. *Arch Dis Child* 1990;**65**:1067–71.
10. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature infants. *JAMA* 1996;**275**:539–44.
11. Mosca F, Bray M, Lattanzio M, Fumagalli M, Tosetto C. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. *J Pediatr* 1997;**131**:549–54.
12. Lago P, Bettiol T, Salvadori S, et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. *Eur J Pediatr* 2002;**161**:202–7.
13. Poon G. Ibuprofen lysine (NeoProfen) for the treatment of patent ductus arteriosus. *Proc (Bayl Univ Med Cent)* 2007;**20**:83–5.
14. Hariprasad P, Sundarrajan V, Srimathy G, Suthagar B, Ramadevi BS. Oral ibuprofen for closure of hemodinamically significant PDA in premature neonates. *Indian Pediatr* 2002;**39**:99–100.
15. Cherif A, Khrouf N, Jabnoun S, et al. Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. *Pediatrics* 2008;**122**:1256–61.
16. Erdeve O, Gokmen T, Altug N, Dilmen U. Oral versus intravenous ibuprofen: which is better in closure of patent ductus arteriosus? *Pediatrics* 2009;**123**:763.
17. Cherif A, Jabnoun S, Khrouf N. Oral ibuprofen in early curative closure of patent ductus arteriosus in very premature infants. *Am J Perinatol* 2007;**24**:339–45.
18. Aly H, Lotfy W, Badrawi N, Ghawas M, Abdel-Meguid IE, Hammad TA. Oral ibuprofen and ductus arteriosus in premature infants: a randomized pilot study. *Am J Perinatol* 2007;**24**:267–70.
19. Fakhraee SH, Badiee Z, Mojtahedzadeh S, Kazemian M, Kelishadi R. Comparison of oral ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. *Zhongguo Dang Dai Er Ke Za Zhi* 2007;**9**:399–403.
20. Chotigeat U, Jirapapa K, Layangkool T. A comparison of oral ibuprofen and intravenous indomethacin for closure of patent ductus arteriosus in preterm infants. *J Med Assoc Thai* 2003;**86**:563–9.
21. Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomised trial at Ramathibodi Hospital. *J Med Assoc Thai* 2002;**85**:1252–8.
22. Gokmen T, Erdeve O, Altug N, Oguz SS, Uras N, Dilmen U. Efficacy and safety of oral versus intravenous ibuprofen in very low birth weight preterm infants with patent ductus arteriosus. *J Pediatr* 2011;**158**. 549–554.e1.
23. Jones LJ, Craven P, Attia J, Thakkinstian A, Wright I. Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2011;**96**:F45–52.
24. Aranda JV, Thomas R. Systematic review: ibuprofen in preterm newborns. *Semin Perinatol* 2006;**30**:114–20.
25. Gimeno Navarro A, Modesto Alapont V, Morcillo Sopena F, Fernández Gilino C, Izquierdo Macián I, Gutiérrez Laso A. Ibuprofen versus indomethacin in the preterm persistent

patent ductus arteriosus therapy: review and meta-analysis. *An Pediatr (Barc)* 2007;**67**:309—18.
26. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2010;**14**(4):CD003481.
27. Heyman E, Morag I, Batash D, Keidar R, Baram S, Berkovitch M. Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. *Pediatrics* 2003;**112**:e354.
28. Sangtawesin V, Sangtawesin C, Raksasinborisut C, et al. Oral ibuprofen prophylaxis for symptomatic patent ductus arteriosus of prematurity. *J Med Assoc Thai* 2006;**89**:314—21.
29. Cherif A, Khrouf N, Jabnoun S, et al. Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. *Pediatrics* 2008;**122**:e1256—61.
30. Niinikoski H, Alanen M, Parvinen T, Aantaa R, Ekblad H, Kero P. Surgical closure of patent ductus arteriosus in very-low-birth-weight infants. *Pediatr Surg Int* 2001;**17**:338—41.
31. Vida VL, Lago P, Salvatori S, et al. Is there an optimal timing for surgical ligation of patent ductus arteriosus in preterm infants? *Ann Thorac Surg* 2009;**87**:1509—15.
32. Tiker F, Yildirim SV. Acute renal impairment after oral ibuprofen for medical Closure of patent ductus arteriosus. *Indian Pediatr* 2007;**44**:54—5.
33. Lee Soo Jin, Kim Ji Young, Park Eun Ae, Sohn Sejung. The pharmacological treatment of patent ductus arteriosus in premature infants with respiratory distress syndrome: oral ibuprofen vs. indomethacin. *Korean J Pediatr* 2008;**51**(9):956—63.
34. Gouyon JB, Kibleur Y. Efficacy and tolerability of enteral formulations of ibuprofen in the treatment of patent ductus arteriosus in preterm infants. *Clin Ther* 2010;**32**(10):1740—8.