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ORIGINAL ARTICLE

Comparison of oral ibuprofen and intravenous indomethacin for the treatment of patent ductus arteriosus in extremely low birth weight infants☆

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KEYWORDS
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Abstract
Objective: There are few published reports concerning the efficacy of oral ibuprofen for the treatment of patent ductus arteriosus (PDA) in extremely low birth weight (ELBW) infants. Oral ibuprofen was compared to intravenous indomethacin regarding efficacy and safety in the treatment of PDA in infants weighting less than 1,000 g at birth.
Method: This was a retrospective study in a single center. Data on ELBW infants who had an echocardiographically confirmed PDA were collected. The infants were treated with either intravenous indomethacin or oral ibuprofen. Rate of ductal closure, need for additional treatment, drug-related side effects or complications, and mortality were compared between the two treatment groups.
Result: 26 infants who received indomethacin and 22 infants who received ibuprofen were studied. The overall rate of ductal closure was similar between the two treatments: it occurred in 23 of 26 infants (88.5%) treated with indomethacin, and in 18 of 22 infants (81.8%) treated with ibuprofen (p = 0.40). The rate of surgical ligation (11.5% *versus* 18.2%; p = 0.40) did not differ significantly between the two treatment groups. No significant difference was found in post-treatment serum creatinine concentrations between the two groups. There were no significant differences regarding additional side effects or complications.
Conclusion: In ELBW infants, oral ibuprofen is as efficacious as intravenous indomethacin for the treatment of PDA. There were no differences between the two drugs with respect to safety. Oral ibuprofen could be used as an alternative agent for the treatment of PDA in ELBW infants.

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PALAVRAS-CHAVE
Persistência do canal arterial;
Ibuprofeno;
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Neonatos com extremo baixo peso ao nascer

Comparação de ibuprofeno via oral e indometacina intravenosa no tratamento da persistência do canal arterial em neonatos com extremo baixo peso ao nascer

Resumo

Objetivo: Existem poucos relatórios publicados com relação à eficácia do ibuprofeno via oral no tratamento da persistência do canal arterial (PCA) em neonatos com extremo baixo peso ao nascer (EBPN). Comparamos o ibuprofeno via oral à indometacina intravenosa no que diz respeito à eficácia e segurança no tratamento de PCA em neonatos com peso inferior a 1.000 g ao nascer.

Método: Este foi um estudo retrospectivo em um único centro. Coletamos dados de neonatos com EBPN que tiveram PCA ecocardiograficamente confirmada. Os neonatos foram tratados tanto com indometacina intravenosa quanto com ibuprofeno via oral. A taxa de fechamento do canal, a necessidade de tratamentos adicionais, os efeitos colaterais ou as complicações relacionadas ao medicamento e a mortalidade foram comparados entre os dois grupos de tratamento.

Resultado: Examinamos 26 neonatos que receberam indometacina e 22 que receberam ibuprofeno. A taxa geral de fechamento do canal foi semelhante nos dois tratamentos: o fechamento do canal ocorreu em 23 dos 26 neonatos (88,5%) no grupo indometacina, e em 18 dos 22 neonatos (81,8%) no grupo ibuprofeno (p = 0,40). A taxa de ligadura cirúrgica (11,5% em comparação a 18,2%; p = 0,40) não diferiu de forma significativa entre os dois grupos de tratamento. Após o tratamento, não foi encontrada nenhuma diferença significativa nas concentrações de creatinina sérica entre os dois grupos. Não houve diferenças significativas com relação a efeitos colaterais ou complicações adicionais.

Conclusão: Em neonatos com EBPN, o ibuprofeno via oral é tão eficaz quanto a indometacina intravenosa no tratamento da PCA. Não há diferenças entre os medicamentos no que diz respeito à segurança. O ibuprofeno via oral poderia ser usado como um agente alternativo no tratamento da PCA em neonatos com EBPN.

Introduction

The incidence of patent ductus arteriosus (PDA) in term infants has been estimated to be 57/100,000 live births, whereas the incidence of PDA in preterm infants weighing 501 to 1,500 g has been estimated to be 31%.[1,2] In addition, 55% of infants who weigh 1,000 g or less (extremely low birth weight – ELBW) have been described as having symptomatic PDA that ultimately requires medical treatment.[3,4]

Intravenous indomethacin has been the conventional pharmacologic treatment for promoting the closure of PDA in premature infants. However, concerns remain regarding the safety of indomethacin, which affects renal, gastrointestinal, and cerebral perfusions, and may lead to complications such as transient or permanent renal dysfunction, necrotizing enterocolitis, gastrointestinal hemorrhage, and reduced cerebral intracellular oxygenation.[5-9]

In April of 2006, ibuprofen lysine (ibuprofen) was introduced as an alternative agent, approved by the U.S. Food and Drug Administration, for the closure of PDA in premature infants.[10] In several randomized controlled trials, ibuprofen was equally efficacious as indomethacin in the promotion of ductal closure, and had less effects on renal, mesenteric, and cerebral perfusions.[11-15] However, there are few published data on the efficacy of oral ibuprofen for PDA treatment targeted to ELBW infants. The aim of this study was to compare oral ibuprofen and intravenous indomethacin regarding their efficacy and safety in the treatment of PDA in infants weighing less than 1,000 g at birth.

Methods

Patients and study design

This was a retrospective cohort study at the neonatal intensive care unit of the Chonnam National University Hospital (Gwangju, Korea) between January, 2007 and June, 2011. The study protocol was approved by the Institutional Review Board of the Chonnam National University Hospital. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. The criteria for enrollment included birth weight of 1,000 g or less; echocardiographic evidence of PDA; and treatment with either intravenous indomethacin or oral ibuprofen. Exclusion criteria were right-to-left shunting; major congenital anomalies; intraventricular hemorrhage of grade 3 or higher according to the classification by Papile et al.[16] within the previous 24 hours; life-threatening infection; urine output below 1 ml/kg/h during the previous 8 hours; a serum creatinine concentration of 1.8 mg/dL or higher; a blood urea nitrogen concentration greater than 30

mg/dL; a platelet count of 60,000/μL or less; a tendency to bleed (defined by the presence of blood in endotracheal aspirate, gastric aspirate, stool or urine, and/or oozing from puncture sites); and hyperbilirubinemia necessitating exchange transfusion.

Data collected

Clinical data and demographic information were collected by reviewing medical records of the enrolled patients. The patients were divided into intravenous indomethacin and oral ibuprofen groups. Rate of ductal closure, number of doses required, need for additional treatments, side effects, and complications were compared between the two groups. Renal function was evaluated by the assessment of urine output, serum creatinine concentrations, and the need for furosemide administration. Oliguria was defined as a urine output of 1 mL/kg/h or less during a 24-hour collection period. Bronchopulmonary dysplasia was defined by the need for supplemental oxygen after 28 days of life, in association with typical radiographic findings. Necrotizing enterocolitis was diagnosed when the clinical signs and radiographic evidence of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air were present. Retinopathy of prematurity was also evaluated. Cranial ultrasound examination was performed before and after treatment for the assessment of intraventricular hemorrhage or periventricular leukomalacia.

Echocardiography

The clinical diagnosis of PDA was confirmed by echocardiography (iE33 ultrasound system; Philips Medical Systems – Andover, MA, USA) with a 7.5-MHz probe. Echocardiographic criteria for PDA included an increased left atrial diameter compared with the aortic root (left-atrium-to-aortic-root ratio ≥ 1.3), visualization of the ductus (≥ 1.5 mm), and evidence of left-to-right blood flow through the open duct. Color and pulsed wave spectral Doppler scans were applied to assess the direction and velocity of ductal flow. After the first dose of treatment in both groups, an echocardiographic evaluation was performed to determine the need for a second or third dose. Ductal closure was documented by the absence of ductal blood flow on the color Doppler scan.

Treatment regimens of indomethacin and ibuprofen

Intravenous indomethacin (Indocin; Merck – West Point, PA, USA) was administered from January, 2007 to April, 2010, and oral ibuprofen (Brufen syrup; Sam-il – Seoul, Korea) was used between May, 2010 and June, 2011. Indomethacin was given in three doses, and the interval varied with age. The dosage administered was 0.2 mg/kg as the initial dose and 0.1 mg/kg every 24 hours in infants less than 48 hours old; 0.2 mg/kg as the initial dose, 0.1 mg/kg at the 12-hour interval, followed by 0.1 mg/kg at 24-hour interval in infants over 48 hours old. Ibuprofen was administered in three doses of 10 mg/kg, 5 mg/kg, and 5 mg/kg at 24-hour intervals. Indomethacin (1 mg) was dissolved in normal saline solution (0.9%) to a final concentration of 0.1 mg/mL, and infused over 30 minutes. Ibuprofen was administered in a five-fold dilution, using a 5% dextrose solution in distilled water through a feeding tube. For all patients, ventilator management, fluid therapy, and other supportive care were applied by the same guidelines during the treatment.

Statistical analysis

A study group of 48 patients should be necessary for the study to be able to detect a difference of at least 25 percentage points in the closure rate between the oral ibuprofen and intravenous indomethacin groups, assuming a closure rate of 75 percent with intravenous indomethacin, with a p-value of 0.05 and a power of 80%. Continuous data are presented as the mean±standard deviation. Comparisons between groups were performed using the independent-samples t test for continuous variables, and Fisher's exact test or the chi-squared test were used for categorical variables. To assess the changes in serum creatinine concentrations after treatment, the paired t-test and repeated measures ANOVA were performed. The statistical significance was set at $p < 0.05$. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc. – Chicago, IL, USA) version 18.0.

Results

Baseline characteristics

A total of 48 infants were examined: 26 received intravenous indomethacin and 22 received oral ibuprofen. Indomethacin and ibuprofen groups were similar in their baseline characteristics, including gestational age, birth weight, gender, delivery method, rate of administration of antenatal steroid, ductal diameter, among others (Table 1).

Efficacy of treatment

The rate of ductal closure was similar between the two treatment groups. Primary ductal closure occurred in 17 of 26 infants (65.4%) treated with indomethacin, and in 13 of 22 infants (59.1%) treated with ibuprofen ($p = 0.44$). The number of infants who received a second or third pharmacologic treatment included six infants (23.1%) in the indomethacin group and five infants (22.7%) in the ibuprofen group ($p = 0.62$). The overall closure rate was 23 of 26 infants (88.5%) in the indomethacin group, and 18 of 22 infants (81.8%) in the ibuprofen group ($p = 0.40$). The rate of surgical ligation did not differ significantly between the two groups (11.5% *versus* 18.2%; $p = 0.40$) (Table 2).

Safety of treatment

During treatment, three infants (11.5%) developed oliguria in the indomethacin group, and one infant (4.5%) in the ibuprofen group ($p = 0.37$). The change of serum creatinine concentrations during treatment did not differ

Table 1 Baseline characteristics of the indomethacin and ibuprofen groups.

	Indomethacin group (n = 26)	Ibuprofen group (n = 22)	p-value
Gestational age (weeks)	27.0±1.3	26.7±1.0	0.28
Birth weight (g)	869.2±90.8	814.5±117.0	0.08
Male/female	6/20	9/13	0.15
Antenatal steroid (%)	16 (61.5)	16 (72.7)	0.30
Delivery by cesarean section (%)	21 (80.8)	17 (77.3)	0.52
Apgar score			
1 min	3.42±1.39	2.77±1.41	0.11
5 min	5.50±1.55	5.27±1.95	0.65
Surfactant use			
1 dose	25	17	0.62
≥ 2 doses	1	5	0.62
*Inspired O_2, FiO_2 (%)**	25.0±3.9	25.8±7.9	0.67
HFV	3	0	0.15
Ventilator (days)	22.8±14.4	28.0±17.0	0.26
Inotropics 1st 48 hours (%)	18 (69.2)	14 (63.6)	0.45
Ductal diameter (mm)	2.10±0.72	1.90±0.42	0.25
Age at drug administration (days)	5.34±6.02	5.36±3.69	0.99

FiO_2, fraction of inspired oxygen; HFV, high-frequency oscillatory ventilation.
*Values for the day of treatment initiation.

Table 2 Efficacy of treatment for the indomethacin and ibuprofen groups.

	Indomethacin group (n = 26)	Ibuprofen group (n = 22)	p-value
Primary closure rate[a] (%)	17 (65.4)	13 (59.1)	0.44
Secondary closure rate[b] (%)	6 (23.1)	5 (22.7)	0.62
Overall closure rate (%)	23 (88.5)	18 (81.8)	0.40
Surgical ligation rate (%)	3 (11.5)	4 (18.2)	0.40

[a]Ductal closure rate after the first drug administration.
[b]Ductal closure rate after the second or third drug administration in patients whose duct failed to close after the first drug administration.

significantly between the two groups (p = 0.21). However, serum creatinine concentrations increased significantly after treatment in each group (indomethacin group, p = 0.001; ibuprofen group, p = 0.003). The number of furosemide administrations per patient was similar in the two groups (0.76 ± 1.39 *versus* 0.63 ± 0.65; p = 0.66) (Table 3). The incidence of intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia did not differ significantly between the two groups. The survival rate was also similar between treatment groups (Table 4).

Discussion

In 1973, Coceani and Olley first reported that E-series prostaglandins induced relaxation of isolated strips of ductus arteriosus in sheep.[17] Subsequent studies have demonstrated that PGE1 and PGE2 are the most potent endogenous dilators of the ductus arteriosus, although PGI2 and its metabolites may also play an important vasodilatory role. Successful pharmacological closure of PDA with indomethacin was first reported in 1976, and indomethacin became the conventional pharmacologic treatment for PDA in premature infants.[18] In April of 2006, ibuprofen was introduced as an alternative agent for PDA closure in premature infants.[10] Several randomized controlled trials proved similar efficacies to that of the standard course of treatment and limited side effects.[11-15] In the Cochrane review, which comprised 956 infants from 19 randomized controlled trials, there was no significant difference in failure rates of PDA closure between infants treated with indomethacin and ibuprofen.[19] The risk of developing necrotizing enterocolitis was reduced with ibuprofen. There was less evidence of transient renal insufficiency in infants who received ibuprofen compared to indomethacin. No other important differences were observed for common neonatal morbidities.

Table 3 Effects on renal function in the indomethacin and ibuprofen groups.

	Indomethacin group (n = 26)	Ibuprofen group (n = 22)	p-value
Occurrence of oliguria[a] *(%)*	3 (11.5)	1 (4.5)	0.37
Serum creatinine (mg/dL)			
Before treatment	0.84±0.34	0.64±0.41	0.21[c]
After treatment	1.21±0.44[b]	1.11±0.72[b]	
Furosemide[d]	0.76±1.39	0.63±0.65	0.66

[a]Oliguria was defined as a urine output of 1 ml/kg/h or less during 24 hours.
[b]Serum creatinine concentrations were increased significantly after treatment in each group (indomethacin group, p = 0.001; ibuprofen group, p = 0.003).
[c]There were no statistically significant differences between the two groups (p = 0.21).
[d]Mean number of administrations of furosemide per patient.

Table 4 Complications in the indomethacin and ibuprofen groups.

	Indomethacin group (n = 26)	Ibuprofen group (n = 22)	p-value
IVH (%)	6 (23.1)	6 (27.3)	0.49
NEC (%)	1 (3.8)	2 (9.1)	0.43
ROP (%)	16 (61.5)	16 (72.7)	0.41
BPD (%)	24 (92.3)	18 (81.8)	0.39
Death (%)	4 (15.4)	4 (18.1)	0.54

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

As mentioned above, most of the previous studies demonstrate that treatment with indomethacin and ibuprofen have had similar effects to the present results regarding PDA closure. However, there are few published reports on the efficacy and safety of ibuprofen for PDA confined to ELBW infants. Van Overmeire et al.[11] studied the efficacy of indomethacin and ibuprofen administered to infants born at 24 to 32 weeks of gestation. They reported that the closure rates were 66% and 70% after the first course of treatment with indomethacin and ibuprofen, respectively. Lago et al.[13] enrolled infants born at 23 to 34 weeks of gestation. The efficacy after the first course of treatment was 69% and 73% for indomethacin and ibuprofen, respectively. These two studies established that infants of lower gestational age (28 weeks or less) had a lower pharmacological closure rate and underwent surgical ligation more frequently; however, there was no difference in the efficacy between the drugs within each category of gestational age. In the present study, the primary closure rate (indomethacin group, 65%; ibuprofen group, 59%) was lower than that reported in other studies involving larger premature infants, most likely because the enrolled patients were solely ELBW infants. However, the overall closure rates (indomethacin group, 88.5%; ibuprofen group, 81.8%) did not demonstrate a difference when compared to other studies. There was no statistically significant difference in the efficacy between the two drugs. The present study confirms that oral ibuprofen is as effective as intravenous indomethacin for the treatment of PDA, even in ELBW infants.

Several studies involving oral ibuprofen for ductal closure have been published.[20-22] Chotigeat et al.[20] reported PDA closure in seven of 15 premature infants (35 weeks or less) given oral ibuprofen and in ten of 15 premature infants given intravenous indomethacin (p = 0.46). Fakhraee et al.[21] reported that PDA was closed in all of the 18 premature infants (34 weeks or less) given oral ibuprofen, and in 15 of the 18 premature infants given oral indomethacin (p > 0.05). Aly et al.,[22] in a randomized pilot study, reported that PDA was closed in seven of nine premature infants (35 weeks or less) given oral ibuprofen, and in ten of 12 premature infants given intravenous indomethacin (p = 0.75). Gokmen et al.,[23] in a prospective randomized study, reported that oral ibuprofen was more effective than intravenous ibuprofen (84.6% *versus* 62%) for ductal closure in preterm infants (32 weeks or less, 1,500 g or less). The authors concluded that oral ibuprofen might constitute an alternative agent for the treatment of PDA. In addition, Sosenko et al.[24] recently studied the timing of ibuprofen treatment for PDA. They reported that patients with mild signs of PDA did not benefit from early PDA treatment compared with treatment delayed until the onset of clear hemodynamic signs.

There are not enough reports on the pharmacokinetics of oral ibuprofen in premature infants. Raju et al.[25] reported that ibuprofen was absorbed rapidly after oral administration, and peak concentrations in plasma were

observed after 1 to 2 hours in premature infants. Recently, Barzilay et al.[26] evaluated the pharmacokinetic profile of oral ibuprofen in premature infants, showing that oral ibuprofen levels peaked 8 hours after administration, and remained relatively stable for at least 24 hours. Several trials regarding the pharmacokinetics of oral ibuprofen in premature infants revealed a wide interindividual variability for plasma concentrations, elimination half-life, and area under the plasma concentration-time curve.[26-28] The slower absorption of oral ibuprofen, compared with the intravenous route, and the longer half-life probably prolonged the time of contact with the ductus, leading to a higher responsiveness. In addition, oral ibuprofen has the advantages of easy availability, simple administration, and reduced cost. In Korea, the use of intravenous indomethacin was suspended in April, 2010, and ibuprofen has been solely used as an alternative agent to promote ductal closure. The authors have used oral ibuprofen instead of intravenous ibuprofen due to the difficulties in obtaining the latter, as well as its higher cost.

Previous studies concluded that indomethacin treatment improves PDA closure, but is associated with increased renal side effects and more severe complications, such as necrotizing enterocolitis, gastrointestinal hemorrhage, and reduced cerebral intracellular oxygenation.[5-9] In the present study, though not significantly different, more infants treated with indomethacin presented a tendency to develop oliguria than infants treated with ibuprofen. Of the two cyclooxygenase isoenzymes (COX-1 and COX-2), COX-1 appears to be primarily involved in basal physiological processes of the kidney.[29] Although both isoenzymes are inhibited by ibuprofen and indomethacin, indomethacin is more potent against COX-1.[30]

The present study has several limitations. The major limitation is its retrospective design, and thus the present results may be vulnerable to confounding errors and bias. Second, this study may not have had sufficient statistical power for this outcome, due to the relatively small sample size. Future research should include increased sample size to increase the statistical power. A prospective randomized study based on a larger population is necessary for further conclusive data.

In summary, the present data indicate that oral ibuprofen is as efficacious as intravenous indomethacin for the treatment of PDA in ELBW infants. There are no differences between the two drugs with regards to safety. Oral ibuprofen could be used as an alternative agent for the treatment of PDA in ELBW infants.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890-900.
2. The Vermont-Oxford Trials Network: very low birth weight outcomes for 1990. Investigators of the Vermont-Oxford Trials Network Database Project. Pediatrics. 1993;91:540-5.
3. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics. 2006;117:1113-21.
4. Richards J, Johnson A, Fox G, Campbell M. A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. Pediatrics. 2009;124:e287-93.
5. Betkerur MV, Yeh TF, Miller K, Glasser RJ, Pildes RS. Indomethacin and its effect on renal function and urinary kallikrein excretion in premature infants with patent ductus arteriosus. Pediatrics. 1981;68:99-102.
6. 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.
7. Rennie JM, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. Arch Dis Child. 1986;61: 233-8.
8. Edwards AD, Wyatt JS, Richardson C, Potter A, Cope M, Delpy DT, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet. 1990;335:1491-5.
9. McCormick DC, Edwards AD, Brown GC, Wyatt JS, Potter A, Cope M, et al. Effect of indomethacin on cerebral oxidized cytochrome oxidase in preterm infants. Pediatr Res. 1993;33:603-8.
10. Poon G. Ibuprofen lysine (NeoProfen) for the treatment of patent ductus arteriosus. Proc (Bayl Univ Med Cent). 2007;20: 83-5.
11. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med. 2000;343:674-81.
12. Sekar KC, Corff KE. Treatment of patent ductus arteriosus: indomethacin or ibuprofen? J Perinatol. 2008;28:S60-2.
13. Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L, 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.
14. Aranda JV, Thomas R. Systematic review: intravenous Ibuprofen in preterm newborns. Semin Perinatol. 2006;30:114-20.
15. Su PH, Chen JY, Su CM, Huang TC, Lee HS. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Pediatr Int. 2003;45:665-70.
16. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92:529-34.
17. Coceani F, Olley PM. The response of the ductus arteriosus to prostaglandins. Can J Physiol Pharmacol. 1973;51:220-5.
18. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med. 1976;295:526-9.
19. 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;(4):CD003481.
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:S563-9.
21. 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.
22. 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.

23. 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;158:549-54.
24. Sosenko IR, Fajardo MF, Claure N, Bancalari E. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. J Pediatr. 2012;160:929-35.
25. Raju NV, Bharadwaj RA, Thomas R, Konduri GG. Ibuprofen use to reduce the incidence and severity of bronchopulmonary dysplasia: a pilot study. J Perinatol. 2000;20:13-6.
26. Barzilay B, Youngster I, Batash D, Keidar R, Baram S, Goldman M, et al. Pharmacokinetics of oral ibuprofen for patent ductus arteriosus closure in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2012;97:F116-9.
27. Sharma PK, Garg SK, Narang A. Pharmacokinetics of oral ibuprofen in premature infants. J Clin Pharmacol. 2003;43:968-73.
28. Van Overmeire B, Touw D, Schepens PJ, Kearns GL, van den Anker JN. Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther. 2001;70:336-43.
29. Smith WL, DeWitt DL. Biochemistry of prostaglandin endoperoxide H synthase-1 and synthase-2 and their differential susceptibility to nonsteroidal anti-inflammatory drugs. Semin Nephrol. 1995;15:179-94.
30. Vane JR, Botting RM. Mechanism of action of anti-inflammatory drugs. In: Sinzinger H, Samuelsson B, Vane JR, Paoletti R, Ramwell P, Wong PY-K, editors. Recent advances in prostaglandin, thromboxane, and leukotriene research. Vol. 433 of Advances in experimental medicine and biology. New York: Plenum Press; 1997. p. 137-8.