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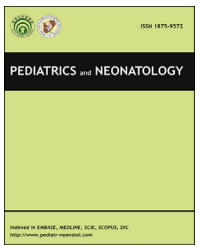

ORIGINAL ARTICLE

Repeated Courses of Oral Ibuprofen in Premature Infants with Patent Ductus Arteriosus: Efficacy and Safety

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Key Words
ibuprofen;
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preterm infants

Background: There are limited data about the results of repeated oral ibuprofen (OIBU) treatment. This study aimed to describe patent ductus arteriosus (PDA) closure rates and adverse events after repeated courses of OIBU in premature infants with PDA.
Methods: Preterm infants with hemodynamically significant (hs)PDA were enrolled in the study. If the first course of OIBU treatment failed, a second and, if required, third course was administered.
Results: A total of 100 patients received OIBU. In six patients, treatment could not be completed due to death ($n = 3$) and side effects ($n = 3$). In three patients, adverse effects related to OIBU (thrombocytopenia and impairment of renal function) developed during the first course. During the second and third courses, no new adverse event occurred. After all courses, the PDA closure rate was determined as 88%. The rate was 71% after the first course, 40% after the second course, and 35% after the third course. Although the second course resulted in a significant increase in the closure rate ($p < 0.05$), the rate did not increase significantly with the third course ($p > 0.05$). The mean postnatal age at the start of the first dose of OIBU was not significantly different among the responders and non-responders to the first course ($p > 0.05$). Clinical characteristics did not affect the closure rate significantly. The number of courses did not have a significant effect on death, when gestational age and birth weight were used as covariates [$p = 0.867$, Exp(B) = 0.901, 95% confidence interval = 0.264–3.1].
Conclusion: A second course of OIBU seems effective and safe for use in preterm infants with hsPDA. Although a third course of OIBU results in PDA closure in some additional patients, the

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difference is not significant. Thus, surgical ligation should be considered after the second course, especially in patients with signs of severe heart failure.

1. Introduction

Hemodynamically significant patent ductus arteriosus (hsPDA) is one of the most common problems in premature infants. Many studies have shown that cyclooxygenase (COX) inhibitors [indomethacin, ibuprofen (IBU)][1–3] and surgical closure[4] are effective in closing the ductus arteriosus in premature infants. However, the debate is ongoing about the selection of the treatment method, and there is still no consensus about the benefit—side effect relation. Because of the reported association of surgical ligation with an increased risk of chronic lung disease, retinopathy of prematurity, and neurodevelopmental impairment compared to indomethacin therapy,[4,5] repeated courses of COX inhibitors are being tried. Although there are previously published data on the efficacy of repeated courses of indomethacin,[6,7] the data available regarding repeated courses of intravenous (IV) IBU are limited.[8,9] Repeated courses of IV IBU are reported to be effective for closure, with a low complication rate.[9] To the best of our knowledge, there is no report in the current literature on the effect of repeated courses of oral ibuprofen (OIBU) on the ductal closure rate. In the present study, we aimed to evaluate the PDA closure rates and frequency of complications related to IBU after single and multiple courses of OIBU in a population of premature infants with hsPDA.

2. Methods

The medical records of preterm infants who had been followed in a single-center tertiary neonatal unit from 2008 to 2010 were evaluated retrospectively. Clinical features of 100 preterm babies with hsPDA who were treated with OIBU were analyzed. Gestational age (GA), birth weight (BW), gender, 5 minute Apgar score, antenatal steroid usage, age at first IBU administration, vasopressor (dopamine, dobutamine) use, and echocardiographic findings were recorded. Institutional Review Board approval (Ethics committee of Ataturk University Medical Studies Department, Erzurum) was obtained for the study. For diagnosis and follow-up, echocardiography and Doppler ultrasonography were used for PDA.

In our unit, preterm babies with clinical signs of PDA (e.g., cardiac murmur, bounding pulses, hyperdynamic precordium, and/or significant respiratory distress) are evaluated clinically and by echocardiography. If PDA is detected, it is considered to be hemodynamically significant and to necessitate treatment when the ductus is moderate to large in size (diameter of ductal area at the narrowest site $>$ 1.5 mm on color Doppler echocardiography), with evidence of left-to-right ductal shunting and an increased left atrium to aortic ratio ($>$ 1.3). The first dose of IBU (10 mg/kg) is administered via nasogastric tube. Afterwards, two additional doses of OIBU of 5 mg/kg are given at 24-hour intervals (1 course).[10] The patient is assessed clinically and echocardiographically at 24 hours following the third dose. The treatment is accepted to be successful if clinical signs improve, PDA flow disappears, or the ductal shunt is minimal on echocardiography. If hsPDA persists, a second and, if required, third course of IBU treatment is initiated. Indications for immediate surgical closure are congestive heart failure and respiratory instability due to PDA after two courses of OIBU and a persistent PDA with a significant left-to-right shunt after the third course.

OIBU is not administered in the presence of major congenital anomalies, Grade 3 intraventricular hemorrhage according to Papile classification, tendency to hemorrhage, hyperbilirubinemia requiring blood exchange, and necrotizing enterocolitis (NEC) or suspected NEC, or in patients with serum creatinine $>$ 1.6 mg/dL, blood urea nitrogen (BUN) $>$ 50 mg/dL, and platelet count $<$ 60,000/mL^3. IBU-administered patients are followed for renal, gastrointestinal, and cerebral side effects. Serum BUN, creatinine, sodium levels, and platelet counts are evaluated before and after treatment in each course. During treatment, elevation in serum creatinine level to $>$ 1.6 mg/dL and decreases in urine output to $<$ 1 mL/kg/h, serum sodium level to $<$ 125 mEq/L, and platelet count to $<$ 60,000/mL^3 are accepted as side effects of IBU.

2.1. Statistical analysis

Statistical analysis was performed with SPSS for Windows version 20 (IBM, Armonk, NY, USA). The normality of the distribution of the quantitative variables was assessed by Shapiro—Wilk test. Descriptive statistics are shown as mean ± standard deviation or median (minimum—maximum) for constant variables. Nominal variables are defined as number of cases and percentage. The significance of differences between groups in terms of mean values was evaluated with Mann—Whitney *U* test. Nominal variables were analyzed using Pearson's Chi-square test or Fisher's exact test. Cochran's Q and McNemar tests were used for evaluation of the significance of an increase in cumulative closure rates with an increasing number of courses. Binary logistic regression analysis was used to analyze the effect of repeated courses on death. A p value $<$ 0.05 was accepted as significant.

3. Results

Five hundred and seventy-six preterm babies (gestational age $<$ 37 weeks) were admitted to the Newborn Intensive Care Unit of Atatürk University, School of Medicine (Erzurum, Turkey), between March 2008 and May 2010. PDA was detected in 134 of them. Shunting in 34 (25.3%) of the 134 patients was hemodynamically insignificant and the PDAs

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closed spontaneously. The remaining 100 babies in whom OIBU treatment was started were included in this study. Three patients were excluded due to death before completion of a full course of OIBU. The data of the remaining 97 patients were evaluated.

Of the 97 patients, 52 (53.6%) were male and 45 (46.4%) were female infants. Mean GA was 30.6 ± 3.4 weeks (range, 24–36 weeks) and BW was 1220 ± 480 g (range, 490–3000 g). Sixty-nine (71.1%) of the patients were very low birth weight or extremely low birth weight infants. Demographic features of the patients are given in Table 1 and clinical features in Table 2. There was only one patient with a length of hospital stay of 3 days. He was diagnosed as having hsPDA on the Postnatal Day 3 at a pediatric cardiology outpatient clinic. The infant was a 35-week infant. Because of the clinical condition of the patient, we thought that present ductus should be closed. The patient responded to OIBU. After the last dose of ibuprofen, PDA was closed and the family discharged the patient without permission of the newborn team. Follow-up of the patient was done at the outpatient clinic. No adverse event related to OIBU developed and duct reopening was not observed at follow-up visits.

3.1. Adverse events

In three patients, IBU was stopped prior to completion of a whole course of OIBU due to the development of thrombocytopenia ($n = 1$), thrombocytopenia and impairment of renal function ($n = 1$), and impairment of renal function ($n = 1$). These were considered as complications of OIBU. All complications developed during the first course, and when IBU was ceased, the PDA remained patent. Complications resolved after discontinuation of the drug. These patients were not considered in the calculation of closure rates.

3.2. Closure rate

PDA was closed in 67 (71%) of 94 patients after the first course. No reopening was observed among these patients. A second course was administered in 27 (29%) patients, and in 11 (40%) patients the PDA was closed after the second course. Among the responders to the second and third courses, no reopening was observed. Two patients, in whom the second course failed, underwent surgical ligation due to ongoing significant heart failure. The neonatology team carefully evaluated the patients and could not identify any other reason that could explain the present congestive heart failure and respiratory instability. The patients did not have any other known congenital heart disease. A third course was administered to the remaining 14 patients, and in five (35%) the PDA closed. In the remaining nine patients, surgical ligation was performed (Figure 1). The cumulative closure rate was 71% after the first course, 83% after the second, and 88% after the third. When all groups were taken into account, increasing the course number resulted in a significant increase in the cumulative closure rate (Cochran's $Q = 25.125$, $p < 0.001$). Comparison of groups individually showed that the closure rate with a second course increased significantly ($p = 0.001$); however, there was no significant increase in the closure rate following the third course ($p = 0.063$; Figure 2).

Symptomatic PDA was diagnosed at a mean 97.4 ± 130.7 postnatal hours (range, 24–624 hours). In 76 of 94 infants, the first course was started during the first four postnatal days (4/94 during the first 48 hours), and in 72.4% (55/76) the PDA closed. In 18 infants, the first course was started after Postnatal Day 4 (≥ 5 days), and in 66.7% (12/18) the PDA closed. The difference was not statistically significant ($\chi^2 = 0.231$, $p = 0.631$).

A comparison of patients who were given single and multiple courses in terms of clinical features is given in Table 3. Clinical features other than the need for inotropic agents were not significantly different between responders and non-responders to the first course. Need for inotropic agents was more frequent among patients who needed multiple courses ($p = 0.007$).

Table 1 Demographic features of patients in whom at least one oral ibuprofen course could be completed.

Variables	$n = 97$
Sex	
Male	50 (53.2)
Female	44 (46.8)
Gestational age (y)	30.6 ± 3.4 (24–36)
Gestational age groups (wk)	
< 30	38 (40.4)
30–34	41 (43.6)
> 34	15 (16.0)
Birth weight (g)	1220 ± 480 (490–3000)
Birth weight groups (g)	
< 1000	30 (31.9)
1000–1500	37 (39.4)
> 1500	27 (28.7)

Data are presented as *n* (%) or mean ± standard deviation (range).

Table 2 Clinical features of the cases ($n = 94$).

	n	%
Use of antenatal steroids	36	38.3
Chorioamnionitis	4	4.3
Asphyxia	14	14.9
RDS	67	71.3
Sepsis	56	59.6
Use of inotropic agents	39	41.5
Course No.		
1	67	71.3
2	13	13.8
3	14	14.9
IVH	4	4.3
PVL	1	1.1
BPD	31	33
NEC, isolated perforation	8	8.5
Death (mean, d)	24	25.5
ROP	16	17
Length of hospital stay (d, range)	44	(3–126)

BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity.

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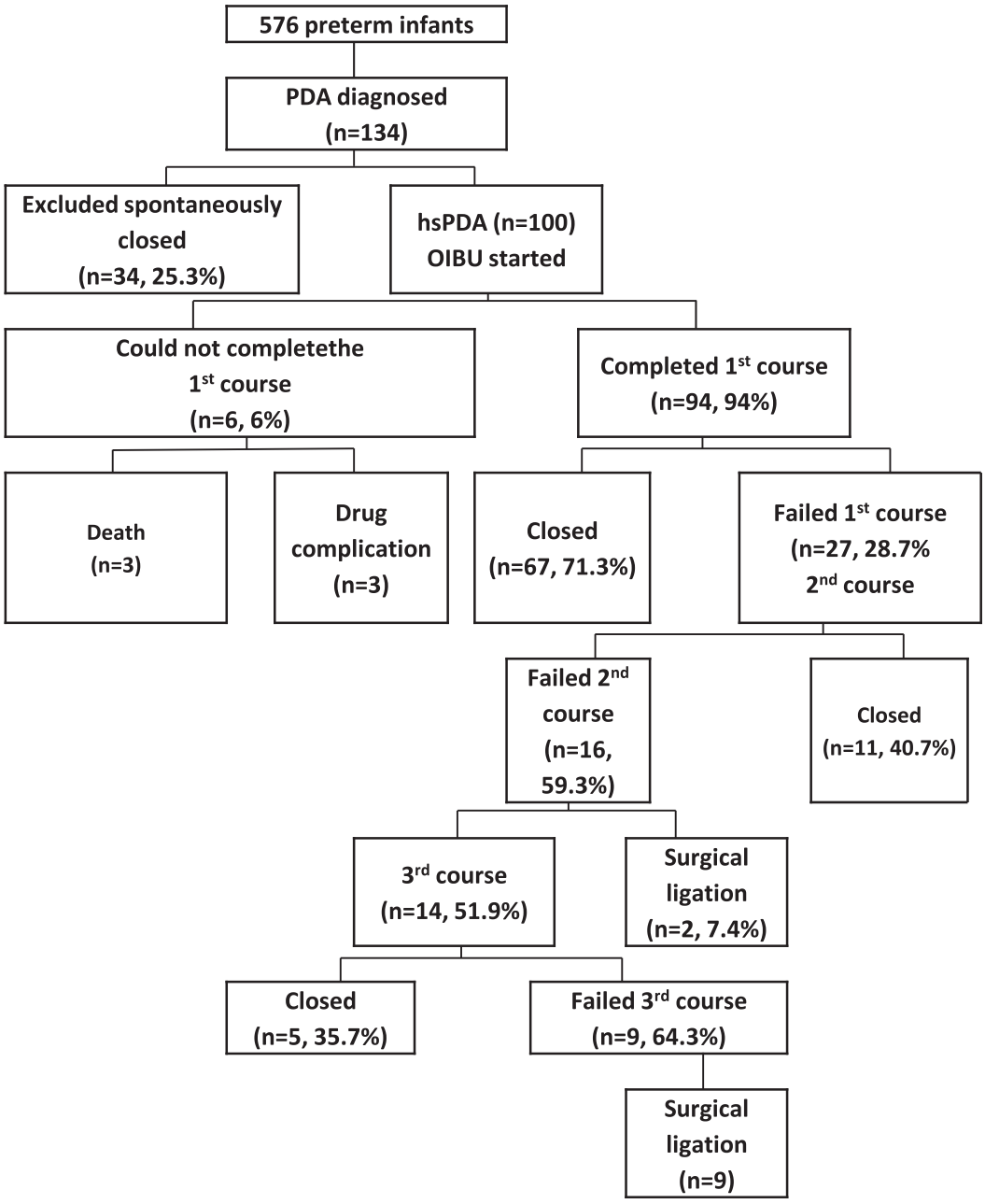

Figure 1 A flowchart of the study population. hsPDA = hemodynamically significant; OIBU = oral ibuprofen; PDA = patent ductus arteriosus.

3.3. Fluid uptake and urine output

Fluid intake and urine output were evaluated before the treatment and during each course. Daily fluid intake and urine output were not significantly different between patients in whom PDA was closed with single and multiple courses (Table 3). Mean daily fluid intake was similar between responders and non-responders to the first course (Table 3).

3.4. Plasma creatinine level and platelet counts

There were no significant differences in mean urea levels and median platelet counts before and after each course of treatment (Table 3).

3.5. Death

A total of 24 patients died (25.5%). The mean GA (27.4 ± 2.4 weeks) and the mean BW (883.5 ± 221.9 g) of the deceased patients were significantly lower than those of surviving patients (31.6 ± 2.9 weeks, 1498.0 ± 582.3 g, respectively). When the GA and BW were added to the model as covariates, binary logistic regression analysis showed that course number had no significant effect on death [$p = 0.867$, Exp(B) = 0.901, 95% confidence interval = 0.264—3.1]. Of 83 patients whose PDAs closed after single or multiple courses of OIBU, 33.9% died. Of 11 non-responder patients, 37.5% died. The difference was not significant ($p = 0.571$).

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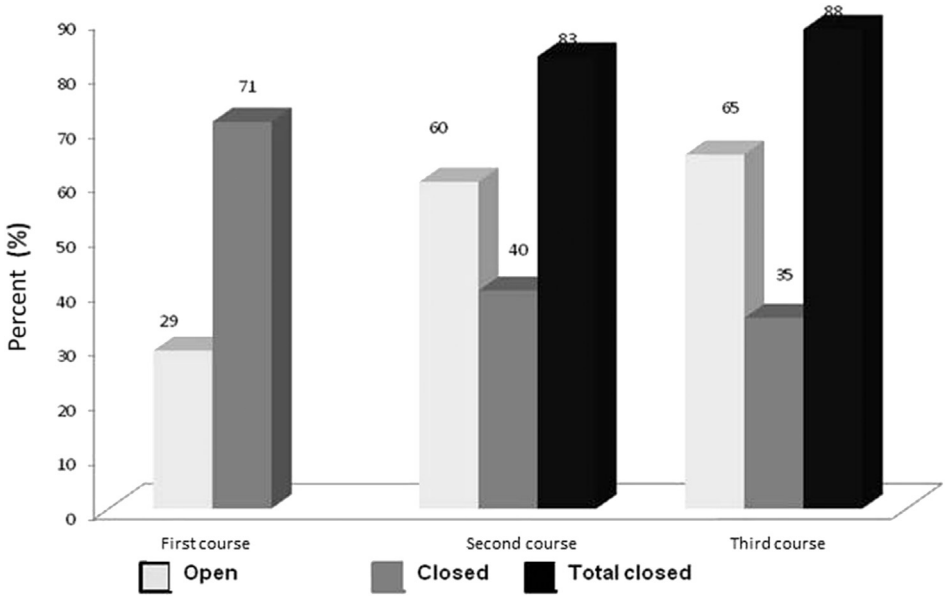

Figure 2 Closure rates after each course of oral ibuprofen.

4. Discussion

There is a significant amount of published data on the efficacy of single-course OIBU;[11–18] however, to the best of our knowledge, no study in the English literature has reported the results of repeated courses of OIBU. The present study provides important information about the PDA closure rates in preterm infants who received single or multiple courses of OIBU for closure of hsPDA.

After the first course of treatment with OIBU, the PDA closure rate was reported as between 77% and 100%.[10–18] If the PDA does not close with pharmacological therapy, surgical ligation is the treatment of choice. Use of multiple courses of IV IBU treatment has been reported since 2009.[8,9] Richards et al[8] reported a PDA closure rate of 45% with a single course and of 40.3% with a second course of IV IBU. They gave a third course to only three patients. They showed that closure rates were similar with the first and second IBU treatments in very low birth weight infants, and they emphasized that second-course treatment could be considered prior to surgical ligation in very low birth weight babies in whom the first course had failed. van der Lugt et al[9] reported the closure rates as 66.5% (109/164), 55.8% (24/43), and 54.5% (6/11) for first, second, and third courses, respectively, and the difference between the closure rates was not significant. In our study, the closure rate was 71% after the first course, 40% after the second course, and 35% after the third course. Thus, total closure rates of 71% (67/94) with the first course, 82.9% (78/94) with the second course, and 90.2% (83/92) with the third course were achieved. Because of the administration route and the different BWs and GAs, it is hard to compare our results to those of Richards et al[8] or van der Lugt et al[9] Although the cumulative closing rate increased significantly (Cochran's $Q = 25.125$, $p =< 0.001$) with an increasing course number, a third course did not increase the closure rate significantly ($p = 0.063$: Figure 1). This result suggests that although a third course of OIBU results in PDA closure in some additional patients, surgical ligation may be considered after the second course, especially in patients with signs of severe heart failure. However, this suggestion needs to be evaluated by comparing the clinical outcomes of patients who were operated after two and three courses of OIBU.

van der Lugt et al[9] reported a positive correlation between the postnatal age at the start of the first dose of IBU and the need for a second course of IBU. The closure rate in patients who received a first course in the first 4 postnatal days was found to be significantly higher.[9] However, our study did not indicate such a relation (Table 3).

The most frequently seen complications of IBU in premature infants are: thrombocytopenia, oliguria, decrease in serum sodium level, increase in serum creatinine level, decrease in urinary sodium excretion, and reductions in glomerular filtration rate and renal blood flow, together with an increase in renal vascular resistance, acute renal failure and feeding intolerance and a potential increase in the risk for kernicterus.[19–27] The reported rates have differed significantly.[10,13,16,17,28,29] van der Lugt et al[9] reported oliguria in 10 of 164 infants, thrombocytopenia in four of 164, and increased serum creatinine level in one of 164 infants. The complication developed after the second course in only one infant and during the first course in the others. In our study, OIBU-related complications were observed in only three patients (3.2%). As in the study of van der Lugt et al[9], none of the complications observed in our study was severe, and all resolved after discontinuation of the drug and were not related to repeated courses.

Although most of our patients were low birth weight or very low birth weight preterm infants, the mean GA of our patients was relatively higher, and this may have affected our results. For premature infants, many factors may affect patient outcome. Thus, we could not analyze the effects of repeated courses of OIBU on the occurrence of the common problems of preterm infants like retinopathy of

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Table 3 Comparison of patients who were given single and multiple courses of oral ibuprofen in terms of clinical features

Variables	1 course (responders) ($n = 67$)	Multiple courses (non-responders to 1st course) ($n = 27$)		p
Gestational age (wk)	30.8 ± 3.6	30.1 ± 2.9	χ^2	0.352
Gestational age groups (wk)				
< 30	26	12	2.065	0.356
30–34	28	13		
>34	13	2		
Postnatal age at 1st course (h)	99.3 ± 143.6 (24–624)	92.7 ± 93.4		0.825
Postnatal age at 1st course (d)				
≤ 4	55	21	0.231	0.631
≥ 5	12	6		
Birth weight (g)	1398 ± 608	1191 ± 484		0.102
Presence of				
Chorioamnionitis	4	3	0.738	0.390
Perinatal asphyxia	10	4	0.000	0.989
Sepsis	36	20	3.307	0.069
Use of antenatal steroids	28 (41.8)	8 (29.6)		0.272
Use of inotropic agents	22 (32.8)	17 (63.0)		0.007
Success rate	67 (71)	16 (59.0)		< 0.001

Average fluid intake and urine output

	Before the treatment	1st course			2nd course			3rd course			
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	
Fluid intake (mL/kg/d)	164 ± 65	145 ± 60	166 ± 59	196 ± 66	172 ± 57	183 ± 67	182 ± 103	172 ± 83	176 ± 74	183 ± 81	> 0.05
Urine output (mL/kg/h)	3.2 ± 1.1	3.6 ± 1.5	3.7 ± 1.6	4.2 ± 1.6	4.3 ± 1.2	5.3 ± 1.0	3.8 ± 0.7	6.3 ± 0.5	4.1 ± 0.3	4.8 ± 0.3	> 0.05

	Closed after 1st course ($n = 67$)	Remained patent after 1st course ($n = 27$)	
Fluid intake (ml/kg/dL	98.8 ± 27.9	106.7 ± 25.9	> 0.05

Plasma creatinine level and platelet counts before and after each course of oral ibuprofen

	Pretreatment	After 1st course	After 2nd course	After 3rd course	
Serum creatinine mg/dL	0.67 ± 0.19	0.64 ± 0.17	0.69 ± 0.22	0.69 ± 0.21	> 0.05
Platelet count/mL^3 (median)	2.2×10^5	1.9×10^5	2.0×10^5	3.3×10^5	> 0.05

Data are presented as n, n (%), or mean $\pm$ standard deviation, unless otherwise indicated.

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prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, and NEC.

In conclusion, in preterm babies with hsPDA, repeated courses of OIBU seem to be effective and safe in PDA closure. However, the closure rate does not increase significantly with a third course. Thus, surgical ligation may be offered after a failed second course, especially in the case of severe heart failure. New, prospective studies are needed to evaluate the effects of repeated courses of OIBU on the prevalence of prematurity problems and the possible effect of early surgical ligation on the prevention of these problems with early elimination of ductal shunt.

Conflict of interest

All authors declare no conflicts of interest.

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