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Research Article

Acetaminophen vs. Ibuprofen in Early Treatment of Patent Ductus Arteriosus in Preterm Infants: A Non-Inferiority Randomized Clinical Trial

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Abstract

Introduction: Patent ductus arteriosus (PDA) is one of the most common cardiovascular problems that occur in preterm infants. This trial aimed to investigate whether acetaminophen is non-inferior to ibuprofen in closing PDA in very preterm infants.

Patients and Methods: A randomized non-inferiority trial was conducted on preterm infants with a gestational age <32 weeks, birth weight <1500 g, postnatal age <72 h, and PDA size >1.5 mm. Infants were randomly assigned to receive either intravenous acetaminophen (n=52) or rectal ibuprofen (n=52). The primary study outcome was the ductus closure within 24 hours after completion of the first and/or second course of pharmacological treatment.

Results: The incidence of PDA closure after completion of the first and/or second course of pharmacological treatment was identical 81% (42/52). After the first course of treatment, PDA closed in 37 infants (71%) in the ibuprofen group and 41 patients (79%) in the acetaminophen group (p>0.05). The median age (IQR) at the time of ductus closure was also the same in both groups, 5 (5-6) days. There were no statistically significant differences between the groups in the incidence of severe complications associated with preterm birth and mortality (p>0.05). No side effects related to pharmacological treatment were detected.

Conclusions: Acetaminophen is non-inferior to ibuprofen for the closure of PDA in very preterm infants.

***Keywords:** patent ductus arteriosus; PDA; acetaminophen; ibuprofen; very preterm infants.*

Introduction

Patent ductus arteriosus (PDA) is one of the most common cardiovascular problems that occur in preterm infants. An increase in the concentration of prostaglandins in the blood results in the maintenance of ductal patency, therefore justifying appropriate pharmacological interventions.[1] Nonsteroidal anti-inflammatory drugs (ibuprofen and indomethacin) inhibit cyclooxygenase (COX), an enzyme necessary for the conversion of arachidonic acid to prostaglandins G2. In contrast to ibuprofen, acetaminophen acts on the peroxidase region of the prostaglandin synthetase (PGHS) complex, blocking the synthesis of prostaglandin H2, which is the main precursor of prostaglandins with vasoactive action.[1]

Historically, ibuprofen and indomethacin are the two most commonly used drugs for the treatment of hemodynamically significant PDA (HSPDA) in preterm infants.[2,3] The rate of successful PDA closure with ibuprofen after the first and second courses does not differ significantly from indomethacin – 70% and 50%, respectively.[1] The Cochrane review of randomized controlled trials (n=2842) showed that ibuprofen was no less effective than indomethacin.[4] Currently, ibuprofen is the drug of choice because of significantly better safety profile and known reduced risk of necrotizing enterocolitis (NEC), oliguria, and elevated serum creatinine. A recent systematic review and meta-analysis of randomized trials showed that a high dose of oral ibuprofen (20/10/10 mg/kg) was associated with a higher likelihood of HSPDA closure compared to standard doses of intravenous ibuprofen, or indomethacin.[5]

The results of the Cochrane Review of 8 randomized trials (n=916) showed that acetaminophen was as effective in PDA closing as ibuprofen and indomethacin.[6] PDA closure rates with acetaminophen range from 71% to 100%, but in most studies this drug has been used in infants with a gestational age of more than 28 weeks, so the efficacy and side effects of acetaminophen in the population of extremely preterm infants remain largely unknown.[6] However, several studies showed a lower incidence of PDA closure in infants treated with acetaminophen compared to those treated with ibuprofen.[7,8] Possible advantages of acetaminophen over ibuprofen are still being studied, as available data suggest that acetaminophen has no peripheral vaso-constrictive effects, and therefore has a better safety profile in preterm infants. Thus, it can be an attractive equally efficient, yet safer alternative to the traditional ibuprofen or indomethacin.

This randomized controlled non-inferiority trial aimed to compare the efficacy and safety of intravenous acetaminophen with rectal ibuprofen in the treatment of PDA in very preterm infants. We hypothesized that acetaminophen is non-inferior to ibuprofen in the rate of successful PDA closure.

Methods

Study design and patients

Data from 104 preterm infants enrolled in a randomized controlled trial (n=208), with the goal to evaluate comparative efficacy and safety of the early treatment and expectant management of PDA in very preterm infants (*ClinicalTrials.gov* - NCT03860428), between March 2019 and July 2021, were used in this study (Fig. 1). This trial was conducted in the neonatal intensive care unit (NICU) of the Lviv Regional Clinical Hospital, Ukraine. The trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials. It was approved by the local ethics committee, and patients were recruited after written parental consent was obtained.

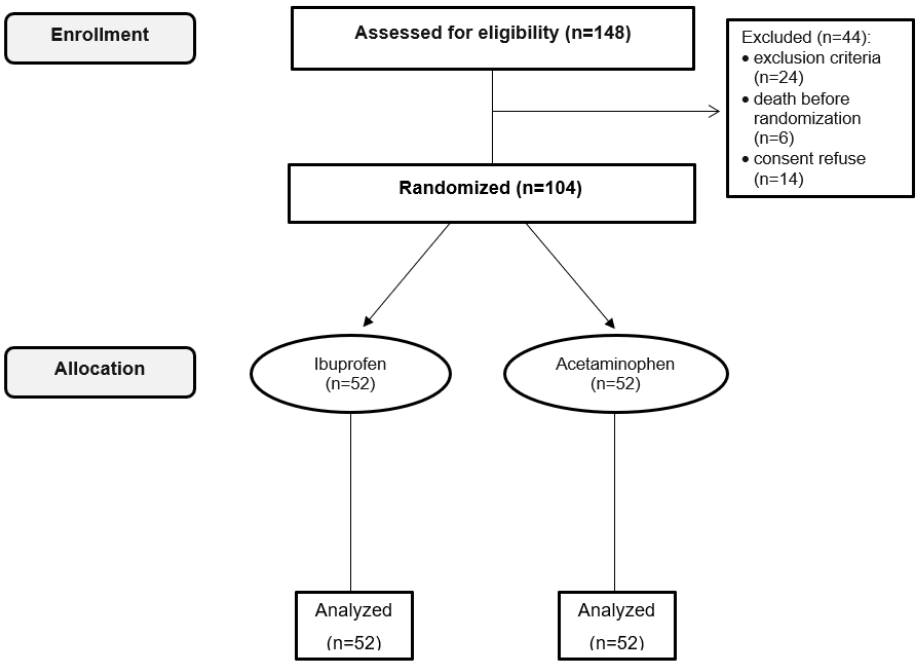

Fig. 1. *Flow chart of study patients.*

The trial enrolled infants with a birth weight <1500 g, gestational age <32 weeks, postnatal age <72 h, and PDA diameter >1.5 mm. Patients with congenital heart defect other than PDA, significant congenital anomalies, clinically apparent hemorrhagic syndrome, suspected/apparent NEC, any intraventricular haemorrhage (IVH) within the first 48 hours or IVH grade 3-4 at in the first 72 hours, platelet count of <50.000/mm^3, oliguria <1 ml/kg/h, and absence of informed consent of the parents were excluded.

After informed consent was obtained, the first echocardiographic evaluation was performed at a chronological age between 24 and 72 hours. When PDA size measured more than 1.5 mm and a predominantly left-to-right shunt was observed, the patient was randomized to either ibuprofen or acetaminophen group. The randomization was performed using a computer-generated random sequence of numbers.

Interventions

Due to unavailability of intravenous ibuprofen in our settings, the medication was administrated rectally at an initial dose of 20 mg/kg, followed by 10 mg/kg at 24 and 48 hours. Acetaminophen was given intravenously, 15 mg/kg/dose every six hours for three days.

Echocardiographic evaluation was performed at least 12 hours after the last dose of the first course. If the ductus was closed, no further investigation or treatment followed. Ductus arteriosus was considered closed if it could not be visualized using colour Doppler imaging, or if its size was <0.5 mm.[9]

Study outcomes

The efficacy and safety of early PDA treatment with ibuprofen and acetaminophen in very preterm infants were evaluated until death, postmenstrual age (PMA) of 36 weeks, or hospital discharge.

The primary outcome of this trial was the ductus closure within 24 hours after completion of the first and/or second course of pharmacological treatment.

The secondary study outcomes were:

- PDA closure within 24 hours after the first course of pharmacological treatment
- PDA re-opening rate
- Need for surgical ligation of PDA
- Incidence of bronchopulmonary dysplasia (BPD), NEC (stage Bell ≥ IIA), retinopathy of prematurity (ROP), severe IVH (grade 3-4), gastrointestinal bleeding, pulmonary haemorrhage, and oliguria < 1 ml/kg/h
- Age at the administration of full volume of enteral nutrition (160 ml/kg/day)
- Mortality

Echocardiographic assessment

All patients underwent planned daily echocardiographic evaluation within the first 10 days after birth, with a follow-up examination at 28 days of life and PMA of 36 weeks and/or discharge (whatever came first). Echocardiographic examination was performed according to recently published guidelines using two-dimensional, M-mode, colour flow mapping, and Doppler imaging.[10] Echocardiographic indices were obtained from standard subxiphoid, precordial, apical, and suprasternal imaging windows using standard transducers (Samsung Medison SonoAce X8 ultrasound machine, South Korea). The PDA size was measured at the narrowest point of the parasternal short-axis view. The pattern of PDA flow was registered from the parasternal short-axis window. The ratio of left atrial to aortic root diameter was calculated in M-mode obtained in the parasternal long-axis view.

Clinical data and monitoring

Standard protocols of respiratory and hemodynamic support, disease management, nutrition, as well as routine vital signs monitoring, were applied to all newborns. Overall illness severity on the first day of hospitalization was standardly assessed with the SNAPPE-II scores.[11] BPD was defined as the need for oxygen or respiratory support at 36 weeks' PMA and/or hospital discharge according to the consensus recommendations of the National Institutes of Child *Health and Human Development* in the modification of Walsh et al.[12,13] IVH and periventricular leukomalacia (PVL) were assessed by head ultrasound and on autopsy when applicable. The severity of IVH was classified according to Papille.[14] NEC was diagnosed based on Bell criteria.[15]

Sample Size Estimation and Statistical Analyses

The observed rate of PDA closure with ibuprofen treatment in one of the previous studies was 97%.[16] Assuming an equal rate of closure for acetaminophen with a non-inferiority margin of 10%, one-sided alpha error of 5%, and power of 90%, 100 neonates would be required in this trial. However, taking into account the relatively high mortality in infants with gestational age <32 weeks and birth weight <1500 g in our settings, we included 104 babies. The primary outcome of the rate of PDA closure was compared between the study groups by calculating the RR expressed with 95% CI.

Standard methods of descriptive and comparative analyses were used applying the χ^2, Mann-Whitney, and Wilcoxon criteria. Nonparametric data are presented as a median (IQR). All values were considered significant if $p < 0.05$.

Results

During the trial period from March 2019 to July 2021, 148 infants with gestational age <32 weeks and birth weight <1500 g were admitted to the neonatal intensive care unit at Lviv Regional Clinical Hospital. Forty-four of the 104 infants were excluded before enrolment according to the exclusion criteria (Fig.1). 52 infants received intravenous acetaminophen and 52 patients were treated with rectal ibuprofen within the first 72 h of life.

The study groups were not different in terms of gestational age and birth weight. There were no differences between the groups in maternal infectious morbidity during pregnancy, the incidence of the most common complications of pregnancy and delivery, and frequency of antenatal steroids use. The clinical characteristics of the groups are summarized in Table 1.

Table 1. Comparative perinatal data of the patients.

Characteristics	Ibuprofen group (n=52)	Acetaminophen group (n=52)	*p*
Gestational age, wks.	28.5 (27-30)[1]	28.0 (27-29.5)	0.34
Birth weight, g	1190 (840-1360)	990 (820-1250)	0.22
Male	23 (44)[2]	29 (56)	0.24
Small for gestational age	4 (8)	9 (17)	0.14
Pre-eclampsia	14 (27)	11 (21)	0.49
Preterm rupture of the membranes	12 (23)	16 (31)	0.38
Clinical chorioamnionitis or fever >38° C during labour	5 (10)	2 (4)	0.40
Placental abruption	14 (27)	10 (19)	0.35
Antenatal steroids	38 (73)	38 (73)	1.00
Caesarean section	32 (62)	23 (44)	0.08
Apgar score at the 1st min	5 (4-6)	5 (3-5)	0.28
Apgar score at the 5th min	6 (5-6)	6 (5-6)	0.27
Mask ventilation after birth	8 (15)	7 (13)	0.78
Intubation and ventilation after birth	29 (56)	37 (71)	0.10
Surfactant therapy	42 (81)	45 (87)	0.43
The first dose of surfactant, hours	1 (0.7-3.5)	1 (0.9-2)	0.81
SNAPPE-II scores	23 (18-36.5)	24.5 (16.5-34)	0.57

Notes: 1 – median (interquartile range); 2 – number of cases (%).

Ibuprofen and acetaminophen did not differ in their effectiveness. The frequency of successful ductus closure 24 hours after completion of the first and/or second course of pharmacological treatment was the same in the groups and was 81% (Table 2). The incidence of severe complications associated with preterm birth, mortality, and causes of death did not differ between the groups (Table 3). There was no statistically significant difference between the groups for secondary outcomes. Incidence of BPD, severe IVH, ROP, NEC (stage Bell ≥ IIa), sepsis, PVL at a PMA of 36 weeks or discharge did not significantly differ between the groups. The duration of respiratory support and the median age at the administration of full volume of enteral nutrition, incidence of oliguria, renal failure, gastrointestinal and pulmonary haemorrhage did not differ significantly between the groups either.

Table 2. Comparative primary and secondary outcomes in the groups.

Outcomes	Ibuprofen group (n=52)	Acetaminophen group (n=52)	RR (95 % CI)	*p*
Ductus closed within 24 hours after completion of the first and/or second course of pharmacological treatment	42 (81)[1]	42 (81)	1 (0.829-1.206)	1.00
Ductus closed after the first course of pharmacological treatment	37 (71)	41 (79)	1.1 (0.886-1.385)	0.09
PDA re-opening	8 (17)	9 (20)	1.1 (0.471-2.688)	0.79
The need for surgical ligation of PDA	0	0	-	-
Bronchopulmonary dysplasia	16 (31)	13 (25)	0.81 (0.435-1.513	0.51
Retinopathy of prematurity	17 (33)	14 (27)	0.82 (0.455-1.491)	0.52
NEC (Bell ≥ IIA)	5 (10)	4 (8)	0.8 (0.227-2.812)	0.73
Severe IVH (3-4 grade)	9 (18)	8 (15)	0.89 (0.371-2.124)	0.76
Oliguria	4 (8)	5 (10)	1.25 (0.355-4.395)	0.73
Pulmonary haemorrhage	10 (19)	6 (12)	0.6 (0.235-1.53)	0.28
Gastrointestinal bleeding	4 (8)	5 (10)	1.25 (0.355-4.395)	0.73
Age of administration of full volume of enteral nutrition	15 (10-21)[2]	15.5 (10-25)	-	0.71
Death	11 (21)	9 (17)	0.82 (0.37-1.807)	0.62

Notes: 1 – number of cases (%); 2 – median (interquartile range). IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.

Table 3. Comparative morbidity and mortality in the groups.

Outcomes	Ibuprofen group (n=52)	Acetaminophen group (n=52)	RR (95 % CI)	p
Intraventricular haemorrhage	17 (33)[1]	17 (33)	1 (0.567-1.735)	1.00
BPD (moderate or severe)	6 (12)	3 (6)	0.5 (0.132-1.893)	0.29
BPD/death	26 (50)	21 (40)	0.81 (0.527-1.239)	0.32
Periventricular leukomalacia	2 (6)	1 (2)	0.5 (0.047-5.346)	0.31
Early onset sepsis	16 (31)	13 (25)	0.81 (0.436-1.515)	0.51
Late onset sepsis	8 (15)	7 (13)	0.87 (0.342-2.237)	0.78
Acute renal failure	4 (8)	3 (6)	0.75 (0.176-3.187)	0.69
Hypotension	5 (10)	7 (13)	1.4 (0.475-4.128)	0.54
Duration of MV[3], days	1.8 (0.5-5.3)[2]	1.8 (0.5-5)	-	0.67
Duration of non-invasive respiratory support[3], days	7.3 (3.2-17.2)	8.1 (5-18.4)	-	0.51
Length of hospital stay[3], days	62 (47-98)	65 (48-96)	-	0.74
Age at the time of death, days	7.9 (3.2-16)	8.1 (6.3-14.3)	-	0.76
The causes of death				
Severe intraventricular haemorrhage[4]	4 (37)	5 (56)	1.53 (0.576-4.054)	0.39
Necrotizing enterocolitis[4]	3 (27)	3 (33)	1.22 (0.321-4.649)	0.77
Perinatal brain injury[4]	2 (18)	0	0	0.18
Severe respiratory distress syndrome[4]	1 (9)	1 (11)	1.22 (0.088-16.92)	0.88
Late onset sepsis[4]	1 (9)	0	0	0.35

Notes: 1 – number of cases (%); 2 – median (interquartile range); 3 – for infants who survived; 4 – for infants who died. BPD, bronchopulmonary dysplasia; MV, mechanical ventilation.

The median PDA diameter in the first 72 hours of life was almost the same in both groups. The frequency of successful ductal closure after the first course of treatment did not differ probably between groups. The median age at the time of ductus closure did not differ significantly between the groups. There were no significant differences between the groups in the rate of re-opening, and ductus closure by the time of discharge (Table 4). At the time of discharge, all patients had closed or hemodynamically insignificant PDA, so none of the infants required surgical ligation.

Table 4. Comparative characteristics of the patent ductus arteriosus in the groups.

Outcomes	Ibuprofen group (n=52)	Acetaminophen group (n=52)	RR (95 % CI)	*p*
PDA diameter in the first 72 hours of life, mm	2.5 (2-3)[1]	2.5 (2-3)	-	0.23
Age at the time of ductus closure, days	5 (5-6)	5 (5-6)	-	0.67
Ductus closed at the time of discharge	44 (85)[2]	42 (81)	0.95 (0.8-1.138)	0.60

Notes: 1 – median (interquartile range); 2 – number of cases (%). PDA, patent ductus arteriosus.

Discussion

The results of our study showed that the effectiveness of early PDA closure with acetaminophen is non-inferior to ibuprofen. Our trial did not reveal any significant differences between the groups in closing PDA after the first and second courses of treatment. The frequency of successful ductus closure was the same for both groups – 81%. This level of efficacy is consistent with a recent randomized study by Meena et al., which showed that the frequency of successful ductus closure after the first and second course of treatment was almost the same between the groups – 77% in the group of oral ibuprofen and 71% in the group of intravenous acetaminophen (p>0.05).[17] At the same time, the results of the study by Karabulut et al. showed slightly higher rates of successful PDA closure after receiving the first and second courses of treatment with oral ibuprofen and acetaminophen (ductus closure occurred in 96% and 97% of infants, respectively).[18] The results of a study by Bagheri et al. also demonstrated high rates of successful ductus closure after completion of the first and second courses of pharmacological treatment with ibuprofen and acetaminophen.[19] Ductus closure occurred in 90% of infants who received oral ibuprofen and in 91% of infants who were treated with oral acetaminophen.[19] A systematic review and meta-analysis of studies showed that oral ibuprofen was more effective than intravenous in successfully ductus closing.[20] Oral ibuprofen was associated with a significantly lower failure rate of PDA closure compared with intravenous ibuprofen (15.5% versus 37.8%, respectively; RR-0.41; 95% CI: 0.23-0.73).[20] Also, taking into account the results of a recent meta-analysis, it can be assumed that acetaminophen is non-inferior to ibuprofen in its effectiveness in PDA closing.[21] At the same time, the authors of meta-analysis noted that the incidence of renal dysfunction and gastrointestinal bleeding was higher in the ibuprofen group.[21] Therefore, it may not be unreasonable to assume that acetaminophen constitutes a safer alternative. However, we did not find such a pattern, because patients in our study were prescribed ibuprofen rectally, and this was not associated with a higher risk of these complications compared with the acetaminophen group (p>0.05). A randomized controlled trial by Dang et al., which compared the effectiveness of ibuprofen against acetaminophen in the closure of HSPDA demonstrated ductus closure in 81.2% of infants in the acetaminophen group versus 78.8% of patients in the ibuprofen group (p>0.05).[22] After the first course of treatment, ductus was closed in 56.3% of infants receiving acetaminophen and in 47.5% of children treated with ibuprofen (p>0.05).[18] Our trial also found no significant difference in the frequency of successful ductus closure after the first course of pharmacological treatment (PDA closed in 71% of infants in the ibuprofen group and 79% of children in the acetaminophen group). The study of Oncel et al. also showed similar rates of successful ductus closure after the first course of treatment with ibuprofen and acetaminophen (77.5% and 72.5%, respectively, p>0.05).[7] The results of a systematic review and meta-analysis of 7 randomized controlled trials (n=861) showed that the rate of ductus closure after the first course of treatment did not differ between groups of infants who received COX inhibitors and acetaminophen (RR-0.90; 95% CI: 0.72-1.13).[23]

Our results demonstrated the similar safety profiles of intravenous acetaminophen and rectal ibuprofen. It is known that the main side effects of ibuprofen are oliguria and gastrointestinal bleeding. Acetaminophen use can be associated with hepatotoxicity, hemodynamic and thermodynamic effects.[1] However, the results of our trial did not show any significant difference between the groups in the incidence of renal failure, gastrointestinal and pulmonary haemorrhage. At the same time, no statistically significant differences were found between the groups in the mortality, incidence of BPD, NEC (stage Bell ≥ IIa), severe IVH, ROP, PVL, and sepsis at PMA of 36 weeks or hospital discharge. The results of the systematic review of published studies, as well as our data, showed no statistically significant differences in mortality, the need for surgical PDA closure, the incidence of BPD, NEC, ROP, and pulmonary haemorrhage between the groups of infants who received pharmacological PDA treatment with COX inhibitors and acetaminophen.[23] Instead, PDA treatment with acetaminophen was associated with a tendency to reduce the risk of renal failure (RR-0.20; p=0.07), and reduction of gastrointestinal bleeding (RR-0.28, p=0.009).[23] We did not find such a trend as the risks of developing renal failure (RR-0.75, 95% CI: 0.176-3.187, p=0.69) and gastrointestinal bleeding (RR-1.25, 95% CI: 0.355-4.395, p=0.73) did not significantly differ between the groups. Similar conclusions were made by other authors, who also found that both drugs were safe based on analysis of several indicators of renal and hepatic function. Statistically significant differences in major morbidities (NEC, IVH, ROP, BPD) were not established either.[7,8,22]

Our results did not show statistically significant differences in the rate of re-opening and ductus closure by the time of discharge, duration of respiratory support, and the median age at the administration of full volume of enteral nutrition between the groups. At the time of discharge, all infants had closed or hemodynamically insignificant PDA, so none of the infants required surgical ligation.

Our results are consistent with the findings of the Cochrane reviews and numerous meta-analyses and have shown that acetaminophen may be an effective and safe alternative to ibuprofen in an attempt at pharmacological ductal closure.[4,6,21,23]

To our knowledge, this study is the first randomized trial to describe the efficacy and safety of rectal administration of ibuprofen against intravenous acetaminophen in ductal closure in very preterm infants. By now, only one randomized study of the effectiveness and safety of rectal ibuprofen in very preterm infants with HSPDA has been conducted.

Demir et al. demonstrated that rectal ibuprofen was as effective as oral ibuprofen in closing HSPDA (ductus closed in 86% of infants in the rectal ibuprofen group and in 83% of patients in the oral ibuprofen group; p>0.05).[24] Simultaneously, the study authors noted that rectal administration of ibuprofen appeared to be as safe as the oral with regard to the complications associated with PDA treatment (indicators of renal function, incidence of gastrointestinal bleeding, BPD, IVH, NEC, and ROP).[24] Therefore, rectal administration of ibuprofen is an acceptable alternative under the circumstances, when oral intake of the medication may not possible. Considering the relatively high cost of intravenous ibuprofen, rectal ibuprofen may be an affordable alternative in resource-limited countries.

Our study also has several limitations, primarily due to its non-blinding design, lack of follow-up until complete ductus closure in 100% or deterioration with the need for interventions, specific approach to treatment (early administration based only on the PDA size), and a relatively small proportion of the most immature infants.

Conclusion

Our results showed that acetaminophen is non-inferior to ibuprofen in the rate of successful ductal closure. Acetaminophen may be an effective and safe alternative to ibuprofen in an attempt to close the patent ductus pharmacologically, especially if there are contraindications to the use of COX inhibitors. Rectal administration of ibuprofen is an acceptable alternative to the intravenous route.

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Conflicts of Interest

The authors declare no conflicts of interest.

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