Oral Paracetamol vs Oral Ibuprofen in Patent Ductus Arteriosus: A Randomized, Controlled, Noninferiority Trial

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Objective To test the hypothesis that oral paracetamol is non-inferior to oral ibuprofen in closing hemodynamically significant patent ductus arteriosus (hsPDA) with an a priori noninferiority (NI) margin of 15%.

Study design Multicenter, randomized, controlled, NI trial conducted in level III neonatal intensive care units. Consecutively inborn preterm neonates of <32 weeks of gestation with hsPDA were included. Those with structural heart disease, major malformations, and contraindications for enteral feeding or for administration of study drugs were excluded. Interventions included oral paracetamol in the experimental arm and oral ibuprofen in the active control arm. The primary outcome was closure of hsPDA by 24 hours from the last dose of the study drug. Secondary outcome measures included closure of hsPDA by 24 hours after the first course of the study drug, rate of reopening after the first course, and adverse events associated with the study drug.

Results Out of 1250 neonates screened, 161 were randomized. Oral paracetamol was noninferior to oral ibuprofen in closure of hsPDA by both per protocol analysis (62 [95.4%] vs 63 [94%]; relative risk [RR], 1.01 [95% CI, 0.94-1.1]; risk difference [RD], 1.4 [95% CI, −6 to 9]; $P = .37$) and intention-to-treat analysis (63 [89%] vs 65 [89%]; RR, 0.99 [95% CI, 0.89-1.12]; RD, −0.3 [95% CI, −11 to 10]; $P = .47$). All adverse events were comparable in the 2 study arms.

Conclusions Oral paracetamol is noninferior to oral ibuprofen for the closure of hsPDA in preterm neonates of <32 weeks of gestation. No difference was observed in the adverse events studied. *(J Pediatr 2020;222:79-84)*.

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Indomethacin and ibuprofen are the 2 commonly used drugs for closure of a hemodynamically significant patent ductus arteriosus (hsPDA) in preterm neonates.[1-4] Ibuprofen has been found to successfully close hsPDA in 70%-85% of cases,[5-9] and a systematic review has reported superior efficacy of oral ibuprofen over placebo.[10] Unlike ibuprofen, paracetamol (acetaminophen) acts on the peroxidase region of the prostaglandin synthase enzyme and has an arguably superior safety profile.[11-15] Five separate case series (n = 39) have reported an 84%-100% closure rate with paracetamol.[13-17] One systematic review of 16 studies (2 randomized controlled trials and 14 uncontrolled studies) concluded that the efficacy and safety of oral paracetamol were comparable to that of oral ibuprofen; however, the authors cautioned about the suboptimal quality of the studies and the limited number of neonates treated with oral paracetamol to date and advised that additional well-designed studies on oral paracetamol should be conducted before it can be incorporated in current clinical practice.[18]

A more recent Cochrane database systematic review that included 5 controlled trials comparing paracetamol (oral or IV) and ibuprofen (oral or IV) (n = 559) found paracetamol to be as effective as ibuprofen for closure of hsPDA following a single course of therapy.[19] No differences in the adverse outcomes studied were observed, except for the duration of supplemental oxygen and hyperbilirubinemia, both favoring paracetamol. However, these studies were downgraded to moderate quality evidence, owing primarily to a lack of blinding. Four of these 5 trials, with a total sample size of 359, compared oral administration of both drugs.[20-23] Even though all 4 trials concluded that oral paracetamol is as effective as oral ibuprofen, none of the foregoing studies tested the study drugs with a noninferiority (NI) or an equivalence design, making such a conclusion inappropriate. We conducted this randomized

hsPDA	Hemodynamically significant patent ductus arteriosus
ITT	Intention to treat
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NI	Noninferiority
RD	Risk difference
RR	Relative risk

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controlled, blinded trial to compare oral paracetamol with oral ibuprofen for closure of hsPDA in preterm neonates (<32 weeks). Because oral paracetamol has potential safety advantages over oral ibuprofen, we chose an NI design with an expectation that NI of oral paracetamol would be sufficient to tilt the risk-benefit ratio in its favor.

Methods

This randomized, 2-arm, active-controlled, blinded NI trial was conducted in 3 centers across India between April 2014 and June 2017. Ethics Committee approval was obtained from all 3 participating centers before enrollment of the first subject. The trial was registered with Clinical Trials Registry India (CTRI/2014/08/004805). Informed written consent was obtained from parents for participation after providing a parent information sheet. The study protocol has been published previously.[24]

Study Population

Consecutively born preterm neonates of <32 weeks of gestation with hsPDA were included. A screening echocardiography was performed in asymptomatic neonates to detect hsPDA (between 48 and 72 hours of age in those at 29-31 weeks of gestation and in the first 48 hours in those at ≤28 weeks of gestation). We excluded infants with suspected or diagnosed structural heart disease, those with major congenital malformations, those with contraindications for enteral feeding or contraindications for administration of any of the study drugs (blood urea >60 mg/dL, serum creatinine >1.6 mg/dL, platelet count <60 000/uL, clinical bleeding from any site, deranged coagulation, clinical or radiologic evidence of necrotizing enterocolitis [NEC], intraventricular hemorrhage [IVH] grade III with or without intraparenchymal extension or progression of IVH from an earlier ultrasound, or serum bilirubin level within 2 mg/dL from the exchange transfusion cutoff value), and those whose parents refused consent.

hsPDA was defined as either PDA with transductal diameter of ≥1.6 mm along with at least 2 of the predefined set of abnormal clinical signs and/or investigative measures mentioned below or the presence of 1 or more echocardiographic signs suggestive of hsPDA even in the absence of clinical/biochemical signs. The clinical signs were classified as signs suggestive of a significant left-to-right shunt (hyperdynamic precordium, bounding peripheral pulses and wide pulse pressure [>25 mmHg]) and signs suggestive of either systemic underperfusion or pulmonary overperfusion (eg, poor peripheral pulse volume, prolonged capillary refill time, decreased urine output, abnormal renal function tests, metabolic acidosis, hypotension, abnormal weight gain, increase in liver size, new onset or increase in ventilatory requirements, respiratory acidosis, pulmonary crepitations, hemorrhagic pulmonary edema). In patients with signs of significant left-to-right shunt, a second neonatologist confirmed the clinical sign.

The echocardiographic features of hsPDA include a transductal diameter of ≥1.5 mm plus 1 of the following: left atrium:aorta diameter ratio ≥1.4, transductal blood flow velocity <2 m/s, antegrade main pulmonary artery diastolic flow velocity >20 cm/s, mitral valve inflow E wave:A wave ratio >1, isovolemic relaxation time ≤45 ms, and absent or reversed diastolic flow in the descending aorta.[25,26] At each center, an investigator experienced in neonatal echocardiography performed the procedures. In a run-in period before study initiation, a high level of agreement for the primary outcome variable among the echocardiographers at the 3 sites was ensured.

Study Interventions

Study subjects were randomly assigned to receive either oral paracetamol suspension (experimental arm) or oral ibuprofen suspension (active control arm). Paracetamol oral suspension (Calpol; Glaxo Smith Kline Asia, Gurgaon, India) was administered through an orogastric tube at 15 mg/kg per dose in 6 hourly intervals for 3 consecutive days. Ibuprofen oral suspension (Ibugesic; Cipla India, Mumbai, India) was administered at 10 mg/kg/dose, followed by 5 mg/kg/dose at 24 and 48 hours after the first dose. Following administration, the drugs were flushed with 1 mL of sterile water. Adherence to the drug administration process was monitored by the treating team, and cases were reported for drug spillage and vomiting or regurgitation immediately after administration so that the investigators could determine whether to repeat the dosage. Those infants in whom the hsPDA remained open or reopened received a second course of the study drug or an appropriate open-label drug if any contraindication to the study drug was observed.

Randomization

Stratified block randomization was used in this study. Stratification was based on study center and gestational age group (<28, 28-29, and 30-31 weeks). Randomly varying, permuted, even-numbered blocks (sizes 4, 6, and 8) were generated from a website (http://www.randomization.com). The person who generated the random sequence was not involved in any other aspect of the trial.

Allocation Concealment and Blinding

The drugs were prepared by the institutions' Clinical Pharmacy Department in 5-mL volumes. Allocation concealment was ensured by dispensing the prepared drugs in serially numbered opaque vials according to allocation group. The drugs were prepared with a similar color, flavor, and viscosity to facilitate blinding. The blinding process was tested on adult volunteers, who were unable to differentiate the drugs based on their color, flavor, and viscosity. To avoid unblinding due to differences in dosage, a 15 mg/mL concentration of paracetamol suspension and 10 mg/mL and 5 mg/mL concentrations of ibuprofen suspension were prepared, so that for a given body weight, an identical volume of each drug would be administered. To avoid unblinding due to

Table I. Characteristics of study subjects at baseline

Characteristics	Oral paracetamol (N = 81)	Oral ibuprofen (N = 80)
Gestational age, wk, mean (SD)	28.7 (1.6)	28.7 (1.7)
Birth weight, g, mean (SD)	1167 (249)	1129 (268)
Extreme prematurity (<28 wk), n (%)	20 (25)	20 (25)
Extremely low birth weight (<1000 g), n (%)	18 (22)	23 (29)
Small for gestational age, n (%)	8 (10)	14 (18)
Male sex, n (%)	42 (52)	38 (48)
Vaginal delivery, n (%)	32 (40)	42 (53)
Antenatal steroids (any dose), n (%)	68 (84)	64 (80)
Antenatal steroids (complete course), n (%)	40 (50)	35 (44)
Maternal clinical chorioamnionitis, n (%)	5 (6)	4 (5)
Preterm premature rupture of membranes, n (%)	20 (25)	30 (38)
Antepartum hemorrhage, n (%)	10 (12)	23 (29)
Pregnancy-associated hypertension, n (%)	26 (32)	20 (25)
Antenatal umbilical artery Doppler abnormalities, n (%)	8 (10)	10 (13)
Need for resuscitation at birth, n (%)	49 (61)	45 (57)
Respiratory distress, n (%)	72 (89)	74 (93)
Received surfactant, n (%)	55 (68)	53 (66)
Required respiratory support (any type), n (%)	73 (90)	76 (95)
Required mechanical ventilation, n (%)	28 (35)	21 (26)
Received caffeine, n (%)	50 (62)	52 (65)
Culture-proven sepsis, n (%)	6 (7)	1 (1)
Hypotensive shock, n (%)	11 (14)	6 (8)
Oxygen concentration, %, median (IQR)	25 (21-32)	27 (21-32)
CPAP pressure, cmH_2O, median (IQR)	5 (5-6)	5 (5-6)
Platelet count, $mm,^3$ median (IQR)	182 000 (103 500-232 500)	178 000 (119 500-220 000)
Transductal diameter, mm, median (IQR)	2.3 (1.8-2.6)	2.1 (1.9-2.5)
Transductal diameter ≥1.5 mm, n (%)	81 (100)	80 (100)
Left atrium: aorta root diameter ≥1.4, n (%)	78 (96)	67 (84)
Ductal velocity <2 m/s, n (%)	28 (35)	32 (40)
Antegrade LPA diastolic velocity >20 cm/s, n (%)	78 (96)	75 (94)
E:A ratio >1, n (%)	23 (29)	20 (25)
Isovolumic relaxation time ≤45 ms, n (%)	29 (36)	23 (29)
Absent or reversed diastolic flow in descending thoracic aorta, n (%)	15 (19)	13 (16)

CPAP, continuous positive airway pressure; *E:A*, early diastolic filling:late diastolic filling of left ventricle; *LPA*, left pulmonary artery.

differences in frequency of administration, an identical-looking placebo was used for extra sham doses in the ibuprofen arm, so that the dose regimen in the ibuprofen arm was identical to that in the paracetamol arm. The treating team, investigators, outcome assessors, and pharmacy personnel were blinded.

Study Outcomes

The primary outcome (NI comparison) was closure rate of hsPDA by 24 hours from the last dose of the study drug, irrespective of the course of the drug. Secondary outcome measures included rate of hsPDA closure by 24 hours after the first course of the study drug, rate of reopening following the first course, need for surgical ligation for hsPDA closure, all-cause mortality in hospital and adverse events with onset after the start of administration of the study drug. The adverse events studied were azotemia, oliguria, hepatitis with deranged liver transaminase values, deranged coagulation, severe IVH (grade 3 and intraparenchymal extension), periventricular leukomalacia, NEC (definite and advanced stage per modified Bell staging), bronchopulmonary dysplasia, and retinopathy of prematurity necessitating therapy. All subjects were followed until discharge or death, whichever was earlier.

Sample Size Estimation and Statistical Analyses

The reported frequency of failure of hsPDA closure with oral Ibuprofen treatment is 15%.[10] Assuming an NI margin of 15%, a one-sided α error of 2.5%, power of 90%, and a 1:1 allocation ratio, 196 neonates were required in this trial. However, we could enroll only 161 neonates owing to slow recruitment. A margin size of 15% was considered clinically irrelevant. Both intention-to-treat (ITT) and per-protocol analyses were conducted. Because this was an NI trial, per-protocol analysis was considered the primary analysis. Apart from hypothesis testing, the CI approach was also used to test NI.[27] We calculated the NI limit of the NI zone (d_{max}) and derived d (the operative weighted margin) from *dmax* by weighing for fractional preservation (f) using the formula $d = d_{max}^{1 - f}$. To establish the superiority (when the derived RR with its 95% CI was >1.0) of oral paracetamol over placebo, we followed a putative placebo approach.[28] Effect preservation was calculated, and the efficacy of oral paracetamol was established when the lower limit of the CI exceeded the target fractional threshold of 0.5.[29,30] The time to closure of hsPDA was tested by the log-rank test. A P value of 0.025 was considered significant for the primary outcome, and 0.05 was considered significant for the remaining outcomes. SPSS version 23 (IBM, Armonk, New York) was used for data entry and statistical analyses.

Table II. Primary and major secondary outcomes

Characteristics	Oral paracetamol, (N = 81), n (%)	Oral ibuprofen, (N = 80), n (%)	RR or RD or MD (95% CI)	*P* value
Primary outcome				
Closure of ductus arteriosus after 2 courses (modified ITT analysis*): primary outcome	63/71 (89)	65/73 (89)	RR: 0.99 (0.89-1.12) RD: −0.3 (−11 to 10)	.47 (one-tailed)
Closure of ductus arteriosus after 2 courses of trial drug (per protocol analysis)	62/65 (95.4)	63/67 (94)	RR: 1.01 (0.94-1.1) RD: 1.4 (−6 to 9)	.37 (one-tailed)
Secondary outcomes				
Closure of ductus arteriosus after first course (ITT analysis)†	52/81 (64)	62/80 (78)	0.82 (0.68-1.01)	.07
Closure of ductus arteriosus after 2 courses of trial drug (worst-case scenario for experimental arm)	63/74 (85)	70/74 (94.6)	0.9 (0.8-1.004)	.063
Rate of reopening of ductus arteriosus after first course of trial drug	5/57 (8.8)	4/66 (6.1)	1.45 (0.41-5.1)	.58
Closure after second course of trial drug (N = 17)	9/12 (75)	1/5 (20)	3.8 (0.63-22.3)	.063
Ductus arteriosus that underwent surgical ligation	2/81 (2.5)	4/80 (5)	0.49 (0.09-2.62)	.44
Noncompliance with trial drug	1/81 (1.2)	5/80 (6.3)	0.19 (0.02-1.7)	.1
Received alternate trial drug	0 (0)	0 (0)		
Received nontrial open-label drug	1/81 (1.2)	5/80 (6.3)		

At-risk subjects are shown as denominators.
MD, mean difference; *RR*, relative risk.
*Subjects who died before receiving the second course and thus were not available for outcome assessment were excluded from the analysis.
†Reopened ductus arteriosus within 24 hours from completion of the first course was considered nonclosure.

Results

A total of 1250 neonates were screened for eligibility, of whom 161 met our eligibility criteria and were randomized (**Figure 1**; available at www.jpeds.com). Baseline variables were comparable between the study groups (**Table I**). Barring those who died after randomization, all randomized infants completed the trial. A total of 132 mothers (82%) received at least 1 dose of antenatal steroids before delivery; 108 neonates (67%) received surfactant and 102 (63%) received caffeine. Out of 161 neonates, 37 (23%) did not receive the complete first course of trial drug (paracetamol vs ibuprofen: 18 [22] vs 19 [24]; RR, 0.94; 95% CI, 0.5-1.6; $P = .82$), either due to death from a comorbid condition (24; 65%) or due to an adverse event related to the trial drug (13; 35%). None of the study subjects in either arm received the trial drug of the alternate arm. Six neonates (3.8%) received an open-label drug, IV paracetamol, for closure of hsPDA.

Primary and Other Major Outcomes

The primary outcome of ductus arteriosus closure was similar in the oral paracetamol arm and oral ibuprofen arm by per-protocol analysis (62 [95.4%] vs 63 [94%]; RR, 1.01 [95% CI], 0.94-1.1]; RD, 1.4 [95% CI, −6 to 9]; $P = .37$) (**Table II**). The time to closure of hsPDA was not different between the oral paracetamol and ibuprofen arms (median, 66 hours [95% CI, 61-71 hours] vs 49 hours [95% CI, 44-54 hours]; $P = .71$, log-rank test) (**Figure 2**; available at www.jpeds.com). No difference in adverse outcomes was observed between the study arms (**Table III**).

Subgroup Analysis

A subgroup analysis by gestational age strata showed similar closure rates following both courses as well as single course between the study groups (**Table IV**; available at www.jpeds.com).

Establishment of NI

For the primary outcome, the risk difference was −0.3% by ITT analysis and 1.4% by per-protocol analysis, with one-sided *P* values of .47 and .37, respectively. The historical RR comparing oral ibuprofen with placebo or no treatment was 2.08 (95% CI, 1.33-3.24) for closure of ductus arteriosus, and thus the d_{max} value was 1.33.[10] By the CI approach, the upper bound of the one-sided 97.5% CI of the observed RR of 1.1 was observed to lie within the d_{max}. Furthermore, the upper bound of observed RR of 1.1 was still less than *d*, establishing NI.[30] The superiority of oral paracetamol over placebo was established, as the derived RR with its 95% CI was >1.0. Effect preservation of oral paracetamol was established when the lower limit of the CI exceeded the target fractional threshold of 0.5.[28,29]

Discussion

Oral paracetamol was found to be noninferior to oral ibuprofen by both the hypothesis approach and the CI approach.[27] The paracetamol group demonstrated a lower closure rate following first course of the drug compared with the ibuprofen group, even though the difference was not statistically significant (64% vs 78%), similar findings reported by Dang et al.[21] This might imply that oral paracetamol may require a higher dosage and/or a longer duration to effect a comparable PDA closure rate as oral ibuprofen. This observation is contrary to a recent network meta-analysis that reported high-dose IV ibuprofen and standard-dose oral acetaminophen as the best-ranked drugs for reducing the need for repeat pharmacotherapy.[31] More subjects experienced oliguria and major IVH in the oral ibuprofen arm

Table III. Safety outcomes

Outcomes	Oral paracetamol, (N = 81); n (%)	Oral ibuprofen, (N = 80); n (%)	RR (95% CI)	*P* value
Azotemia	12/81 (15)	14/79 (18)	0.84 (0.4,1.7)	.62
Oliguria	10/81 (12)	16/80 (20)	0.62 (0.3,1.3)	.2
Deranged transaminases	1/78 (1.3)	0/78 (0)	2.0 (0.07,59)	.78
Deranged coagulogram	10/80 (12.5)	9/78 (11.5)	1.08 (0.5,2.5)	.86
Major intraventricular hemorrhage (≥ grade 3)	2/71 (3)	7/70 (10)	0.28 (0.06,1.3)	.09
Periventricular leukomalacia (≥ grade 2)	3/74 (4)	0/75 (0)	6.1 (0.3,120)	.23
Necrotizing enterocolitis (definite & advanced stages)	11/73 (15)	4/66 (6)	2.5 (0.83,7.4)	.09
Bronchopulmonary dysplasia	11/78 (14)	6/75 (8)	1.8 (0.7,4.5)	.24
Retinopathy of prematurity (requiring therapy)	7/76 (9)	6/77 (8)	1.2 (0.4,3.4)	.76
Mortality by discharge	27/81 (33)	21/80 (26)	1.3 (0.8,2.1)	.33

RR, relative risk.

and more definite or advanced-stage NEC in the paracetamol arm. However, these differences did not attain statistical significance.

The current trial and both previous studies are in agreement in terms of safety-related outcomes. Previous controlled trials have reported higher incidences of gastrointestinal bleeding, oliguria, and hyperbilirubinemia in the ibuprofen group compared with the oral paracetamol group, which were not statistically significant.[19] Safety outcomes, even though not different between the study arms, should be interpreted with caution, because the sample size was not calculated to have adequate power for these outcomes.

Administering a second course of pharmacotherapy in neonates in whom the hsPDA did not close after the first course is a standard practice. Thus, we chose closure rate of hsPDA after a complete course, including those who required a second course as a primary outcome. The criteria for defining hsPDA has varied among controlled trials, ranging from clinical definitions to a combination of clinical and echocardiographic measures.[25] Less stringent criteria run the risk of enrolling neonates with ductus that otherwise would have closed spontaneously with prudent fluid management alone, thereby erroneously inflating the pharmacologic closure rate. We used comprehensive criteria combining clinical signs grouped based on their severity and 7 echocardiographic measures that encompassed features of shunt size, shunt volume, and effects on the pulmonary and systemic circulation.

Establishing NI in clinical trials is fraught with several assumptions that cannot be validated explicitly.[27] An indirect CI comparison approach ("95-95" approach) and a hypothesis-testing framework approach have been used to establish NI.[27] In the former approach, NI is inferred when the upper limit of the CI of the difference between the new treatment and the standard treatment is below the lower limit of the 95% CI of the standard treatment effect. In the latter approach, a null hypothesis of inequality (risk difference greater than or equal to the NI margin) is rejected in favor of the alternate hypothesis of equality (reverse of superiority trials) when the one-sided *P* value is <.025.[32] Previous controlled trials that concluded that oral paracetamol is as effective as oral ibuprofen for closure of hsPDA after the first course of therapy were not designed to test equivalence or NI in their truest sense.[20-23] Even though the a priori NI margin of 15% is arguably high, we have satisfactorily demonstrated NI by both approaches. Moreover, by a formal, indirect method (putative placebo approach) as well as the fractional preservation approach, we further demonstrated the therapeutic efficacy of oral paracetamol, thereby proving effect constancy and assay sensitivity (discriminating ability), the 2 key concepts of NI.[27]

Our study has some limitations. First, we did not analyze the osmolality of the final preparation of the study drugs. However, we did not observe any adverse effects attributable to a change in osmolality and the agents used to alter the concentrations of the study drug and prepare the placebo were innocuous. Second, analysis of plasma levels of paracetamol could have helped determine the dose and duration adequacy of paracetamol, because a significant number of neonates in the paracetamol arm required a second course of the trial drug. Third, evaluating the long-term neurodevelopmental outcomes of the study subjects was not an objective of this study, and thus the long-term safety of either study drug cannot be ascertained from this trial. Fourth, even though the safety outcomes did not differ between the study arms, we could not prove that oral paracetamol was safer than oral ibuprofen or that our study was adequately powered to prove this hypothesis.

In conclusion, the present study shows that oral paracetamol is not inferior to oral ibuprofen in closure of hsPDA in preterm neonates of <32 weeks of gestation. No difference was observed between the study arms in the adverse events related to the trial drugs. The reopening rate was higher in the oral paracetamol arm, but the difference was not statistically significant. More neonates in the paracetamol arm required a second course of the trial drug, implying that a dose-response design study is needed to determine the optimum right dose, frequency, and duration of oral paracetamol therapy for effective PDA closure. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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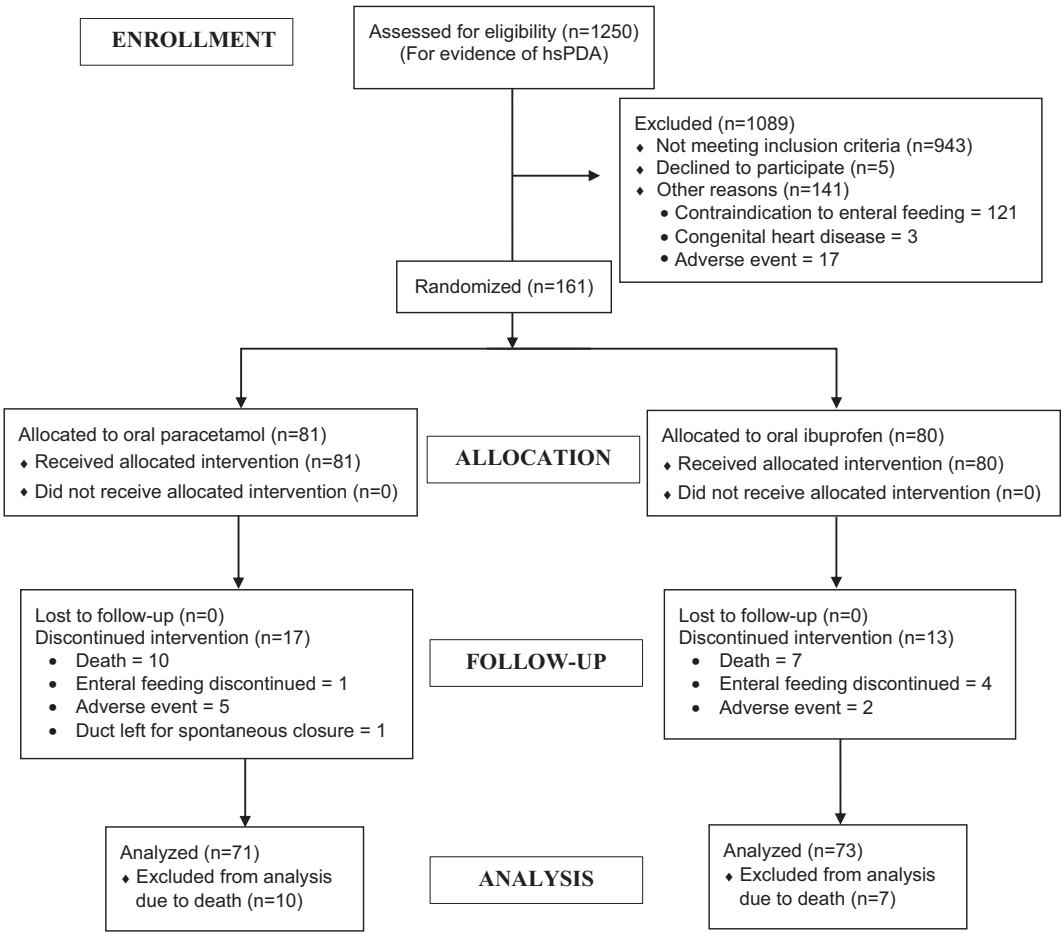

Figure 1. CONSORT flow diagram.

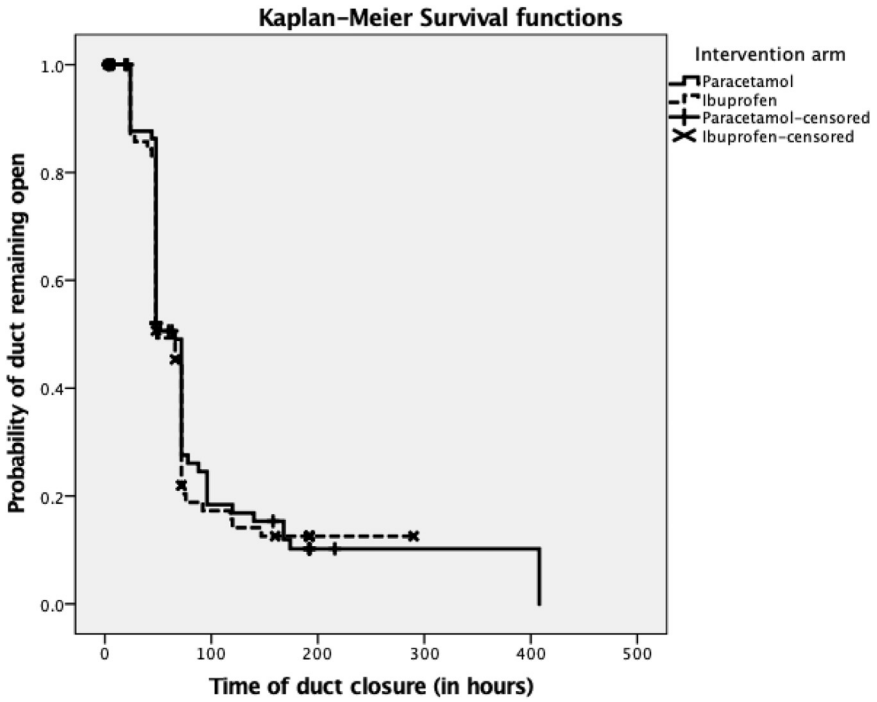

Figure 2. Kaplan-Meier survival curve for time to closure of ductus arteriosus.

Table IV. Primary and major secondary outcomes: subgroup analysis

Characteristics	Oral paracetamol, n/N (%)	Oral ibuprofen, n/N (%)	RR (95% CI)	*P* value
Subgroup: Gestational age <28 wk (n = 40)				
Closure of ductus after first course (ITT)*	10/20 (50)	13/20 (65)	0.8 (0.4-1.3)	.36
Closure of ductus after 2 courses (modified ITT)†	12/16 (89)	11/15 (89)	1.02 (0.7-1.6) RD: 1.7 (−29 to 33)	.46 (one-tailed)
Closure of ductus after 2 courses (per protocol)	12/13 (95.4)	11/12 (94)	1.1 (0.8-1.3) RD: 0.6 (−21 to 22)	.48 (one-tailed)
Reopening after first course of trial drug	0 (0)	2/13 (15.4)	0.32 (0.02-6.4)	.9
Subgroup: Gestational age 28-29 wk (n = 65)				
Closure of ductus after first course (ITT)*	27/33 (82)	28/32 (88)	0.94 (0.8-1.2)	.55
Closure of ductus after 2 courses (modified ITT)†	28/30 (93)	29/32 (91)	1.2 (0.9-1.2) RD: 2.7 (−11 to 16)	.36 (one-tailed)
Closure of ductus after 2 courses (per protocol)	28/29 (97)	27/29 (93)	1.3 (0.9-1.2) RD: 3.5 (−8 to 15)	.31 (one-tailed)
Reopening after first course of trial drug	5/27 (18.5)	2/28 (7)	2.6 (0.55-12)	.24
Subgroup: Gestational age 30-31 wk (n = 56)				
Closure of ductus after first course (ITT)*	20/28 (71)	25/28 (89)	0.8 (0.6-1.05)	.11
Closure of ductus after 2 courses (modified ITT)†	23/25 (92)	25/26 (96)	0.96 (0.8-1.1) RD: −4 (−17 to 8.8)	.29 (one-tailed)
Closure of ductus after 2 courses (per protocol)	22/23 (96)	25/26 (96)	0.99 (0.89-1.1) RD: −0.5 (−12 to 11)	.46 (one-tailed)
Reopening after first course of trial drug	0 (0)	0 (0)	–	–

RR, relative risk.
*Reopened ductus arteriosus within 24 hours from completion of the first course was considered nonclosure.
†Subjects who died before receiving the second course and thus were not available for outcome assessment were excluded from the analysis.