PDA- Evidence against
Pharmacological treatment of PDA

- PDA TOLERATE Trial
- Sung et al , RCT (effect of nonintervention vs oral ibuprofen in PDA)
- BeNeDuctus trial
- Cochrane review 2020
- Baby OSCAR trial

ARTICLE IN PRESS

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ORIGINAL ARTICLES

PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age

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Objective To compare early routine pharmacologic treatment of moderate-to-large patent ductus arteriosus (PDA) at the end of week 1 with a conservative approach that requires prespecified respiratory and hemodynamic criteria before treatment can be given.

Hypothesis- Routine treatment of a moderate to-large PDA that was likely to persist for several weeks would reduce neonatal morbidity compared with a conservative approach that delayed treatment until prespecified respiratory and hemodynamic "rescue" criteria were met.

remia (ERT, 24%; CT,6%) and death (ERT, 16%; CT, 2%).

Conclusions In preterm infants age <28 weeks with moderate-to-large PDAs who were receiving respiratory support after the first week, ERT did not reduce PDA ligations or the presence of a PDA at discharge and did not improve any of the prespecified secondary outcomes, but delayed full feeding and was associated with higher rates of late-onset sepsis and death in infants born at ≥26 weeks of gestation. *(J Pediatr 2018;■■:■■-■■).*

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Methods

Moderate-to-large PDA was defined as an internal ductus diameter ≥1.5 mm (or a PDA:left pulmonary artery diameter ≥0.5) and 1 or more of the following

(1) left atrium-to aortic root ratio ≥ 1.6

(2) ductus flow velocity ≤ 2.5 m/second or mean pressure gradient across the ductus ≤8 mmHg

(3) left pulmonary artery diastolic flow velocity > 0.2 m/second.

(4) reversed diastolic flow in the descending aorta.

Exclusion criteria

- Infants were excluded from participation if they had received previous treatment with indomethacin or ibuprofen.
- Chromosomal anomaly
- Congenital or acquired gastrointestinal anomaly.
- Previous episodes of necrotizing enterocolitis (NEC) or intestinal perforation
- Contraindications to the use of indomethacin or ibuprofen.

- Randomization was stratified by gestational age ($23^{0/7}$ - $25^{6/7}$ or$26^{0/7}$-$27^{6/7}$)
- Early routine treatment (ERT) group received either **indomethacin, ibuprofen, or acetaminophen** (with indomethacin backup if the PDA failed to constrict after the initial treatment).
- After completing the initial treatment, infants were followed to determine if they met eligibility criteria for“rescue”treatment.

- **Conservative treatment(CT)** group did not receive any initial pharmacologic treatments to close the PDA.
- Both groups- Repeat Echo at 7-10 days after randomization.
- Persistent moderate to large PDA after the 1st week were followed with frequent (every 1 to 2 weeks) Echo.

Early Treatment group

Treatment Protocols:

Indomethacin (intravenous): 0.2 mg/kg at 0, 12, 24, 48 hr (4 doses) - obtain echocardiogram after 4th dose:
if PDA closed – No further treatment
(determine need for "rescue treatment")
if PDA open (any size): give doses 5 & 6 (72hrs & 96hrs) - obtain echocardiogram after dose 6
(determine need for "rescue treatment")

Ibuprofen (intravenous): Loading dose = 10 mg/kg followed by maintenance dose of 5 mg/kg every 24 hours for up to 4 maintenance doses - obtain echocardiogram after last dose:
if PDA closed – No further treatment
(determine need for "rescue treatment")
if PDA open (moderate-to-large) use indomethacin protocol as backup

Acetaminophen (intravenous): Loading dose = 20 mg/kg followed by maintenance dose of 15 mg/kg every 6 hours for a 20 doses (obtain "trough" acetaminophen level before 3rd maintenance dose: if >25 mg/L decrease the dose to 12.5 mg/kg, every 6 hours) - obtain echocardiogram after last dose:
if PDA closed – No further treatment
(determine need for "rescue treatment")
if PDA open (moderate-to-large) use indomethacin protocol as backup

Conservative Treatment group

Treatment Protocols:

No treatment
(obtain echocardiogram 10 d after study entry)
(determine need for "rescue treatment")

- CT group with a persistent PDA after 7 days were eligible for rescue drug treatment if they met 1 or more of the following criteria:

OUTCOME

Primary outcome - the need for ligation or need for PDA cardiology follow-up after discharge.

Secondary outcomes- serious neonatal morbidities (NEC, BPD, death, BPD/death).

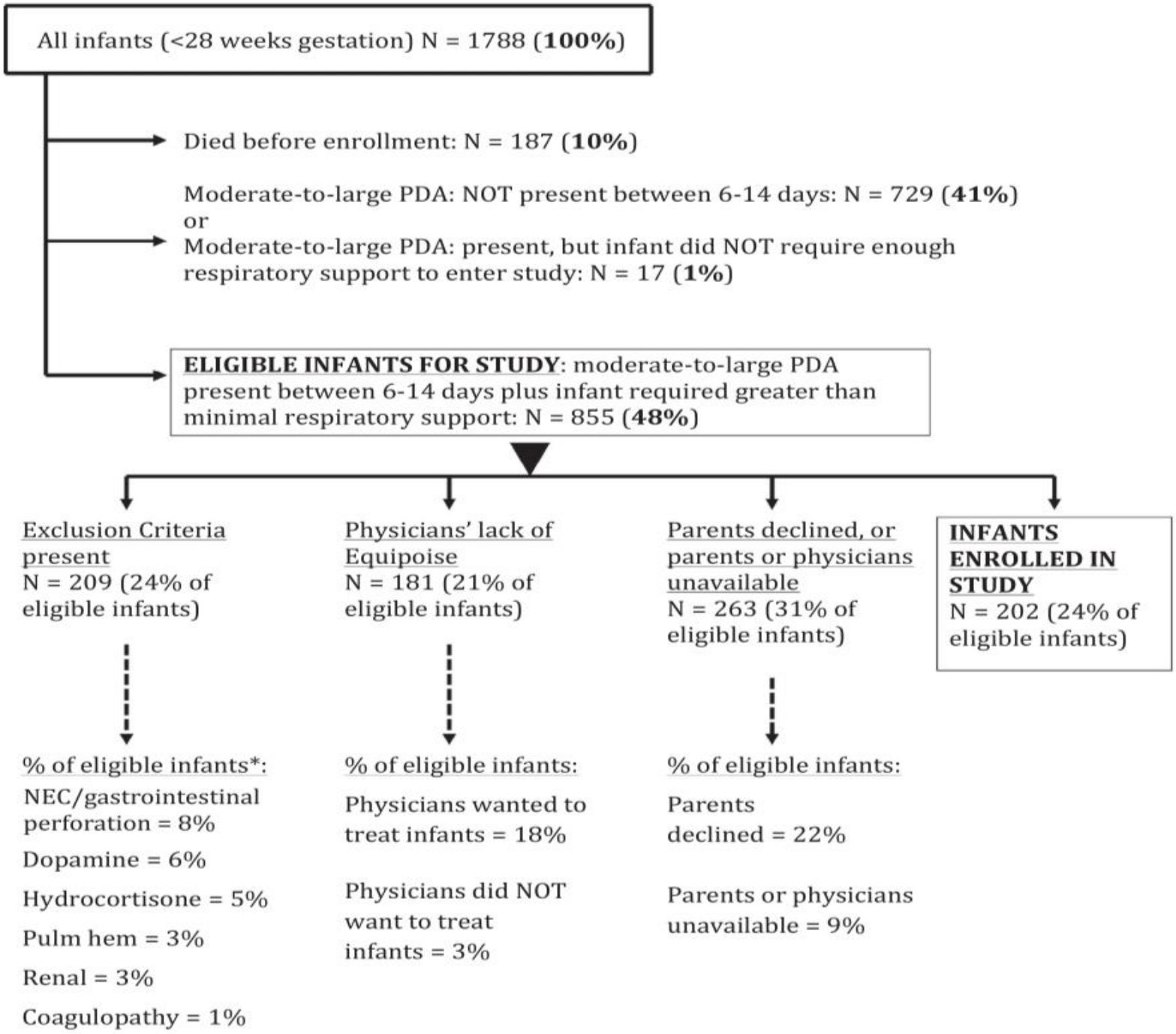

All infants (<28 weeks gestation) N = 1788 (100%)
Died before enrollment: N = 187 (10%)
Moderate-to-large PDA: NOT present between 6-14 days: N = 729 (41%)
or
Moderate-to-large PDA: present, but infant did NOT require enough respiratory support to enter study: N = 17 (1%)
ELIGIBLE INFANTS FOR STUDY: moderate-to-large PDA present between 6-14 days plus infant required greater than minimal respiratory support: N = 855 (48%)
Exclusion Criteria present
N = 209 (24% of eligible infants)
Physicians' lack of Equipoise
N = 181 (21% of eligible infants)
Parents declined, or parents or physicians unavailable
N = 263 (31% of eligible infants)
INFANTS ENROLLED IN STUDY
N = 202 (24% of eligible infants)
% of eligible infants*:
NEC/gastrointestinal perforation = 8%
Dopamine = 6%
Hydrocortisone = 5%
Pulm hem = 3%
Renal = 3%
Coagulopathy = 1%
% of eligible infants:
Physicians wanted to treat infants = 18%
Physicians did NOT want to treat infants = 3%
% of eligible infants:
Parents declined = 22%
Parents or physicians unavailable = 9%

Table II. Baseline demographic data of the CT and ERT groups of the PDA-TOLERATE study

Variables	Total population (n = 202)	
	CT group (n = 98)	ERT group (n = 104)
Prenatal variables		
Maternal age, y, mean ± SD	29.9 ± 6.4	28.9 ± 6.3
Multiple gestation, %	39	25*
Premature rupture of membranes, %	20	20
Preeclampsia, %	19	17
Chorioamnionitis, %	16	15
Diabetes, %	7.1	1.9†
Cesarian delivery, %	70	68
Betamethasone, %		
None or <6 h	26	32
6-23 h	10	4
24-48 h	13	12
>48 h	51	53
Neonatal variables before enrollment		
Gestational age, wk, mean ± SD	25.9 ± 1.1	25.7 ± 1.2
Birth weight, g, mean ± SD	809 ± 179	790 ± 159
Small for gestational age, %	10	5
Female sex, %	56	54
Caucasian, %	55	49
5-min Apgar score ≥6, %	72	71
10-min Apgar score ≥6, %	93	92
Delivery room intubation, %	71	67
Surfactant, %	94	88
Intubation at 24 h, %	70	59
RSS at 24 h after birth, median (IQR)	2.10 (1.47-2.86)	1.89 (1.47-2.70)
Early-onset bacteremia, %	0	6.7*
Pulmonary hemorrhage, %	3.1	4.8
Dopamine, %	35	34
Hydrocortisone, %	3.1	3.9
Enrollment variables		
Enrollment age, d, mean ± SD	8.3 ± 2.3	8.1 ± 2.1
Enrollment weight, g, mean ± SD	799 ± 152	782 ± 155
Intubated at enrollment, %	48	51
RSS at enrollment, median (IQR)	2.00 (1.46-2.75)	1.96 (1.47-2.81)
Dopamine at enrollment, %	6.1	6.7
Maximal enteral feed before enrollment, mL/kg/d, median (IQR)	28 (10-70)	20 (11-50)

RSS, Respiratory Severity Score.
*$P < .05$.

Table IV. Neonatal outcomes

Outcomes	CT group (n = 98)	ERT group (n = 104)	Risk ratio (95% CI)	Risk difference (95% CI)
Other exploratory analyses				
Pulmonary hemorrhage, %*	2.0	1.9	0.94 (0.14-6.60)	0 (–4 to 4)
sIVH, %	11.2	18.3	1.10 (0.43-2.6)	1 (–7 to 8)
PVL (cystic), %	11	13	1.10 (0.52-2.3)	1 (–8 to 10)
ROP (treated), %	16	18	1.20 (0.61-2.3)	3 (–9 to 14)
Pneumonia,%*	9	8	0.84 (0.34-2.1)	–2 (–9 to 6)
Bacteremia, %*	21	30	1.40 (0.86-2.3)	8 (–4 to 20)
Bacteremia, CONS, %*	4	4	0.94 (0.24-3.7)	0 (–6 to 5)
Bacteremia, non-CONS, %*	17	26	1.50 (0.87-2.6)	9 (–3 to 20)
Received dopamine for ≥3 d, %*	25	13.3†	0.53 (0.29-0.98)	–12 (–23 to –1)
Received corticosteroids for ≥7 d, %*	38	28	0.74 (0.49-1.1)	–10 (–23 to 3)
Days until discharge, median (IQR)*	93 (73-109)	92 (76-120)	Mean difference, 1.0 (1.0-1.2)¶	

Table VI. Neonatal outcomes in infants <26 weeks and ≥26 weeks gestation

Outcomes	<26 wk (n = 106)			≥26 wk (n = 96)		
	CT group (n = 51)	ERT group (n = 55)	Risk ratio (95% CI)	CT group (n = 47)	ERT group (n = 49)	Risk ratio (95% CI)
Other exploratory analyses						
Pulmonary hemorrhage, %*	2.0	1.8	0.93 (0.06-14.4)	2.1	2.0	0.96 (0.06-14.9)
sIVH, %	15.7	23.6	0.93 (0.32-2.70)	6.4	12.2	1.4 (0.25-8.20)
PVL (cystic), %	20	13	0.64 (0.26-1.50)	2.1	12	5.8 (0.72-46.0)
ROP (treated), %	30	24	0.81 (0.41-1.60)	2.2	12§	5.5 (0.67-45.0)
Pneumonia, %*	13	7	0.53 (0.16-1.70)	4	8	1.9 (0.37-10.0)
Bacteremia, %*	29	35	1.17 (0.67-2.10)	13	24	1.9 (0.78-4.70)
Bacteremia, CONS, %*	2	7	0.23 (0.03-2.01)	6	0	**
Bacteremia Non-CONS, %*	27	27	0.99 (0.53-1.90)	6	24†	3.8 (1.20-12.7)
Received dopamine ≥3 d, %*	44	22†	0.49 (0.26-0.90)	6.4	4.3	0.67 (0.12-3.80)
Received corticosteroids ≥7 d, %*	53	42	0.79 (0.53-1.20)	21	12	0.58 (0.23-1.50)
Days until discharge, median (IQR)*	103 (91-129)	106 (89-127)	0.98 (0.95-1.00)¶	76 (62-94)	78 (63-97)	1.2 (1.10-1.20)¶

Univariate analyses examining the effects of treatment assignment on neonatal outcomes are presented

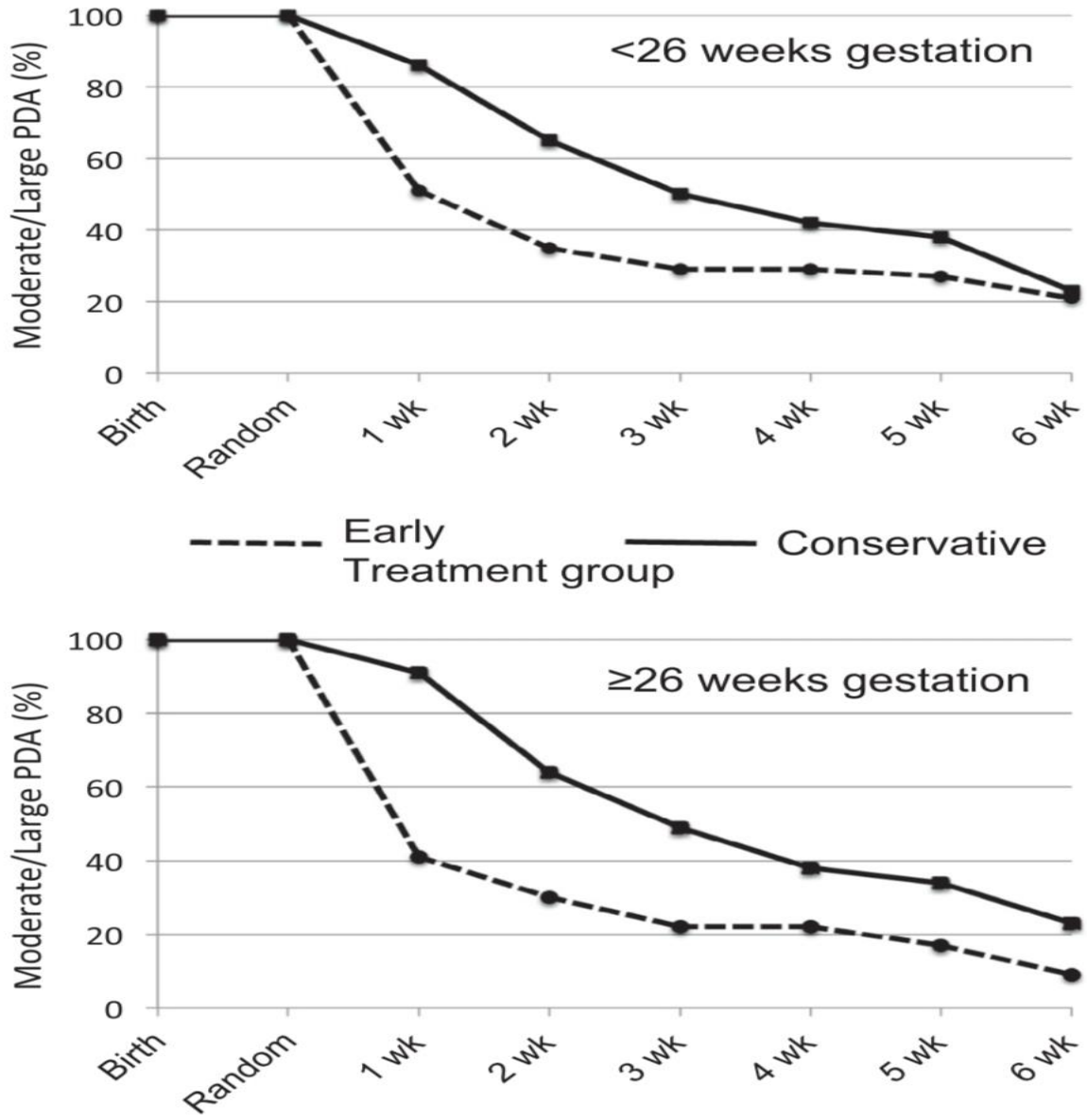
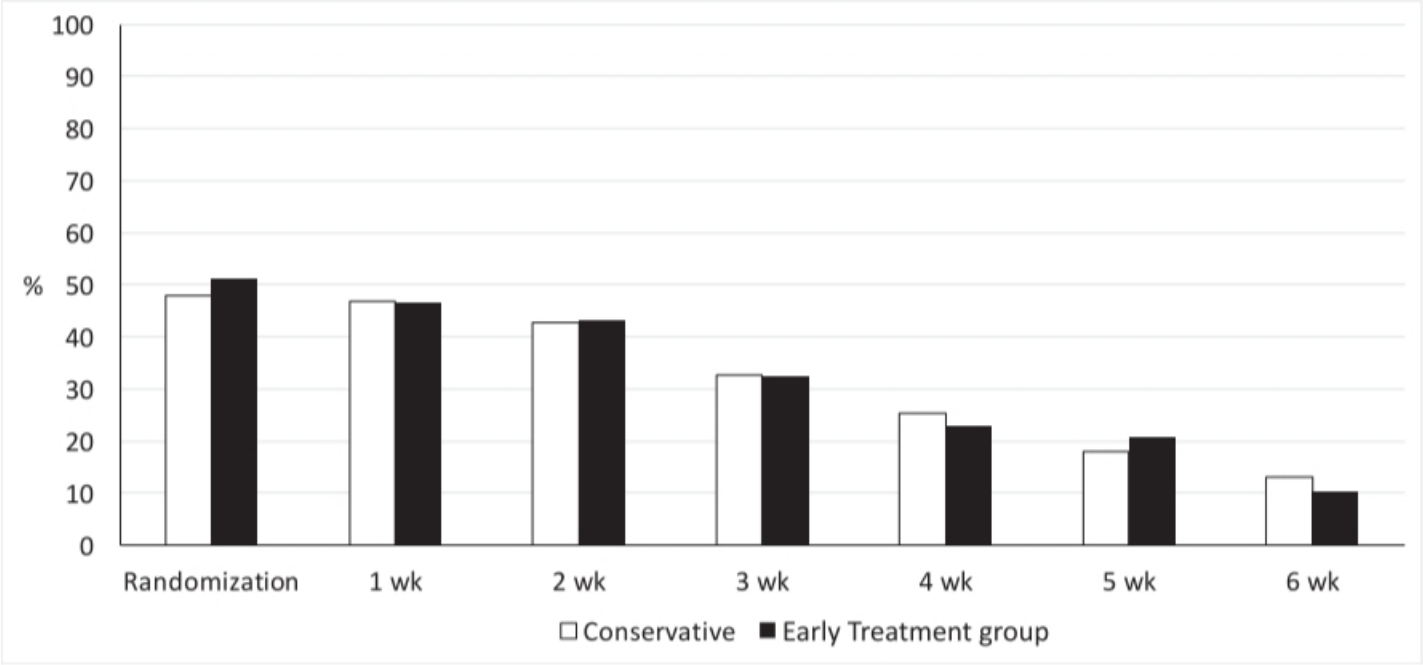


Figure 5. Weekly incidence of moderate-to-large PDA shunts in the CT and ERT groups after randomization. Infants were delivered between $23^{0/7}$ and $25^{6/7}$ weeks (ie, <26 weeks) and between $26^{0/7}$ and $27^{6/7}$ weeks (ie, ≥26 weeks) gestation.



e 3. Weekly incidence of intubation and mechanical ventilation among in the CT and ERT groups after rando

Conclusion

- In preterm infants <28 weeks with moderate-to-large PDAs who were receiving respiratory support after the first week, ERT did not reduce PDA ligations or the presence of a PDA at discharge and did not improve any of the prespecified secondary outcomes, but delayed full feeding and was associated with higher rates of late-onset sepsis and death in infants born at ≥ 26 weeks of gestation.

Research

JAMA Pediatrics | Original Investigation

Effect of Nonintervention vs Oral Ibuprofen in Patent Ductus Arteriosus in Preterm Infants
A Randomized Clinical Trial

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OBJECTIVE- To determine the non-inferiority of non intervention vs oral ibuprofen treatment for PDA in decreasing BPD incidence or death in very preterm infants.

Study design- single-center, randomized, double-blind, placebo-controlled, noninferiority, Randomized trial.

- Study- July24, 2014 - March 15, 2019, at the NICU of Samsung Medical Center, Seoul, Korea.

Inclusion-

- GA 23 to 30 wks.
- The infants required respiratory support.

Hemodynamically significant PDA was defined as ductal size greater than 1.5mm with predominant left to right shunt, Echo performed during post-natal days 6 and 14.

Exclusion criteria –

- congenital heart disease
- life-threatening congenital anomalies
- Predominant right to left shunt through PDA
- Severe IVH (grade ≥ III)
- Contraindications to oral ibuprofen treatment, including life threatening infection, bleeding tendency,thrombocytopenia with platelet count less than 50×103/μL, serum creatinine level greater than 2.0 mg/dL and NEC stage IIb or greater

Treatment arm- oral ibuprofen was administered via gavage tube within 24 hours after randomization. The initial dose of 10mg/kg was followed by a 5-mg/kg dose after 24 hours and a second 5-mg/kg dose after 48hours.

Nonintervention group- Normal saline with the same volume and schedule as used with ibuprofen was given as a placebo

The parents, hospital and research staff, and medical personnel directly involved in patient care were all blinded to group allocation throughout the study.

- Concomitant Treatment- Judicious fluid restriction with diuretics administered as needed was maintained for the first 2months of life.

Backup rescue treatment was considered when the condition was refractory to conservative management, including fluid restriction, use of diuretics and ionotropic drugs and modest increase in mean and end expiratory ventilator airway pressure to reduce pulmonary blood flow.

OUTCOME

Primary outcome- Primary outcome measures included BPD incidence or death

Secondary outcome-
BPD incidence
Death before discharge,
Severe IVH (grade≥III)
Retinopathy of prematurity (stage≥3)
NEC (stage≥IIb)
Gastrointestinal surgery
Nosocomial sepsis confirmed on blood culture results.

- Statistical Analysis- per-protocol analysis was performed; therefore, only infants who completed the intervention (all 3doses of oral ibuprofen or normal saline) were included in analysis.
- Non- inferiority margin- 20%.

Table 1. Clinical Characteristics of the Trial Population

Characteristic	Total (n = 142)		Gestational age			
			23-26 wk (n = 80)		27-30 wk (n = 62)	
	Nonintervention (n = 72)	Ibuprofen (n = 70)	Nonintervention (n = 42)	Ibuprofen (n = 38)	Nonintervention (n = 30)	Ibuprofen (n = 32)
Cesarean delivery, No. (%)	54 (75)	56 (80)	26 (62)	27 (71)	28 (93)	29 (91)
Small for gestational age, No. (%)	12 (17)	14 (20)	4 (10)	5 (13)	8 (27)	9 (28)
Intubation at 24 h, No. (%)	64 (89)	61 (87)	42 (100)	36 (95)	22 (73)	25 (78)
At randomization, No. (%)						
Intubation	40 (56)	37 (53)	31 (74)	26 (68)	9 (30)	11 (34)
N-CPAP	18 (25)	18 (26)	10 (24)	10 (26)	15 (50)	16 (50)
HFNC	14 (19)	15 (21)	1 (2)	2 (5)	6 (20)	5 (16)
Inotropes before randomization	7 (10)	7 (10)	5 (12)	5 (13)	2 (7)	2 (6)
PDA-associated variables						
PDA size at randomization, mean (SD)	2.5 (0.6)	2.5 (0.5)	2.4 (0.5)	2.4 (0.5)	2.8 (0.6)	2.6 (0.6)
LA/Ao ratio, mean (SD)	1.69 (0.35)	1.61 (0.41)	1.65 (0.34)	1.57 (0.37)	1.67 (0.47)	1.74 (0.38)
E/A ratio, mean (SD)	0.88 (0.21)	0.85 (0.20)	0.84 (0.22)	0.78 (0.19)	0.93 (0.19)	0.95 (0.17)
NT-proBNP at randomization, mean (SD), pg/mL	14 514 (10 363)	13 355 (10 126)	13 848 (9922)	15 167 (10 707)	15 447 (11 056)	11 203 (9088)
Age at ibuprofen or placebo administration, mean (SD), d	8.4 (2.5)	8.3 (2.3)	8.6 (2.2)	8.9 (2.3)	8.3 (2.8)	7.5 (2.4)

Table 2. Primary and Secondary Outcomes

Outcome	Total (n = 142)			Gestational age					
				23-26 wk (n = 80)			27-30 wk (n = 62)		
	Noninter-vention (n = 72)	Ibuprofen (n = 70)	*P* value	Noninter-vention (n = 42)	Ibuprofen (n = 38)	*P* value	Noninter-vention (n = 30)	Ibuprofen (n = 32)	*P* value
Primary outcome									
BPD or death	32 (44)	35 (50)	.51	26 (62)	25 (66)	.72	6 (20)	10 (31)	.31
Secondary outcomes									
Major morbidity/mortality, No. (%)									
BPD	27/67 (40)	29/64 (45)	.56	21/37 (57)	21/34 (62)	.67	6 (20)	8/30 (27)	.54
Death before discharge	6 (8)	6 (9)	.96	6 (14)	4 (11)	.74	0	2 (6)	.49
IVH (grade ≥III)	4 (6)	2 (3)	.68	3 (7)	1 (3)	.62	1 (3)	1 (3)	>.99
ROP (stage ≥3)	14 (19)	15 (21)	.77	13 (31)	14 (37)	.58	1 (3)	1 (3)	>.99
NEC (stage ≥IIb)	3 (4)	7 (10)	.21	3 (7)	4 (11)	.70	0	3 (9)	.12
Gastrointestinal surgery	6 (8)	9 (13)	.38	6 (14)	5 (13)	.88	0	4 (13)	.11
Sepsis	4 (6)	10 (14)	.08	4 (10)	9 (24)	.09	0	1 (3)	.49
Oxygen or ventilator dependency until hospital discharge, (IQR), d									
Ventilator support	19 (2-31)	17 (1-36)	.76	25 (18-39)	28 (6-48)	.87	2 (0-18)	3 (0-18)	.66
N-CPAP/HFNC	58 (28-72)	51 (26-73)	.60	71 (66-75)	73 (51-80)	.90	26 (12-46)	27 (9-45)	.70
Supplemental oxygen	22 (8-41)	24 (6-34)	.54	36 (17-43)	30 (24-40)	.91	18 (3-26)	8.5 (1-23)	.25

PDA-related outcomes, No. (%)									
Surgical ligation	0	1 (1)		0	1 (3)		0	0	
Backup oral ibuprofen treatment	0	1 (1)		0	0		0	1 (3)	
NT-proBNP 2 wk after randomization, mean (SD), pg/mL	13 812 (13 468)	11 552 (11 480)	.43	19 206 (13 384)	16 361 (11 040)	.50	6800 (10 028)	5813 (9249)	.53
Ductal closure, No. (%)									
1 wk After randomization	3 (4)	14 (20)	.003	1 (2)	3 (8)	.34	2 (7)	11 (34)	.007
At 36 wk PMA	50 (69)	51 (73)	.49	30 (71)	27 (71)	.86	20 (67)	24 (75)	.2
Before hospital discharge	59 (82)	62 (89)	.27	38 (90)	34 (89)	>.99	21 (70)	6 (81)	.12
Transcatheter PDA occlusion at OPD	4 (6)	2 (3)	.40	1 (2)	1 (3)	.97	3 (10)	1 (3)	.27
Other outcomes									
Full enteral feeding (>120 mL/kg/d), mean (SD), d	26.3 (14.4)	29.2 (16.3)	.39	32.0 (13.3)	36.1 (16.0)	.27	20.1 (13.1)	21.0 (12.6)	.78
Oliguric renal failure, No. (%)[a]	6 (8)	8 (11)	.54	6 (14)	7 (18)	.62	0	1 (3)	.33
Nonoliguric renal dysfunction, No. (%)[b]	9 (13)	15 (21)	.16	6 (14)	9 (24)	.28	2 (7)	7 (22)	.09
Highest serum creatinine after randomization, mean (SD), mg/dL	1.2 (0.9)	1.0 (0.4)	.95	1.5 (1.1)	1.2 (0.4)	.75	0.8 (0.4)	0.8 (0.3)	.38
Body weight at 36 wk PMA, mean (SD), g	1949 (360)	1894 (418)	.42	1885 (312)	1815 (380)	.40	2028 (403)	1986 (447)	.71

Abbreviations: BPD, bronchopulmonary dysplasia; HFNC, high-flow nasal cannula; IQR, interquartile range; IVH, intraventricular hemorrhage; N-CPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; SI conversion factor: To convert serum creatinine to millimoles per liter, multiply by 88.4.

[a] Urine output less than 0.5 mL/kg/d for more than 24 hours combined with

- Conclusion- Non-intervention showed noninferiority compared with ibuprofen treatment in closing of hemodynamically significant PDA and reduction of BPD or death.

The non inferiority of non intervention over ibuprofen might be attributable to the low efficacy of oral ibuprofen for closing PDA, especially in infants born at 23 to 26weeks gestation.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Expectant Management or Early Ibuprofen for Patent Ductus Arteriosus

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Research Question

Whether an expectant management is noninferior to early ibuprofen treatment for PDA in preterm infants with respect to necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death as assessed at a postmenstrual age of 36 weeks.

RESULTS

A total of 273 infants underwent randomization. The median gestational age was

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- International, multicenter, randomized controlled, noninferiority trial conducted at 17 neonatal intensive

Exclusion criteria

- Contraindications to the administration of ibuprofen
- Use of a cyclooxygenase inhibitor before randomization
- Persistent pulmonary hypertension (defined as a transductal right-to-left shunt during ≥33% of the cardiac cycle)
- Congenital heart defect (other than PDA or patent foramen ovale)
- Life threatening congenital defect
- chromosomal abnormality, or a congenital anomaly that was associated with an abnormal neurodevelopmental outcome.

- Stratified according to gestational age (<26 weeks or ≥26 weeks).

Intervention-

- In the **expectant-managemen**t group, no treatment was initiated with the intention of closing the PDA.
- Open-label pharmacologic treatment could be considered only if prespecified criteria had been met for clinical and echocardiographic findings of cardiovascular failure associated with a clinically significant left-to-right shunt.

Open label criterion

- Exclusion of other causes of cardiovascular failure (e.g. sepsis or congenital heart defect)

AND

- Clinical findings of cardiovascular failure secondary to significant ductal left-to-right shunting:
  - Signs of systemic hypoperfusion (refractory systemic hypotension and/or serum lactate> 2.5 mmol/L)

    and
  - Signs of pulmonary hyperperfusion (prolonged ventilator dependency).

AND

- Echocardiographic findings of significant ductal left-to-right shunting
  a) Diameter of PDA > 1.5 mm, and;
  b) Unrestricted ductal L-R shunting ('pulsatile pattern'): end-diastolic flow velocity < 50% of peak flow velocity, and;
  c) End-diastolic flow velocity of LPA> 0.3 m/s, and;
  d) LA/Ao> 1.5

  AND

  a) Severe left ventricular failure (mitral regurgitation), and;
  b) Disturbed end-organ perfusion (retrograde diastolic blood flow in descending aorta)

In the **early-ibuprofen group**

- Ibuprofen was administered within 3 hours after randomization
- After complete course of ibuprofen, echo was performed at least 12 hours after the last dose
- If closure was not achieved, 2nd dose ibuprofen course was given
- If still not achieved then either 3rd dose or ductal ligation was done

- Non-inferiority margin 10%.
- Trial enrollment ended on December 15, 2020,

Outcome

Primary outcome- composite of necrotizing enterocolitis (defined as Bell's stage IIa or higher), moderate-to-severe bronchopulmonary dysplasia, or death as assessed at a postmenstrual age of 36 weeks.

done

Maternal and Neonatal Characteristics at Baseline.*

Characteristic	Expectant Management (N=136)	Early Ibuprofen (N=137)
Maternal		
Age — yr	30.4±5.4	31.0±5.1
Race or ethnic group — no. (%)†		
White	102 (75.0)	110 (80.3)
Mediterranean	10 (7.4)	9 (6.6)
African	12 (8.8)	7 (5.1)
Asian	2 (1.5)	4 (2.9)
Latin American	2 (1.5)	3 (2.2)
Unknown	8 (5.9)	4 (2.9)
Obstetrical condition — no. (%)		
Preeclampsia	15 (11.0)	18 (13.1)
HELLP syndrome	7 (5.1)	1 (0.7)
Placental abruption	6 (4.4)	3 (2.2)
PPROM	36 (26.5)	40 (29.2)
Clinical chorioamnionitis	52 (38.2)	53 (38.7)
Medication history — no./total no. (%)		
NSAID	15/136 (11.0)	19/137 (13.9)
Magnesium sulfate	86/136 (63.2)	85/137 (62.0)
Antenatal glucocorticoid		
Any	119/135 (88.1)	126/135 (93.3)
Course completed	73/135 (54.1)	76/135 (56.3)
Tocolysis	79/136 (58.1)	84/135 (62.2)
Type of delivery — no. (%)		
Vaginal	86 (63.2)	76 (55.5)
Cesarean section	50 (36.8)	61 (44.5)
Multiple birth — no. (%)	47 (34.6)	50 (36.5)

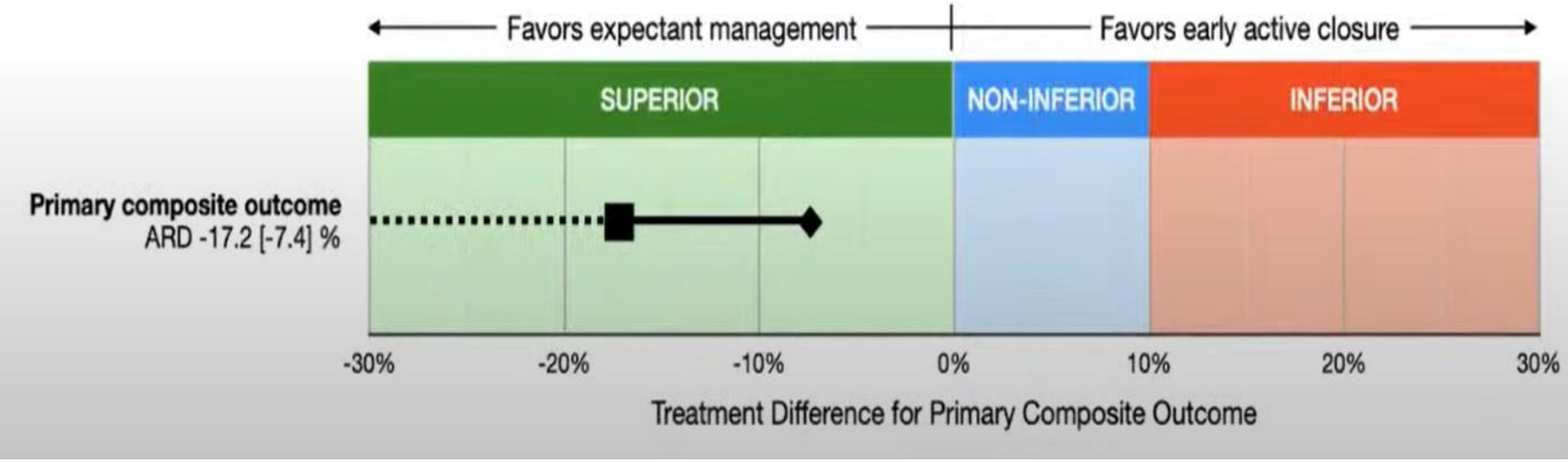
Cesarean section	90 (90.8)	81 (44.5)
Multiple birth — no. (%)	47 (34.6)	50 (36.5)
Neonatal		
Median gestational age (IQR) — wk	26.1 (25.4–27.0)	26.0 (25.1–27.0)
Median birth weight (IQR) — g	863 (748–984)	825 (715–970)
Outborn — no. (%)	10 (7.4)	8 (5.8)
Male sex — no. (%)	70 (51.5)	70 (51.1)
Median Apgar score at 5 min (IQR)	7 (6–8)	8 (7–8)
Support during fetal–neonatal transition — no. (%)	133 (97.8)	137 (100)
Noninvasive respiratory support	101 (74.3)	103 (75.2)
Invasive respiratory support	32 (23.5)	34 (24.8)
Circulatory support	0	0
Respiratory distress syndrome — no. (%)	117 (86.0)	116 (84.7)
Surfactant administration		
Infants — no./total no. (%)	103/117 (88.0)	106/116 (91.4)
Median no. of surfactant doses (IQR)	1 (1–2)	1 (1–2)
Median postnatal age at time of echocardiography (IQR) — hr	57 (47–65)	57 (44–64)
Median diameter of patent ductus arteriosus (IQR) — mm	2.1 (1.8–2.5)	2.1 (1.8–2.6)

* Plus–minus values are means ±SD. IQR denotes interquartile range; HELLP hemolysis, elevated liver enzymes, and low platelets; NSAID nonsteroidal antiinflammatory drug; and PPROM preterm premature rupture of membranes.
† Race or ethnic group was reported by the mothers.

PRIMARY OUTCOME

Table 2. Primary Outcome and Its Components.*

Outcome	Intention-to-Treat Analysis				Per-Protocol Analysis			
	Expectant Management (N=136)	Early Ibuprofen (N=137)	Difference (95% CI)†	Risk Ratio (95% CI)	Expectant Management (N=133)	Early Ibuprofen (N=132)	Difference (95% CI)†	Risk Ratio (95% CI)
	number (percent)		*percentage points*		*number (percent)*		*percentage points*	
Composite primary outcome								
Necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death‡	63 (46.3)	87 (63.5)	−17.2 (−7.4)§	0.73 (0.59 to 0.91)	60 (45.1)	83 (62.9)	−17.8 (−7.9)§	0.72 (0.57 to 0.90)



Primary Outcome and Its Components.*

Outcome	Intention-to-Treat Analysis				Per-Protocol Analysis			
	Expectant Management (N=136)	Early Ibuprofen (N=137)	Difference (95% CI)†	Risk Ratio (95% CI)	Expectant Management (N=133)	Early Ibuprofen (N=132)	Difference (95% CI)†	Risk Ratio (95% CI)
	number (percent)		*percentage points*		*number (percent)*		*percentage points*	
Composite primary outcome								
Necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death‡	63 (46.3)	87 (63.5)	−17.2 (−7.4)§	0.73 (0.59 to 0.91)	60 (45.1)	83 (62.9)	−17.8 (−7.9)§	0.72 (0.57 to 0.90)
Components of primary outcome¶								
Necrotizing enterocolitis	24 (17.6)	21 (15.3)	2.3 (−6.5 to 11.1)	1.15 (0.67 to 1.97)	23 (17.3)	21 (15.9)	1.4 (−7.6 to 10.3)	1.09 (0.63 to 1.87)
Moderate-to-severe bronchopulmonary dysplasia‖	39 (33.3)	57 (50.9)	−17.6 (−30.2 to −5.0)	0.66 (0.48 to 0.90)	37 (32.2)	55 (50.5)	−18.3 (−31.0 to −5.6)	0.64 (0.46 to 0.88)
Death	19 (14.0)	25 (18.2)	−4.3 (−13.0 to 4.4)	0.77 (0.44 to 1.32)	18 (13.5)	23 (17.4)	−3.9 (−12.6 to 4.8)	0.78 (0.44 to 1.37)

CI denotes confidence interval

Secondary Outcome Measures (Intention-to-Treat Analysis).*

Secondary Outcome	Expectant Management (N=136)	Early Ibuprofen (N=137)	Difference (95% CI)†	Risk Ratio (95% CI)†
	number (percent)		*percentage points*	
Surgical patent ductus arteriosus ligation	0	3 (2.2)	−2.2 (−4.6 to 0.3)	NA
Death at 28 days	13 (9.6)	25 (18.2)	−8.7 (−16.8 to −0.5)	0.52 (0.28 to 0.98)
Pulmonary hemorrhage	4 (2.9)	1 (0.7)	2.2 (−1.0 to 5.4)	4.03 (0.46 to 35.59)
Pulmonary air leakage	6 (4.4)	16 (11.7)	−7.3 (−13.7 to −0.9)	0.38 (0.15 to 0.94)
Pneumothorax	2 (1.5)	3 (2.2)	−0.7 (−3.9 to 2.5)	0.67 (0.11 to 3.96)
Pulmonary interstitial emphysema	5 (3.7)	13 (9.5)	−5.8 (−11.7 to 0.0)	0.39 (0.14 to 1.06)
Cardiovascular support	60 (44.1)	57 (41.6)	−2.5 (−9.2 to 14.2)	1.06 (0.81 to 1.40)
Volume expansion	45 (33.1)	48 (35.0)	−1.9 (−13.2 to 9.3)	0.94 (0.68 to 1.31)
Inotropes or vasopressors	44 (32.4)	40 (29.2)	−3.2 (−7.8 to 14.1)	1.11 (0.78 to 1.58)
Respiratory support	55 (34 to 72)	56 (36 to 76)	—	−1.0 (−8.0 to 6.0)
Invasive	4 (0 to 11.5)	5 (1 to 14)	—	0 (−1.0 to 1.0)
Noninvasive	47 (30 to 63)	49 (28 to 62)	—	−1.0 (−7.0 to 5.0)
Time until full enteral feeding	10 (9 to 14)	12 (10 to 19)	—	−2.0 (−3.0 to −1.0)

CONCLUSION

Expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age

PDA TOLERATE Trial (n=202)	Sung et al, RCT (n=146)	BeNeDuctus Trial (n= 273)
GA< 28 weeks, 6-14 days and 8-14, with moderate to large PDA with receipt of greater than minimal repiratory support	GA < 30 wk, 6 – 14 days with hs PDA with requirement of any respiratory support	GA< 28 wk, 24 hour to 72 hour postnatal age with echocardiographically confirmed PDA
Echo- PDA ≥ 1.5 mm or PDA: Left PA diameter ≥ 0.5 mm and 1 or more of following 1. LA:Ao ≥ 1.6 mm, 2. Ductus flow velocity ≤2.5 m/s 3. LPA diastolic flow velocity≥ 0.2 m/s, 4. Reverse diastolic flow in descending aorta	Echo- ductal size greater than 1.5 mm with predominant left to right shunt.	Echo- PDA diameter more than 1.5 mm at smallest point and who had transductal left to right shunt.
Rescue cirteria- 1 or more of following 1. Ionotropes dependent hypotension 2. Oliguria tha persists for at least 2 days 3. Requirement of gavange feeding beyond 35 wk pMA 4. Requirement of respiratory support	Rescue criteria- Backup rescue treatment was considered when the condition was refractory to conservative management, including fluid restriction, use of diuretics and ionotropic drugs and modest increase in mean and end expiratory ventilator airway pressure to reduce pulmonary blood flow.	Rescue criteria- exclusion of other causes of cardiovascular failure(e.g sepsis) AND 1. Clinical findings of cardiovascular failure- signs of systemic hypoperfusion AND signs of pulmonary hyperperfusion AND 2. Echo findings of significant left to right shunt AND 3. Severe left ventricular failure AND 4. Disturbed end organ perfusion
48% received rescue treatment in CT group.	None (0%) received backup rescue treatment in CT group.	0.7 %received backup rescue treatment in CT group.(25% received Paracetamol as cointervention)

Cochrane Library

Cochrane Database of Systematic Reviews

Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants (Review)

Mitra S, Scrivens A, von Kursell AM, Disher T

Objectives - To assess the effectiveness and safety of early treatment strategies versus expectant management for an hs-PDA in reducing mortality and morbidity in preterm infants.

Mitra S, Scrivens A, von Kursell AM, Disher T.
Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants.
Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD013278.
DOI: 10.1002/14651858.CD013278.pub2.

Review question

- Does early treatment (initiated within the first

Inclusion criteria

RCTs in which early pharmacological treatment, defined as treatment initiated within the first seven days after birth, was compared to no intervention, placebo or other non-pharmacological expectant management strategies for treatment of an hs-PDA in preterm (< 37 weeks' postmenstrual age) or low birth weight (< 2500 grams) infants, diagnosed clinically or via echocardiography (or both) in the first seven days of life.

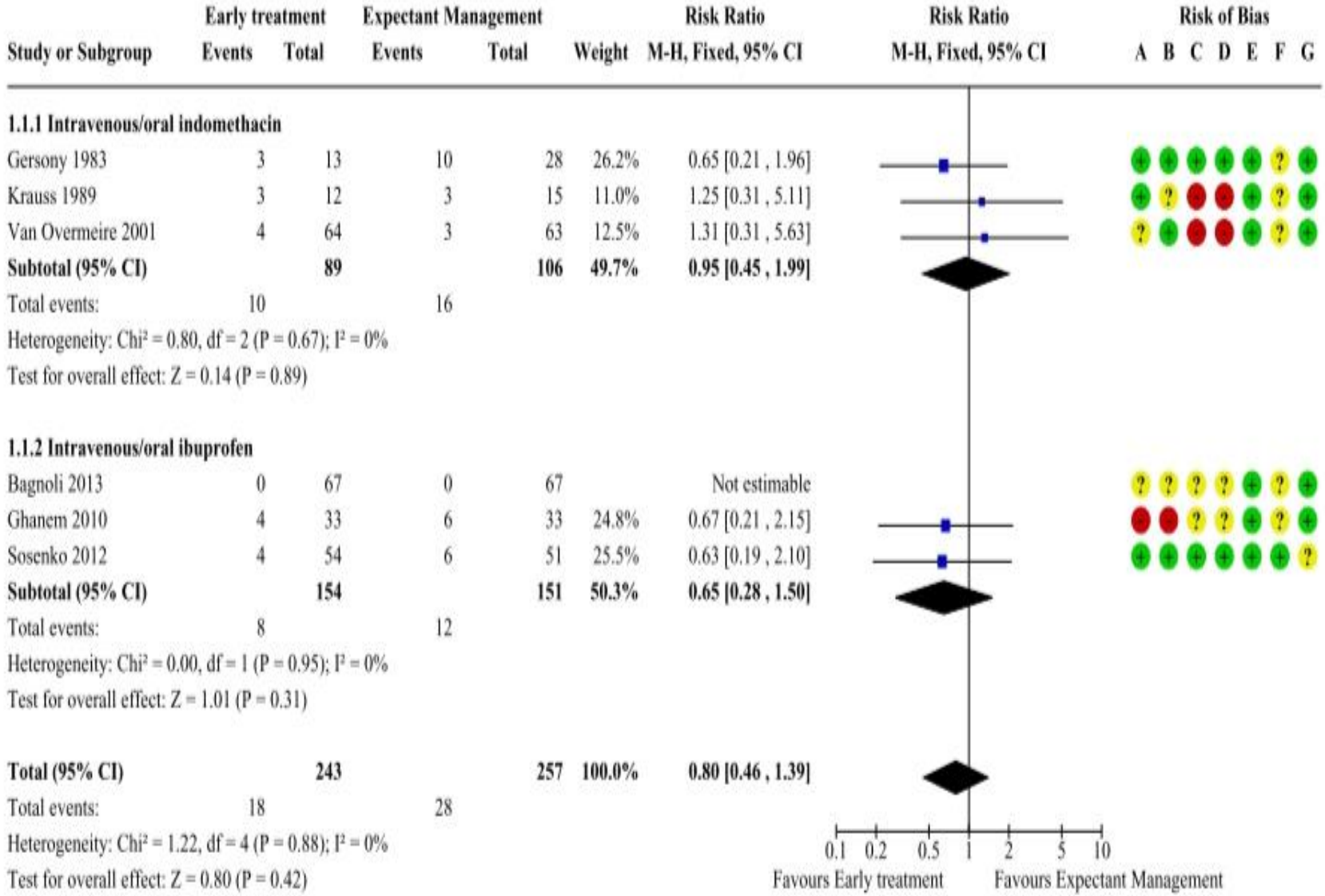
- A hemodynamically significant PDA was defined clinically by the presence of a precordial murmur along with one or more of the following signs: hyperdynamic precordial impulse, tachycardia, bounding pulses, widened pulse pressure, worsening respiratory status, hypotension, or cardiac failure.

- Echocardiographically by a moderate-to-large transductal diameter (PDA diameter greater than 1.5 mm with or without unrestrictive pulsatile flow, i.e. maximum systolic shunt velocity less than 2 m/second) with or without

1. evidence of pulmonary over circulation (left atrium to aortic root ratio greater than 1.5 or
2. isovolumetric relaxation time less than 55 m seconds or
3. E:A ratio of 1.0 or greater or left ventricular output greater than 300 mL/kg/ minute or
4. diastolic disturbance in the main pulmonary artery) with or without evidence of systemic hypoperfusion (absent/reversed diastolic flow in the postductal descending aorta or celiac trunk or middle cerebral artery).

- 14 RCTs, enrolled 910 infants. Seven RCTs compared early treatment (defined as treatment initiated by seven days of age) versus expectant management and seven RCTs compared very early treatment (defined as treatment initiated by 72 hours of age) versus expectant management.
- Primary outcome- All cause mortality during hospital stay.

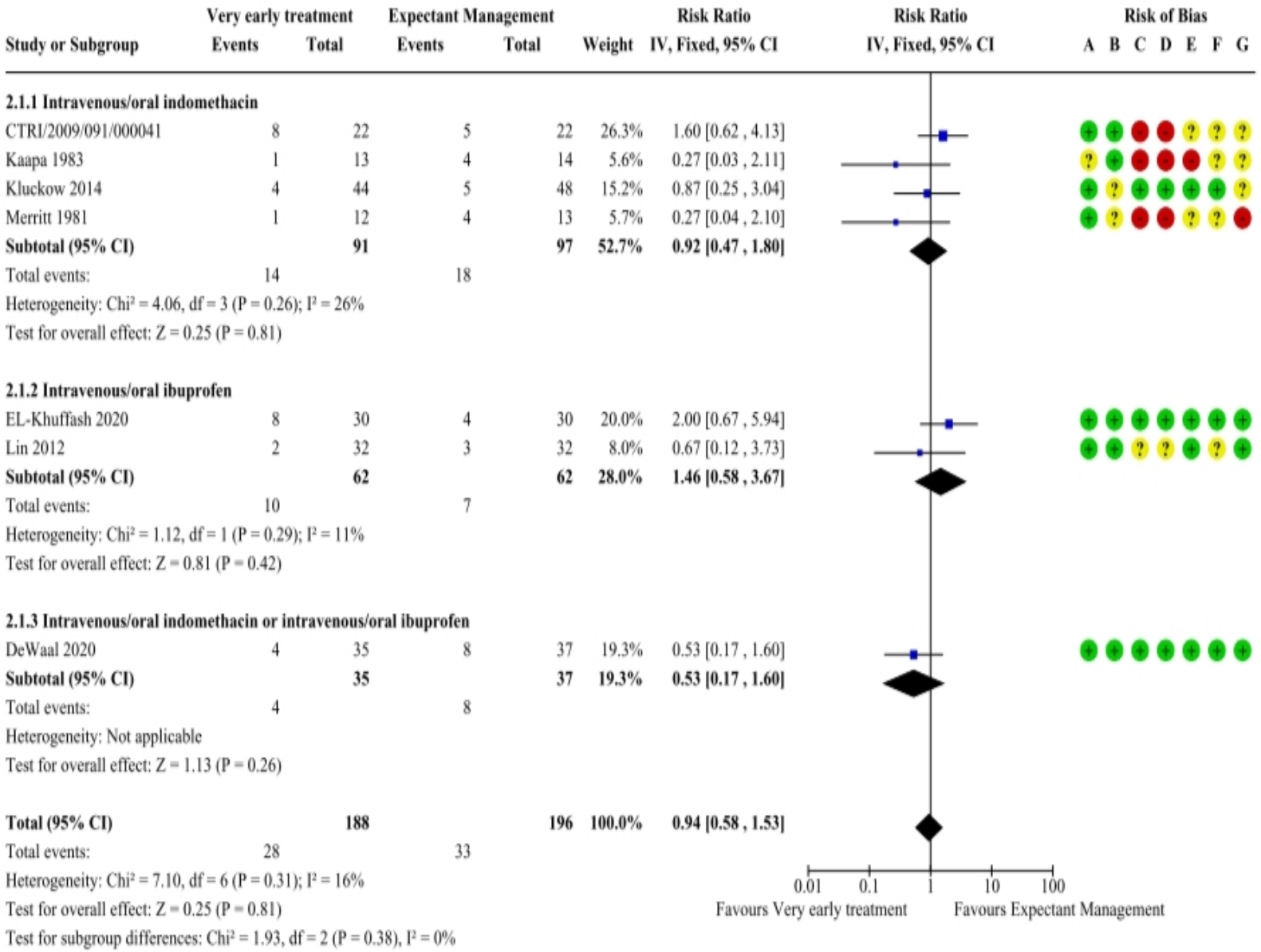
Figure 4. Forest plot of comparison: 1 Early treatment vs expectant management, outcome: 1.1 All-cause mortality during hospital stay.



Early treatment compared to expectant management for preterm infants

Outcomes	Risk with expectant managemnt	Risk with early managemnt	Relative effect(95% CI)	No. of participant	GRADE of evidence
All cause mortality	109/1000	87/1000	RR 0.80(0.46-1.39)	500(6 RCT)	Moderate
surgical ligation or transcatheter occlusion	145/I000	156/1000	RR 1.08(0.65-I.80)	432(4 RCT)	Very low
Chronic lung disease	263/1,000	237/1,000	RR 0.90 (0.62 -I.29)	339 (4 RCT)	Moderate
Severe IVH (grade III and IV)	95/I000	79/I000	RR 0.83 (0.32-2.I6)	I7I (2 RCT)	Low
NEC stage II or greater	29/I000	68/I000	RR 2.34 (0.86-6.4I)	473 (5 RCT)	Low

Figure 6. Forest plot of comparison: 2 Very early treatment vs expectant management, outcome: 2.1 All-cause mortality during hospital stay.



Very Early treatment compared to expectant management for preterm infants

Outcomes	Risk with expectant managemnt	Risk with very early managemnt	Relative effect(95% CI)	No. of participant	GRADE of evidence
All cause mortality	168/1000	158/1000	RR 0.94(0.58-	384(7 RCT)	Moderate
IV)					
NEC stage II or greater	83/I000	89/I000	RR I.08 (0.53- 2.2I)	332 (5 RCT)	Moderate

Conclusion

Early or very early pharmacotherapeutic treatment of an hs-PDA probably does not reduce mortality in preterm infants (moderate-certainty evidence).

THANK YOU!

- Question 1- What should be our screening protocol for PDA. In which set of patient we should screen for PDA?
- Question 2- What should be the timing of screening for PDA?
- Question 3- When should we go for pharmacological closure of PDA? Echo and clinical Parameters?

1. Preterm less than 28 weeks, who are ventilator dependent even after PNA 7 days and who have clinical findings such as increased requirement of respiratory support, bounding pulses, wide pulse pressure, shock acidosis, oliguria that is not otherwise explained.
2. Timing of Echo- After 7-10 days.

Pharmacological closure

1. Clinical findings of significant PDA such as increased requirement of respiratory support e.g., FiO2> 40%, hypoperfusion need for ionotropes, acidosis, oliguria that is not otherwise explained, bounding pulses, wide pulse pressure

AND

2. ECHO- PDA > 2mm or PDA:LPA > 1 with, Diastolic flow reversal in descending aorta, Flow velocity < 2.5 m/sec, mean pressure gradient < 8 mmHg, LA:Ao >1.6

Journal Club- Baby OSCAR trial

Presenter- Dr Sachin

DrNB 3rd year resident

Sir Gangaram Hospital, New Delhi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Selective Early Treatment of Patent Ductus Arteriosus with Ibuprofen

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ABSTRACT

BACKGROUND

The cyclooxygenase inhibitor ibuprofen may be used to treat patent ductus arteriosus (PDA) in preterm infants. Whether selective early treatment of large PDAs with ibuprofen would improve short-term outcomes is not known.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial evaluating early treatment (≤72 hours after birth) with ibuprofen for a large PDA (diameter of ≥1.5 mm with pulsatile flow) in extremely preterm infants (born between 23 weeks 0 days' and 28 weeks 6 days' gestation). The primary outcome was a composite of death or moderate or severe bronchopulmonary dysplasia evaluated at 36 weeks of postmenstrual age.

baby-OSCAR trial: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies.

occurred in 176 of 274 (64.2%) in the ibuprofen group and 169 of 285 (59.3%) in

Background

- Survival among extremely preterm infants has increased.
- Presence of a large patent ductus arteriosus (PDA) in extremely preterm infants - associated with higher mortality and morbidities.

Background

Treatment strategies-

- Prophylactic treatment - within 24 h of birth
- Early symptomatic treatment- usually 3–7 days after birth
- late symptomatic treatment- after one week of age

- Prophylactic treatment - unnecessarily expose to potentially serious side effects.

- However, delaying treatment until babies become symptomatic could result in loss of treatment benefit as irreversible damage may have already been done.

- Functional echocardiography- infants can be screened to identify large PDAs with unrestricted flow that are unlikely to close spontaneously.

- Selective early targeted treatment of patients with these PDAs may make it possible to avoid unnecessary treatment of all patients with PDAs.

Hypothesis

- Among patients with a PDA of 1.5 mm or larger in diameter with unrestricted flow identified with the use of bedside echocardiography, early selective treatment (≤72 hours after birth) with ibuprofen would reduce mortality and improve short-term outcomes such as bronchopulmonary dysplasia to a greater extent than placebo.

Trial design

- Multicenter, double-blind, randomized, placebo-controlled trial
- 32 neonatal intensive care units in the United Kingdom.
- July 2015-December 2020
- 653 infants underwent randomization

Inclusion Criteria

After written informed consent was obtained from the parents

- Infants born between 23 weeks 0 days' and 28 weeks 6 days' gestation
- who were less than 72 hours old
- were confirmed by echocardiography to have a large PDA,
- and for whom there were no associated clinical concerns for acute pulmonary hypertension

A large PDA was defined as a PDA with a diameter of at least 1.5 mm and unrestricted transductal pulsatile (left-to-right shunting) flow

Exclusion criteria

- Severe congenital anomaly
- Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen
- Other conditions that would contraindicate the use of ibuprofen (active bleeding especially intracranial or gastrointestinal bleeding, coagulopathy, thrombocytopenia (platelet count < 50,000), renal failure, life threatening infection, pulmonary hypertension, known or suspected necrotising enterocolitis (NEC).

Randomization and Interventions

- Randomization was performed with a secure Web-based system with 24/7 telephone backup ensuring concealment of the group assignments.
- The trial intervention was ibuprofen sodium, and the matched placebo was a clear sterile solution of 0.9% sodium chloride.

Interventions

- Ibuprofen was administered parenterally as a loading dose of 10 mg per kilogram of body weight, followed by two doses of 5 mg per kilogram at least 24 hours apart.
- Placebo was administered as an equal volume of 0.9% sodium chloride.
- Only one course of ibuprofen or placebo was given.

Echo

- Transthoracic echocardiography was performed to assess eligibility within 72 hours after birth and at 3 weeks (18 to 24 days) of age to assess the patency of the PDA while minimizing open-label treatment.

Open label treatment

- Consider open label (Rescue) treatment, both clinical AND echocardiographic criteria are met

1. Clinical findings of inability to wean on ventilator (ventilated for at least 7 days continuously) AND inability to wean oxygen OR Persistent hypotension and/or pulmonary haemorrhage and/or signs of cardiac failure
2. Echocardiographic findings of a large PDA (PDA $\geq$ 2.0 mm with pulsatile flow)

   AND Hyperdynamic circulation and/or ductal steal

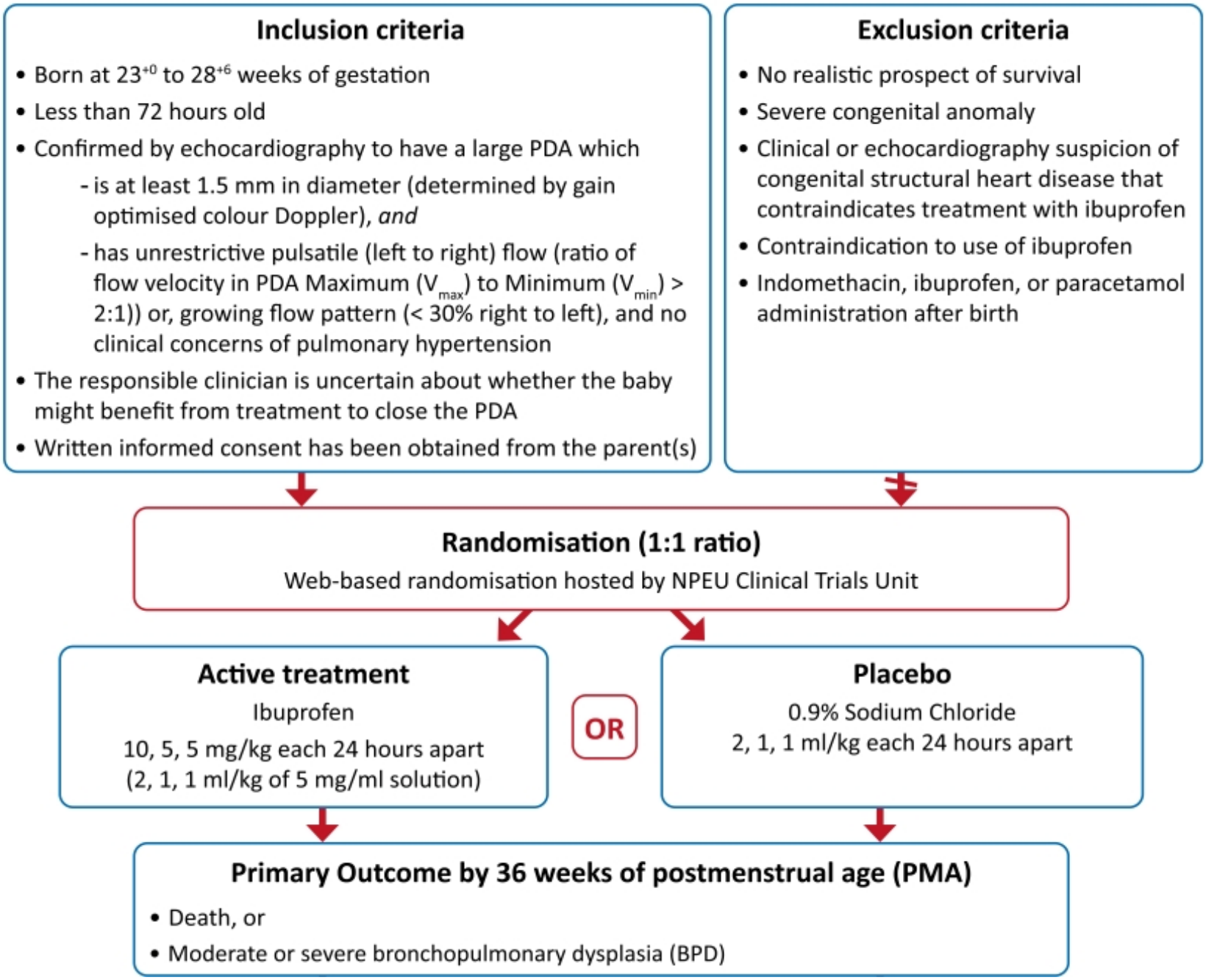
Outcomes

- Primary outcome was a composite of death or moderate or severe bronchopulmonary dysplasia assessed at 36 weeks of postmenstrual age.

Outcomes

Secondary short-term outcomes up to the time of discharge included

- Individual components of the primary outcome
- the severity of bronchopulmonary dysplasia
- severe intraventricular hemorrhage
- cystic periventricular leukomalacia
- retinopathy of prematurity requiring treatment
- clinically significant pulmonary hemorrhage
- acute pulmonary hypertension
- definitive necrotizing enterocolitis
- closed or clinically nonsignificant PDA less than 1.5 mm in diameter with restricted flow at 3 weeks age
- open-label treatment of a PDA causing symptoms
- weight gain, and discharge home while receiving supplemental oxygen


Inclusion criteria
• Born at 23+0 to 28+6 weeks of gestation
• Less than 72 hours old
• Confirmed by echocardiography to have a large PDA which
- is at least 1.5 mm in diameter (determined by gain optimised colour Doppler), and
- has unrestrictive pulsatile (left to right) flow (ratio of flow velocity in PDA Maximum (Vmax) to Minimum (Vmin) > 2:1)) or, growing flow pattern (< 30% right to left), and no clinical concerns of pulmonary hypertension
• The responsible clinician is uncertain about whether the baby might benefit from treatment to close the PDA
• Written informed consent has been obtained from the parent(s)
Exclusion criteria
• No realistic prospect of survival
• Severe congenital anomaly
• Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen
• Contraindication to use of ibuprofen
• Indomethacin, ibuprofen, or paracetamol administration after birth
Randomisation (1:1 ratio)
Web-based randomisation hosted by NPEU Clinical Trials Unit
Active treatment
Ibuprofen
10, 5, 5 mg/kg each 24 hours apart
(2, 1, 1 ml/kg of 5 mg/ml solution)
OR
Placebo
0.9% Sodium Chloride
2, 1, 1 ml/kg each 24 hours apart
Primary Outcome by 36 weeks of postmenstrual age (PMA)
• Death, or
• Moderate or severe bronchopulmonary dysplasia (BPD)

Sample size

- The incidence of the primary outcome was predicted to be 60% in the placebo group.
- A sample of 730 infants was calculated - to detect a clinically important absolute risk reduction of 12 percentage points (i.e., an incidence of 60% in the placebo group and an incidence of 48% in the ibuprofen group) with 90% power and a type I error of 5% under the assumption that 1% of infants would be lost to follow-up.
- Analyses were performed according to the intention-to-treat principle.

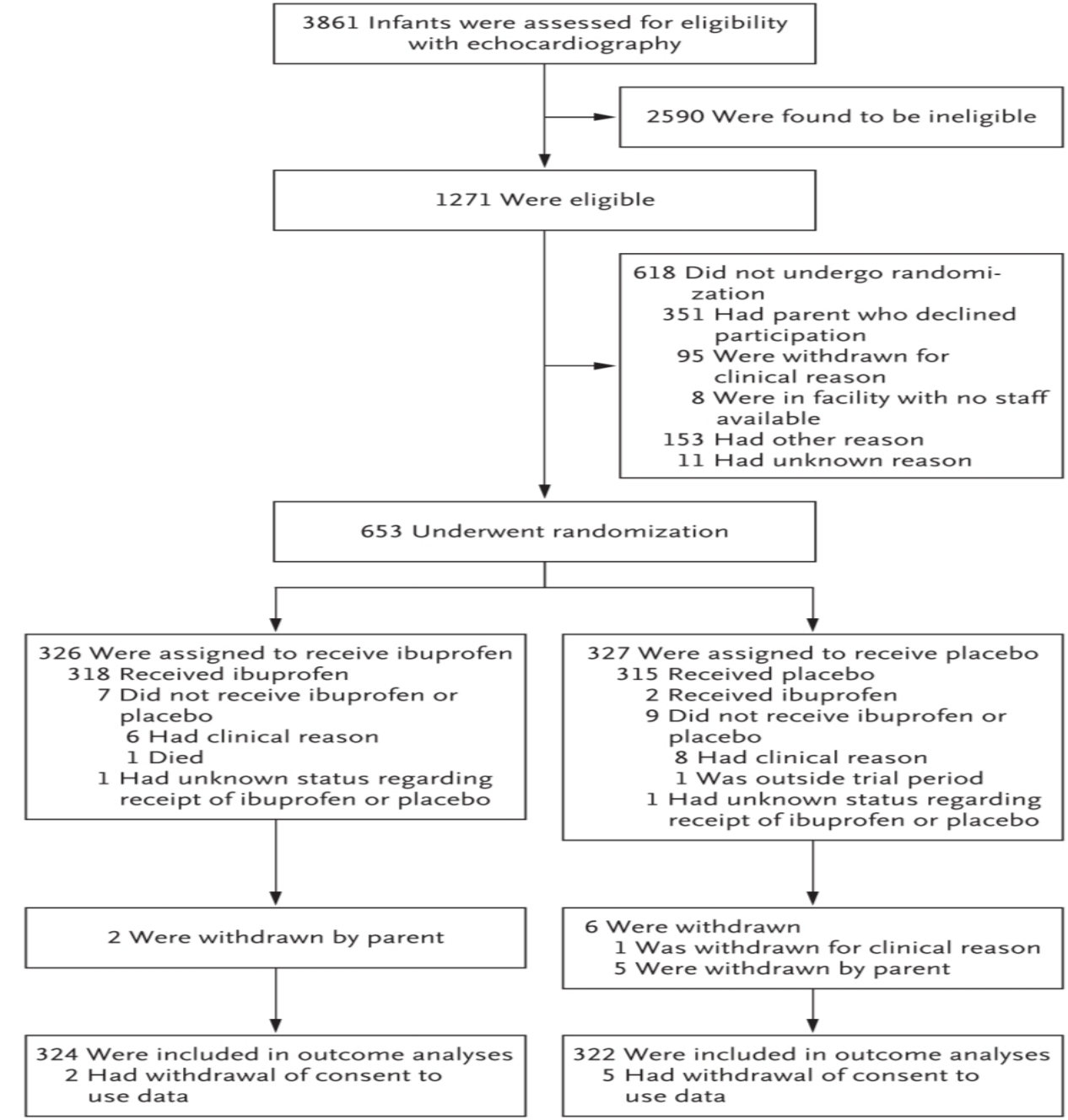


Figure 1. Screening, Randomization, and Inclusion in the Analyses.

Table 1. Maternal and Infant Baseline Characteristics.*

Characteristic	Ibuprofen (N = 324)	Placebo (N = 322)
Maternal characteristics		
Age — yr	30.1±6.5	30.2±6.2
Race — no./total no. (%)†		
White	223/299 (74.6)	223/303 (73.6)
Asian	39/299 (13.0)	45/303 (14.9)
Black	25/299 (8.4)	25/303 (8.3)
Other	12/299 (4.0)	10/303 (3.3)
Infant characteristics at randomization		
Median postnatal age (IQR) — hr	57.5 (43.1–65.6)	56.8 (43.9–66.7)
Postnatal age distribution — no. (%)‡		
<12 hr	2 (0.6)	2 (0.6)
12 to <24 hr	15 (4.6)	14 (4.3)
24 to <48 hr	90 (27.8)	89 (27.6)
48 to <72 hr	217 (67.0)	217 (67.4)

Table 1. Maternal and Infant Baseline Characteristics.*

Characteristic	Ibuprofen (N=324)	Placebo (N=322)
Gestational age — wk‡	26.1±1.5	26.1±1.6
Mode of birth — no. (%)		
Vaginal birth, cephalic	141 (43.5)	138 (42.9)
Vaginal birth, breech	50 (15.4)	46 (14.3)
Cesarean section before onset of labor	83 (25.6)	80 (24.8)
Cesarean section after onset of labor	50 (15.4)	58 (18.0)
Birth weight — g	839.9±204.8	852.9±211.3
Male sex — no. (%)‡	180 (55.6)	175 (54.3)
Apgar score 5 min after birth		
Median score (IQR)	8.0 (6.0–9.0)	7.0 (6.0–9.0)
No. of patients with data	278	288
Median diameter of PDA (IQR) — mm	2.2 (1.9–2.5)	2.2 (1.9–2.6)
Distribution of PDA diameters — no. (%)‡		
≥1.5 mm and <2.0 mm	84 (25.9)	82 (25.5)
≥2.0 mm and <3.0 mm	201 (62.0)	201 (62.4)
≥3.0 mm	39 (12.0)	39 (12.1)
Mode of respiratory support — no. (%)‡		
Invasive ventilation with endotracheal tube	206 (63.6)	204 (63.4)
Noninvasive respiratory support only§	116 (35.8)	115 (35.7)
No mechanical ventilation or pressure support¶	2 (0.6)	3 (0.9)
Receipt of inotropes — no. (%)‡	44 (13.6)	37 (11.5)

Table 2. Primary and Secondary Outcomes.

Outcome	Ibuprofen (N=324)	Placebo (N=322)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Primary outcome: death or moderate or severe bronchopulmonary dysplasia assessed at 36 wk of postmenstrual age — no./total no. (%)†	220/318 (69.2)	202/318 (63.5)	1.09 (0.97–1.22)	1.09 (0.98–1.20)‡
Secondary outcomes				
Death by 36 wk of postmenstrual age — no./total no. (%)	44/323 (13.6)	33/321 (10.3)	1.33 (0.87–2.02)	1.32 (0.92–1.90)
Survival to 36 wk of postmenstrual age — no. of infants	280	289		
Moderate or severe bronchopulmonary dysplasia at 36 wk of postmenstrual age — no./total no. (%)	176/274 (64.2)	169/285 (59.3)	1.08 (0.95–1.23)	1.09 (0.96–1.23)
Any intraventricular hemorrhage — no. (%)	137 (42.3)	132 (41.0)		
Grade I or II without ventricular dilatation	92 (28.4)	98 (30.4)		
Grade III or IV with ventricular dilatation or intraparenchymal abnormality§	45 (13.9)	34 (10.6)	1.32 (0.87–2.00)	1.30 (0.93–1.82)

Table 2. Primary and Secondary Outcomes.

Outcome	Ibuprofen (N=324)	Placebo (N=322)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)*
Cystic periventricular leukomalacia — no. (%)	15 (4.6)	9 (2.8)	1.66 (0.74–3.73)	1.62 (0.69–3.83)
Treatment for retinopathy of prematurity in at least one eye — no. (%)	45 (13.9)	45 (14.0)	0.99 (0.68–1.46)	0.98 (0.68–1.42)
Clinically significant pulmonary hemorrhage — no./total no. (%)¶	24/322 (7.5)	18/322 (5.6)	1.33 (0.74–2.41)	1.39 (0.70–2.77)
Treatment for acute pulmonary hypertension with pulmonary vasodilator — no. (%)	17 (5.2)	16 (5.0)	1.05 (0.54–2.05)	1.04 (0.51–2.13)
Severe necrotizing enterocolitis — no./total no. (%)‖	41/322 (12.7)	41/322 (12.7)	1.00 (0.67–1.49)	1.01 (0.67–1.51)

Open label treatment

•A total of 43 infants (13.3%) in the ibuprofen group and 82 (25.5%) in the placebo group received open-label medical treatment for symptoms attributable to a PDA.

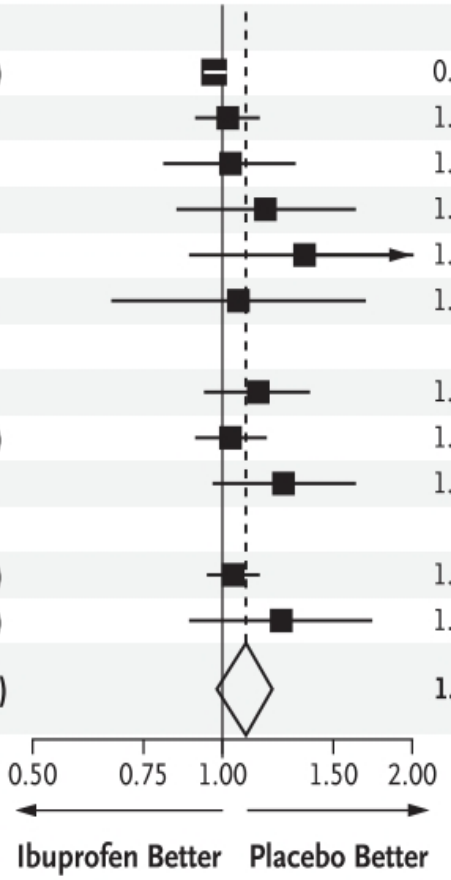
•The percentage of infants who received any open-label treatment (for any indication), including surgical ligation, was 14.2% in the ibuprofen group and 29.8% in the placebo group

• The median interval from randomization to open-label treatment was 11 days (interquartile range, 8 to 17) and 12 days (interquartile range, 7 to 21), respectively.

No. of infants with data	257	265		
Mean change in z score between birth and discharge	−1.0±1.0	−1.1±1.0	0.1 (−0.1 to 0.2)††	0.1 (−0.1 to 0.2)††

A Primary Outcome

Subgroup	Ibuprofen	Placebo	Risk Ratio (95% CI)
	no. of events/total no. (%)		
Gestational age at birth			
23 to 23+6 days	28/29 (97)	29/29 (100)	0.97 (0.94–1.01)
24 to 24+6 days	53/59 (90)	51/58 (88)	1.02 (0.91–1.14)
25 to 25+6 days	46/64 (72)	44/63 (70)	1.03 (0.81–1.30)
26 to 26+6 days	40/65 (62)	35/66 (53)	1.17 (0.85–1.62)
27 to 27+6 days	34/59 (58)	22/54 (41)	1.35 (0.89–2.05)
28 to 29+6 days	19/42 (45)	21/48 (44)	1.06 (0.67–1.68)
Size of PDA at randomization			
1.5 to <2.0 mm	58/83 (70)	50/81 (62)	1.14 (0.94–1.37)
2.0 to <3.0 mm	131/196 (67)	127/198 (64)	1.03 (0.91–1.17)
≥3.0 mm	31/39 (79)	25/39 (64)	1.25 (0.97–1.62)
Mode of respiratory support at randomization			
Invasive ventilation	164/205 (80)	155/202 (77)	1.04 (0.95–1.14)
Noninvasive ventilation or no support	56/113 (50)	47/116 (41)	1.24 (0.89–1.72)
Overall	**220/318 (69)**	**202/318 (64)**	**1.09 (0.98–1.20)**



B Severe Necrotizing Enterocolitis

Subgroup	Ibuprofen	Placebo	Risk Ratio (95% CI)
	no. of events/total no. (%)		
Size of PDA at randomization			
1.5 to <2.0 mm	11/84 (13)	13/82 (16)	0.81 (0.52–1.28)
≥2.0 mm	30/239 (13)	28/240 (12)	1.10 (0.67–1.81)
Overall	**41/323 (13)**	**41/322 (13)**	**1.01 (0.67–1.51)**

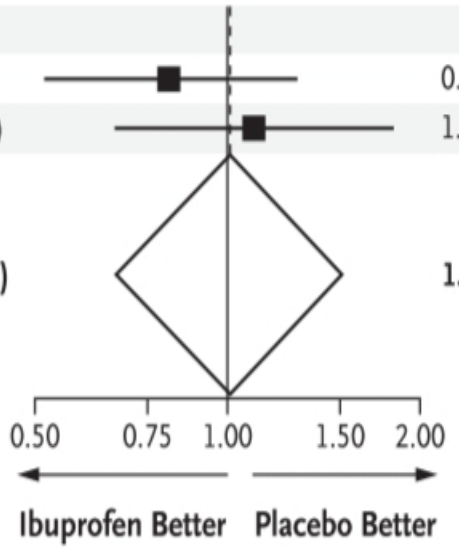


Table 3. Process Outcomes.

Outcome	Ibuprofen (N=324)	Placebo (N=322)
Did not receive assigned intervention — no. (%)	7 (2.2)	11 (3.4)
Did not receive all doses of ibuprofen or placebo — no. (%)	41 (12.7)	34 (10.6)
Doses received — no. (%)		
0	7 (2.2)	9 (2.8)
1	17 (5.2)	11 (3.4)
2	17 (5.2)	14 (4.3)
3	283 (87.3)	288 (89.4)
Reason for early discontinuation — no./total no. (%)*		
Clinical decision	38/41 (92.7)	26/34 (76.5)
Parental request	0	1/34 (2.9)
Infant death	2/41 (4.9)	2/34 (5.9)
Missed dose or doses in error	1/41 (2.4)	2/34 (5.9)
Intervention window outside of trial period	0	2/34 (5.9)
Transfer out of recruiting site	0	1/34 (2.9)
Median age at first dose (IQR) — hr†	61 (47–68)	61 (48–69)
Distribution of median age at first dose — no. (%)		
0 to <24 hr	14/316 (4.4)	14/313 (4.5)
24 to <48 hr	68/316 (21.5)	65/313 (20.8)
48 to <72 hr	220/316 (69.6)	225/313 (71.9)
≥72 hr	14/316 (4.4)	9/313 (2.9)
Received second or third dose outside of dosing window — no./total no. (%)	5/297 (1.7)	4/301 (1.3)
Echocardiography not performed at 3 wk of age — no./total no. (%)‡	65/291 (22.3)	60/301 (19.9)
Oxygen reduction test not performed when infant was eligible — no./total no. (%)§	13/86 (15.1)	13/94 (13.8)

Limitation

- Open-label therapy in 29.8% in the placebo group: difficult to identify between-group differences in clinical outcomes

Conclusion

- Among extremely preterm infants with a large PDA, they found no evidence that early treatment with ibuprofen was associated with a lower risk of death or moderate or severe bronchopulmonary dysplasia than placebo at 36 weeks of postmenstrual age.