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.

RESULTS

A total of 326 infants were assigned to receive ibuprofen and 327 to receive placebo; 324 and 322, respectively, had data available for outcome analyses. A primary-outcome event occurred in 220 of 318 infants (69.2%) in the ibuprofen group and 202 of 318 infants (63.5%) in the placebo group (adjusted risk ratio, 1.09; 95% confidence interval [CI], 0.98 to 1.20; P=0.10). A total of 44 of 323 infants (13.6%) in the ibuprofen group and 33 of 321 infants (10.3%) in the placebo group died (adjusted risk ratio, 1.32; 95% CI, 0.92 to 1.90). Among the infants who survived to 36 weeks of postmenstrual age, moderate or severe bronchopulmonary dysplasia occurred in 176 of 274 (64.2%) in the ibuprofen group and 169 of 285 (59.3%) in the placebo group (adjusted risk ratio, 1.09; 95% CI, 0.96 to 1.23). Two unforeseeable serious adverse events occurred that were possibly related to ibuprofen.

CONCLUSIONS

The risk of death or moderate or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age was not significantly lower among infants who received early treatment with ibuprofen than among those who received placebo. (Funded by the National Institute for Health Research Health Technology Assessment Programme; Baby-OSCAR ISRCTN Registry number, ISRCTN84264977.)

Over the past two decades, survival among extremely preterm infants has increased alongside modest reductions in neonatal morbidity, although the incidence of bronchopulmonary dysplasia has increased.[1] In this gestation group, a large (≥1.5 mm in diameter) patent ductus arteriosus (PDA) that is present beyond 3 days of age is associated with higher mortality and morbidity and a higher risk of bronchopulmonary dysplasia than have been reported among infants without a PDA.[2] The incidence of PDA is inversely proportional to gestational age at birth: more than 40% of infants born at less than 28 weeks' gestation have persistent PDA by 4 months of age.[3,4] The risk of bronchopulmonary dysplasia or death in extremely preterm infants also increases with the persistence of PDA beyond 1 to 2 weeks of age.[5]

Various treatment strategies have been investigated for the management of PDA.[6] Prophylaxis with indomethacin or ibuprofen in the first 12 to 24 hours of life has been reported to reduce the risk of severe intraventricular hemorrhage and pulmonary hemorrhage but has not been found to increase survival without neurosensory impairment at 18 months.[7] However, if a prophylactic approach is used, many infants will receive treatment unnecessarily, since PDAs can close spontaneously.[8] Data on the treatment of infants with a symptomatic PDA are limited, and reports of improvements in clinical outcomes are lacking.[9] Consequently, the number of extremely preterm infants with a PDA who are treated pharmacologically has decreased.[10]

With the use of bedside functional echocardiography,[11] infants can now 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.[12] Parenteral indomethacin and ibuprofen have been used for early targeted treatment of PDA, with no evidence of a difference in their efficacy,[13] although the side-effect profile of ibuprofen has been reported to be superior.[6]

We hypothesized that 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.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN

We conducted a multicenter, double-blind, randomized, placebo-controlled trial in 32 neonatal intensive care units in the United Kingdom in accordance with a published protocol (available with the full text of this article at NEJM.org).[14] The main trial was preceded by an internal pilot phase to assess the suitability of trial procedures and recruitment. The clinicians, the infants' families, and the persons who assessed outcomes were unaware of the randomization assignments.[14] The trial was coordinated by the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit at the University of Oxford, United Kingdom (which was responsible for the conduct of the trial), and was overseen by the trial steering committee, acting on the recommendations of an independent data and safety monitoring committee. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Additional details are provided in the Supplementary Appendix, available at NEJM.org.

PATIENTS

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 were considered to be eligible for participation. 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. A full list of the inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix.

RANDOMIZATION

Dynamic randomization was performed with a secure Web-based system that was created and hosted by the NPEU Clinical Trials Unit with 24/7 telephone backup, ensuring concealment of the group assignments. The randomization program used a probabilistic minimization algorithm and assigned patients in a 1:1 ratio to one of the two groups to ensure balance with respect to the size of the PDA, gestational age at birth, age, sex, trial site, whether the infant was from a multiple birth, mode of respiratory support, and whether inotropes were received. Infants in multiple births underwent randomization individually. Participants were enrolled by the delegated clinician at the trial site.[14]

INTERVENTION AND TRIAL PROCEDURES

The trial intervention was ibuprofen sodium, and the matched placebo was a clear sterile solution of 0.9% sodium chloride. Each carton containing ibuprofen or placebo was labeled with a unique code in compliance with the guidance provided in annex 13 of the European Commission guidelines for Good Manufacturing Practice. 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 (Table S2). Only one course of ibuprofen or placebo was given. Prespecified criteria for open-label medical or surgical treatment after enrollment are shown in Table S3.

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. For quality control, a sample of echocardiograms from 65 infants was reviewed independently by a pediatric echocardiographer who was unaware of the treatment assignments.

OUTCOMES

The primary outcome was a composite of death or moderate or severe bronchopulmonary dysplasia assessed at 36 weeks of postmenstrual age[15] (Tables S4 and S5). A physiological challenge of supplemental oxygen reduction was used to test for oxygen need at 36 weeks of postmenstrual age[16] to differentiate mild from moderate bronchopulmonary dysplasia (Fig. S1). 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 (Table S5).[14] Other secondary short-term outcomes are listed in the Supplementary Appendix and in the statistical analysis plan (available with the protocol).[17] All outcome data were recorded routinely, including demographic data and complications of prematurity; these data were obtained from clinical notes or trial-related assessments (Table S6).

A list of foreseeable serious adverse events that are common in this patient population was prespecified (see section 9.1.4 in the protocol); unforeseeable serious adverse events were defined as those that were not included on this list. A serious adverse reaction was defined as a serious adverse event that was considered to have been caused by the administration of the trial agent; if such an event was not consistent with the safety profile of the trial agent, it was classed as a suspected unexpected serious adverse reaction.[14]

STATISTICAL ANALYSIS

The incidence of the primary outcome was predicted to be 60% in the placebo group (see Supplementary Methods). A sample of 730 infants was calculated to be required in order 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.[14]

Analyses were performed according to the intention-to-treat principle, with infants excluded from the analysis only if their data were miss-

ing. Missing data were not imputed. Analyses were adjusted for minimization factors, such as the size of the PDA at randomization, gestational age at birth, age at randomization, sex, whether the infant was from a multiple birth, mode of respiratory support at randomization, whether inotropes were received at the time of randomization, and trial site, as well as for the correlation between siblings from multiple births, when technically possible (Table S7). Trial site was treated as a random effect in the models, and all other factors were treated as fixed effects. Binary outcomes were analyzed by means of mixed-effects Poisson regression with a robust variance estimator; risk ratios and 95% confidence intervals are reported. The assumptions used in the models were assessed and found to be valid (Fig. S2). Continuous outcomes were analyzed with the use of linear regression models; mean differences and 95% confidence intervals (after checking model assumptions) are reported. Because of the large number of short-term outcomes, reporting of differences between the groups and associated 95% confidence intervals was restricted to a prespecified short list (Table S5). No formal method to adjust for multiplicity was used; the widths of the confidence intervals have not been adjusted for multiplicity, and inferences drawn may not be reproducible and should not be used to infer definitive treatment effects for secondary outcomes. Full details of the statistical analysis are provided in the statistical analysis plan.[17] Additional details are provided in the Supplementary Appendix. Stata/SE, version 15 (StataCorp), was used for all analyses.

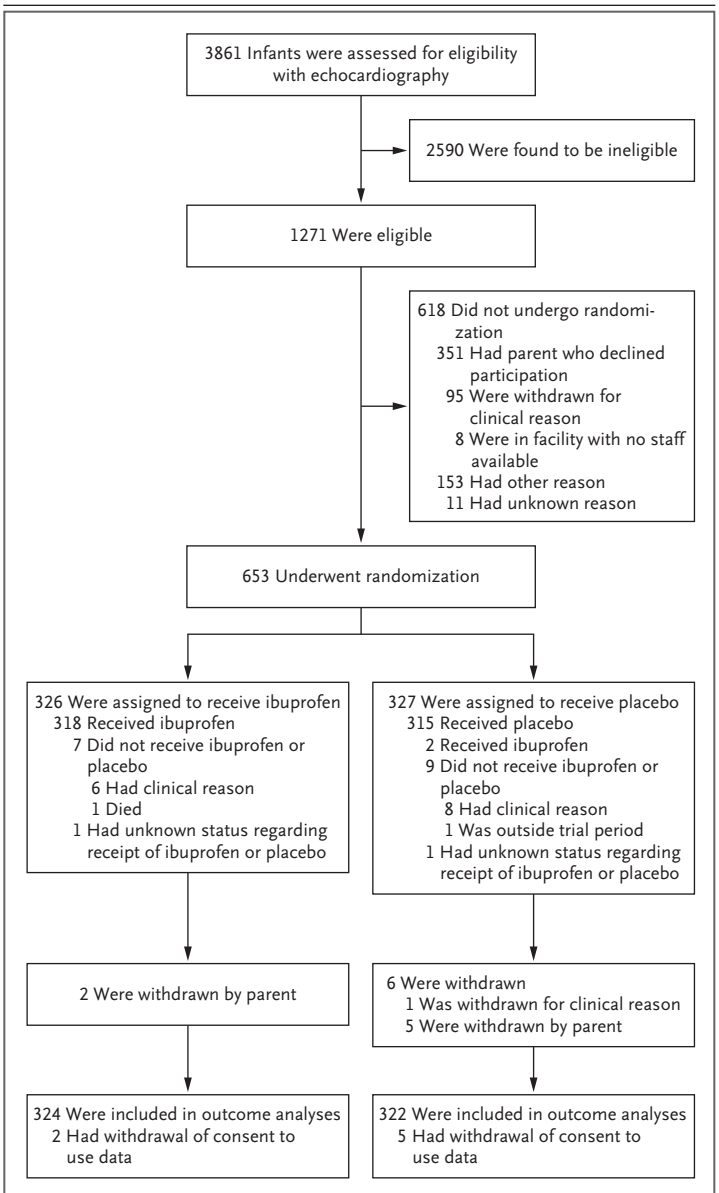

Figure 1. Screening, Randomization, and Inclusion in the Analyses.

RESULTS

PATIENTS

From July 2015 through December 2020, a total of 653 infants underwent randomization: 326 were assigned to receive ibuprofen and 327 to receive placebo. A total of 22 infants underwent randomization during the internal pilot phase and 631 during the main recruitment phase (Fig. 1). Maternal and infant baseline characteristics appeared to be well balanced between the groups (Table 1 and Table S8). The median PDA diameter was 2.2 mm (interquartile range, 1.9 to 2.6). An independent audit of the echocardiograms indicated that 93.8% of infants who underwent randomization in the trial met the prespecified echocardiographic eligibility criteria. The remainder of the echocardiographic images could not be assessed accurately to confirm the eligibility criteria.

A total 318 of 326 infants (97.5%) in the ibuprofen group and 315 of 327 (96.3%) in the placebo group received their assigned intervention

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)
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)

* Plus–minus data are means ±SD. IQR denotes interquartile range, and PDA patent ductus arteriosus.
† Race was reported by the parent.
‡ The characteristic was a factor used in the randomization minimization algorithm.
§ This category included nasal continuous positive airway pressure, nasal ventilation, humidified high-flow nasal cannula therapy, or low-flow oxygen (≥1.1 liters per minute).
¶ This category included low-flow oxygen (<1.1 liters per minute) and ambient oxygen.

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)
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. (%)‖	41/323 (12.7)	41/322 (12.7)	1.00 (0.67–1.49)	1.01 (0.67–1.51)
PDA closed or <1.5 mm at 3 wk of age, confirmed by echocardiography — no./total no. (%)**	176/317 (55.5)	117/316 (37.0)	1.50 (1.26–1.79)	1.50 (1.30–1.74)
PDA ≥1.5 mm at 3 wk of age, not treated medically or by surgical closure — no./total no. (%)**	74/321 (23.1)	109/317 (34.4)	0.67 (0.52–0.86)	0.67 (0.53–0.85)
Open-label surgical treatment of a symptomatic PDA — no. (%)	9 (2.8)	31 (9.6)	0.29 (0.14–0.60)	0.29 (0.18–0.47)
Discharged home with supplemental oxygen — no. (%)	130 (41.3)	123 (39.2)	1.05 (0.87–1.27)	1.06 (0.92–1.22)
Weight gain				
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)††

* Adjusted for minimization factors (size of the PDA, gestational age at birth, age at randomization, sex, trial site, whether the infant was from a multiple birth, mode of respiratory support at randomization, and whether inotropes were received at the time of randomization) and the correlation between siblings from multiple births, where technically possible. Trial site was treated as a random effect in the models, and all other factors as fixed effects.

† In the placebo group, 1 infant was withdrawn before 36 weeks and 3 did not have information on oxygen requirement available at 36 weeks. In the ibuprofen group, 1 infant was lost to follow-up before 36 weeks and 5 did not have information on oxygen requirement available at approximately 36 weeks.

‡ P=0.10.

§ Severe intraventricular hemorrhage was defined as grade III or IV.

¶ Fresh blood in endotracheal tube with increase in respiratory support.

‖ Severe necrotizing enterocolitis was defined as Bell's stage II or higher as confirmed by radiography, histopathological analysis, or both. Stages in the Bell classification system for necrotizing enterocolitis range from I to III, with higher stages indicating more severe illness.

** Echocardiography was planned to be performed at 3 weeks (18 to 24 days) after birth to assess the patency of the PDA.

†† Value is the mean difference (95% confidence interval).

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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)

* Early discontinuation was defined as discontinuation when fewer than three doses had been received.
† The median was assessed among infants who had received at least one dose.
‡ Echocardiography was planned to be performed at 3 weeks (18 to 24 days) after birth to assess the patency of the PDA; infants who died before the 3-week echocardiogram could be obtained were excluded (33 infants in the ibuprofen group and 21 in the placebo group).
§ Denominators are the numbers of infants who were eligible for the test.

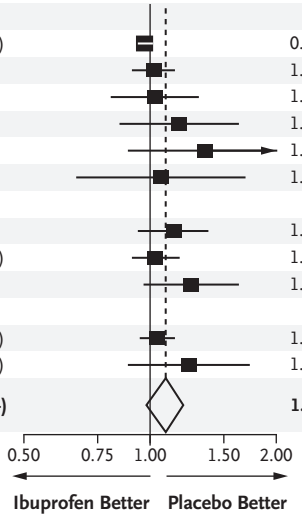
(Fig. 1). Parental consent to use the data from 7 infants was withdrawn, which left data from 324 infants in the ibuprofen group and 322 in the placebo group available for outcome analyses (Fig. 1). Data that were required to assess the primary outcome were missing for an additional 10 infants, and therefore assessment of the primary outcome was possible for 318 infants (97.5%) in the ibuprofen group and 318 (97.2%) in the placebo group.

OUTCOMES

A primary-outcome event (death or moderate or severe bronchopulmonary dysplasia assessed at

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)**

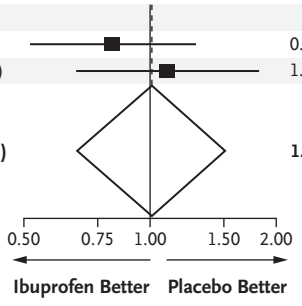


Figure 2. Subgroup Analyses of the Primary Outcome and Severe Necrotizing Enterocolitis.

Panel A shows the subgroup analysis of the primary outcome, a composite of death or moderate or severe bronchopulmonary dysplasia assessed at 36 weeks of postmenstrual age. Panel B shows the subgroup analysis of severe necrotizing enterocolitis, defined as necrotizing enterocolitis of Bell's stage II or higher, as confirmed by radiography, histopathological analysis, or both. Stages in the Bell classification system for necrotizing enterocolitis range from I to III, with higher stages indicating more severe illness. In each panel, the diamond and dashed line indicate the overall measure of effect, and the width of the diamond indicates the 95% confidence interval of the overall effect. Risk ratios and 95% confidence intervals were obtained from an interaction term between treatment assignment and subgroup characteristic of interest in a log binomial model adjusted for the size of the patent ductus arteriosus (PDA) at randomization, gestational age at birth, age at randomization, sex, whether the infant was from a multiple birth, mode of respiratory support at randomization, whether inotropes were received at randomization, and trial site as a random effect; data from siblings were clustered to account for correlation between infants in multiple births. Some of the patient subgroups have been collapsed into fewer subgroups than prespecified because of the small number of patients in each category. No adjustments were made for multiplicity of testing, and therefore interpretation of the confidence intervals should not be used to assess treatment effect.

36 weeks of postmenstrual age) occurred in 220 of 318 infants (69.2%) assigned to ibuprofen and 202 of 318 infants (63.5%) assigned to placebo (adjusted risk ratio, 1.09; 95% CI, 0.98 to 1.20; P=0.10) (Table 2). A total of 44 of 323 infants (13.6%) in the ibuprofen group and 33 of 321 (10.3%) in the placebo group died (adjusted risk ratio, 1.32; 95% CI, 0.92 to 1.90). Among the infants who survived to 36 weeks of postmenstrual age, moderate or severe bronchopulmonary dysplasia was present in 176 of 274 (64.2%) in the ibuprofen group and 169 of 285 (59.3%) in the placebo group (adjusted risk ratio, 1.09; 95% CI, 0.96 to 1.23) (Table 2 and Figs. S3 and S4). Results for the primary outcome excluding infants who received open-label medical treatment without meeting the specified criteria are shown in Tables S9 and S10.

A closed or small PDA (<1.5 mm in diameter) at 3 weeks (18 to 24 days) of age was present in 176 of 317 infants (55.5%) in the ibuprofen group and 117 of 316 (37.0%) in the placebo group (adjusted risk ratio, 1.50; 95% CI, 1.30 to 1.74) (Table 2 and Table S11). After randomization, 571 of 646 infants (88.4%) received all three doses of ibuprofen or placebo (Table 3).

Additional secondary outcomes are shown in Table 2, Figure S5, and Tables S12 and S13. 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; 9 (2.8%) and 31 (9.6%), respectively, received surgical treatment (Table 2). 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. Prespecified subgroup analyses of the composite primary outcome and its components are shown in Figure 2A and Figures S3 and S4. An additional prespecified subgroup analysis of the risk of severe necrotizing enterocolitis (Bell's stage ≥II) according to the diameter of the PDA at randomization is shown in Figure 2B.

SAFETY

Two unforeseeable serious adverse events occurred that were assessed as possibly related to ibuprofen; one of these events was classified as a suspected unexpected serious adverse reaction (Table S15). An additional four unforeseeable serious adverse events that were assessed as not related to ibuprofen occurred in the ibuprofen group. Two unforeseeable serious adverse events occurred in the placebo group, both of which were assessed as not related to placebo. Foreseeable serious adverse events were reportable during the period between the first dose of ibuprofen or placebo and 7 days after the last dose (Table S14).

DISCUSSION

In this double-blind, randomized, placebo-controlled trial involving extremely preterm infants with a large PDA, we found no evidence that early treatment with ibuprofen was associated with a lower incidence of death or moderate or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age than placebo. There was no significant between-group difference in either the risk of death or the risk of moderate or severe bronchopulmonary dysplasia.

Our results are broadly consistent with those of other studies of early targeted treatment of PDA with ibuprofen that have not shown a convincing benefit with respect to clinical outcomes.[12,18-21] Although these studies have shown a reduced risk of pulmonary hemorrhage and patient symptoms attributable to the PDA, intervention with ibuprofen was not shown to be associated with a reduction in the incidence of bronchopulmonary dysplasia, death, or neurodisability.[18,19]

Approximately half the infants we enrolled were born at less than 26 weeks' gestation, the cohort at greatest risk for a hemodynamically significant PDA. We enrolled infants who had a large PDA as determined on the basis of a combination of echocardiographic measures, including the diameter of the PDA and ductal flow characteristics.[22,23] The incidence of death or moderate or severe bronchopulmonary dysplasia in

our trial was high but was similar to that in other randomized trials of early pharmacologic treatment of PDA.[18,19,21]

A single early course of ibuprofen resulted in a closed or small PDA (confirmed by echocardiography at 3 weeks of age) in only 55.5% of infants who were assigned to receive ibuprofen. Although previous studies have reported variable closure rates with early intravenous ibuprofen therapy,[24] our findings are consistent with recent trials involving similar patient populations.[18,21,25] Variation in the rate of PDA closure among studies is likely to be caused by differences in the timing of the intervention, an open-label study design, the route of administration of the ibuprofen, and the dosing regimen used.[6,26] Intravenous ibuprofen administered within a standard dosing regimen was chosen as the intervention in our trial because higher doses are usually used only when an infant is 7 days of age or older, and it was the most common treatment schedule for infants with a PDA in the United Kingdom at the time the trial was designed.[27] Similarly, most units did not routinely repeat echocardiographic assessment after ibuprofen therapy with the intention of offering a second course if the PDA remained patent.

Open-label medical therapy for a symptomatic PDA appeared to be less common in this trial than in other, similar trials[28] and occurred almost twice as frequently in the placebo group as in the ibuprofen group. Although a recent noninferiority trial of early ibuprofen treatment in the management of PDA showed a very low percentage of patients (0.7%) receiving open-label medical therapy in the expectant management group,[19] there was frequent use of acetaminophen as an analgesic after randomization in both groups. Accordingly, exposure to any pharmacologic agent with the potential for ductal closure was approximately 25% among infants who received expectant management, a percentage similar to that in our trial.

The median time from randomization to open-label medical therapy in our trial was 11 to 12 days, well beyond the time when the infant had received the trial intervention (up to 7 days). This was much later than the timing of rescue treatment in a French trial[18] (median of 4 days) that overlapped with the trial intervention. The low percentage of infants with effective closure in the ibuprofen group in our trial combined with the relatively late timing of open-label medical therapy suggests that a large percentage of treated infants may have been exposed to the potentially damaging effects of the ductal shunt for a prolonged period. Combined with the relatively high percentage of patients in the placebo group who received open-label therapy (29.8%), this resulted in poor discrimination between the two groups with respect to ductal patency (55.5% vs. 37.0%) and probably also in prolonged exposure to a ductal shunt. The absence of data from serial echocardiograms precludes detailed analysis and limits interpretation of the effect of shunt duration on outcomes in the two groups. Nevertheless, one might reasonably conclude that the early, echocardiography-targeted course of ibuprofen used in our trial resulted in a percentage of infants with PDA closure or constriction that was 18 percentage points higher than that obtained with placebo, without affecting clinical outcomes.

We found no evidence that ibuprofen resulted in excess serious complications. Unlike Hundscheid et al. in the BeNeDuctus trial,[19] we did not identify an association between ibuprofen therapy and bronchopulmonary dysplasia, a finding that might be explained by differences in the trial populations or drug exposure. Whereas most of the infants enrolled in our trial were receiving invasive ventilation, the BeNeDuctus trial mostly enrolled infants who were receiving noninvasive respiratory support. Another important difference was the use of repeated courses (often with high doses) of ibuprofen in the BeNeDuctus trial. Early exposure to high cumulative doses of ibuprofen in infants with a relatively low baseline risk of bronchopulmonary dysplasia, as in that trial, may be detrimental.

Our trial has limitations. In spite of strict criteria to restrict its use, open-label therapy was received by 29.8% of the infants in the placebo group, the likely effect of which would have been to increase the percentage of infants with PDA closure in this group and make it more difficult to identify between-group differences in clinical outcomes. We did not meet our enrollment goal of 730 patients, in part because of drug nonavailability, changes in clinical practice, competing trials, and

the effect of the coronavirus disease 2019 pandemic. Although early assessment and randomization were encouraged, the first dose of ibuprofen or placebo was administered at a median of 61 hours after birth, which was later than in other, similar trials.[18,20] Trial entry was permitted up to 72 hours after birth to allow a pragmatic approach to enrollment and to ensure the availability of an echocardiographic assessment. However, it is possible that earlier intervention would have achieved more effective ductal closure.[24,29]

Among extremely preterm infants with a large PDA, we 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.

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REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
2. Sellmer A, Bjerre JV, Schmidt MR, et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. Arch Dis Child Fetal Neonatal Ed 2013;98:F505-F510.
3. Semberova J, Sirc J, Miletin J, et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. Pediatrics 2017;140(2):e20164258.
4. Nemerofsky SL, Parravicini E, Bateman D, Kleinman C, Polin RA, Lorenz JM. The ductus arteriosus rarely requires treatment in infants > 1000 grams. Am J Perinatol 2008;25:661-6.
5. Mirza H, Garcia J, McKinley G, et al. Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants. J Perinatol 2019;39:1648-55.
6. Mitra S, Florez ID, Tamayo ME, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. JAMA 2018;319:1221-38.
7. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966-72.
8. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010;30:241-52.
9. Benitz WE, Bhombal S. The use of non-steroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants. Semin Fetal Neonatal Med 2017;22:302-7.
10. Isayama T, Kusuda S, Reichman B, et al. Neonatal intensive care unit-level patent ductus arteriosus treatment rates and outcomes in infants born extremely preterm. J Pediatr 2020;220:34.e5-39.e5.
11. van Laere D, van Overmeire B, Gupta S, et al. Application of NPE in the assessment of a patent ductus arteriosus. Pediatr Res 2018;84:Suppl 1:46-56.
12. 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 Syst Rev 2020;12:CD013278.
13. Su B-H, Lin H-C, Chiu H-Y, Hsieh H-Y, Chen H-H, Tsai Y-C. Comparison of ibuprofen and indometacin for early-targeted treatment of patent ductus arteriosus in extremely premature infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93:F94-F99.
14. Gupta S, Juszczak E, Hardy P, et al. Study protocol: baby-OSCAR trial: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies, a multicentre, masked, randomised placebo-controlled parallel group trial. BMC Pediatr 2021;21:100.
15. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
16. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol 2003;23:451-6.
17. Bell JL, Gupta S, Juszczak E, Hardy P, Linsell L. Baby-OSCAR: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies-a statistical analysis plan for short-term outcomes. Trials 2021;22:368.
18. Rozé J-C, Cambonie G, Le Thuaut A, et al. Effect of early targeted treatment of ductus arteriosus with ibuprofen on survival without cerebral palsy at 2 years in infants with extreme prematurity: a randomized clinical trial. J Pediatr 2021;233:33.e2-42.e2.
19. Hundscheid T, Onland W, Kooi EMW, et al. Expectant management or early ibuprofen for patent ductus arteriosus. N Engl J Med 2023;388:980-90.
20. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 2014;99:F99-F104.
21. El-Khuffash A, Bussmann N, Breatnach CR, et al. A pilot randomized controlled trial of early targeted patent ductus arteriosus treatment using a risk based severity score (the PDA RCT). J Pediatr 2021;229:127-33.
22. Su BH, Watanabe T, Shimizu M, Yanagisawa M. Echocardiographic assessment of patent ductus arteriosus shunt flow pattern in premature infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F36-F40.
23. Harling S, Hansen-Pupp I, Baigi A, Pesonen E. Echocardiographic prediction of patent ductus arteriosus in need of therapeutic intervention. Acta Paediatr 2011;100:231-5.
24. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev 2020;2:CD003481.
25. Lin YJ, Chen CM, Rehan VK, et al. Randomized trial to compare renal function and ductal response between indomethacin and ibuprofen treatment in extremely low birth weight infants. Neonatology 2017;111:195-202.

26. Hills NK, Clyman R. Paracetamol (acetaminophen) for patent ductus arteriosus: where do we stand? J Pediatr 2020;222:18-21.
27. Al-Turkait A, Szatkowski L, Choonara I, Ojha S. Management of patent ductus arteriosus in very preterm infants in England and Wales: a retrospective cohort study. BMJ Paediatr Open 2022;6(1):e001424.
28. Evans N. Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? Semin Fetal Neonatal Med 2015;20:272-7.
29. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2019;6:CD004213.