A Randomized, Double-Blind, Placebo-Controlled Trial on Intravenous Ibuprofen L-Lysine for the Early Closure of Nonsymptomatic Patent Ductus Arteriosus within 72 Hours of Birth in Extremely Low-Birth-Weight Infants

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ABSTRACT

A multicenter, double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy and safety of intravenous (IV) ibuprofen (L-lysine) for the early closure of nonsymptomatic patent ductus arteriosus (PDA) within 72 hours of birth in extremely low-birth-weight (ELBW) infants with evidence of ductal shunting by echocardiogram. Eleven sites enrolled 136 infants with nonsymptomatic early PDA (gestational age < 30 weeks; body weight 500 to 1000 g) to receive a 3-day course (10 mg/kg, 5 mg/kg, and 5 mg/kg) of IV ibuprofen ($n = 68$) or placebo ($n = 68$). Cardiac echocardiogram was performed on study days 1 and 14, and with rescue. Infants were followed to 36 weeks postconceptional age. Patient demographics, mean (standard deviation), were similar between ibuprofen and placebo: birth weight: 798.5 g (128.7) versus 797.3 g (132.8); gestational age: 26.1 weeks (1.3) versus 26.2 weeks (1.4); and age at first dose: 1.5 days (0.7). The intent-to-treat analysis of the primary endpoint, subjects rescued, died, or dropped through study day 14, was 21/68 (30.9%) with ibuprofen and 36/68 (52.9%) for placebo ($p = 0.005$). Death, intraventricular hemorrhage, necrotizing enterocolitis, daily fluid intake/output, liver function, bronchopulmonary dysplasia, and retinopathy of

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prematurity did not differ. A trend toward decreased periventricular leukomalacia by ibuprofen was noted. IV ibuprofen was effective and safe in the early closure of PDA in preterm neonates.

KEYWORDS: Ibuprofen, patent ductus arteriosus, premature newborn, cyclooxygenase inhibitors, randomized clinical trial

Patent ductus arteriosus (PDA) is a common problem encountered in premature infants, especially those with respiratory distress syndrome.[1,2] The incidence is inversely related to gestational age and birth weight,[3,4] with 55 to 70% of infants born before 28 weeks' gestation and weighing < 1000 g at birth requiring treatment.[5] A persistent PDA is usually diagnosed when the ductus fails to close spontaneously after 72 hours.[6] The open ductus produces hemodynamic problems, which can lead to numerous clinical complications including congestive heart failure, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and death.[7,8]

Medical therapy with cyclooxygenase inhibitors, particularly indomethacin, has been shown to be effective in ductal closure. Unfortunately, it has been associated with increased risk of renal failure, hematologic problems, NEC, decrease in cerebral blood flow (CBF) velocity and bioenergetics.[7–12] Furthermore, it is associated with a failure rate between 30% and 35%, requiring retreatment or surgical closure of the ductus arteriosus.[9,13,14]

Ibuprofen is an alternative cyclooxygenase inhibitor available via the intravenous (IV) route. It has been effective in closing the ductus[15–17] without reducing CBF[18] or impacting intestinal[15,19] or renal hemodyamics.[20] Clinical trials have demonstrated equal efficacy versus indomethacin for ductal closure in treating a symptomatic PDA, with a more favorable renal safety profile and lack of effect upon CBF.[17,18,21,22]

PDA prophylaxis trials have shown that ibuprofen reduced the incidence of PDA, but failed to demonstrate any additional benefit over placebo, or in preventing intraventricular hemorrhage.[23,24] The 60% spontaneous closure rate[23] reported in these trials may lead practitioners to hold off treatment until clinical signs and symptoms appear several days after birth. Unfortunately, the delaying of therapy until hemodynamic symptoms of a persistent PDA appear, usually > 3 to 6 days, increases the likelihood of developing PDA-related morbidities and may decrease the success of pharmacological closure.[25]

To date, there has been a lack of placebo-controlled data specific to the effectiveness or safety of early ibuprofen use (< 72 hours), in infants who are treated beyond the prophylactic period (12 hours after birth), but before a hemodynamically symptomatic PDA develops (3 to 9 days). In several prior studies, ibuprofen was given once a symptomatic PDA appeared, ranging from a few days to late in the first week after birth. Furthermore, many of the ibuprofen studies utilized an active comparator (indomethacin). Studies were also conducted in infants of older gestational age and with heavier birth weights than those currently being treated for a symptomatic PDA.[26] This population difference is notable as spontaneous closure is inversely related to birth weight and gestational age, especially infants in under 28 weeks versus those over 29 weeks.[27,28]

As a result, this study aimed to determine the effect of early treatment with intravenous (IV) ibuprofen given to extremely low-birth-weight infants (ELBW) with a nonsymptomatic PDA in the first 72 hours of life compared with intravenous placebo, as the first such trial. The design was to test the hypothesis that ibuprofen given during this time period would accelerate and maintain ductal closure and, thereby, show a significant reduction in rescue therapy (indomethacin or surgical ligation). Furthermore, this trial, the first evaluation of ibuprofen L-lysine in the United States, was able to enroll infants of younger gestational age and lower birth weight (who are more commonly treated in North America)[29,30] than the more mature infants enrolled in the earlier ibuprofen treatment trials.

MATERIALS AND METHODS

This is the first study in the United States to determine the efficacy and safety of the IV formulation of ibuprofen L-lysine in preterm newborns with nonsymptomatic PDA. This trial was a multicenter, randomized, placebo-controlled, double-blind parallel design study evaluation of IV ibuprofen using an intent-to-treat analysis to evaluate early closure of nonsymptomatic PDA within 72 hours of birth in ELBW infants. Eleven centers participated in this trial from March 2002 to March 2005 (Appendix 1). The protocol was approved by the Institutional Review Board for all participating sites, and by The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Pediatric Pharmacology Research Unit Network (PPRU).

Inclusion-Exclusion Criteria

All premature newborns born ≤ 30 weeks' gestation admitted to the neonatal intensive care unit of the

participating hospitals were eligible for this study if they met the inclusion criteria: (1) birth weight of 500 to 1000 g; (2) <72 hours postnatal age; (3) nonsymptomatic PDA with evidence of ductal shunting documented by echocardiogram; and (4) informed consent signed by parent/legal guardian.

Exclusion criteria included: (1) major congenital malformations and/or chromosomal anomalies; (2) proven congenital bacterial infection; (3) maternal antenatal nonsteroidal anti-inflammatory exposure <72 hours before delivery; (4) treatment with a steroid at anytime since birth; and (5) unremitting shock requiring high doses of vasopressors (i.e., inability to maintain mean arterial blood pressure appropriate for gestational age ± 2 standard deviations [SDs] using volume and maximal vasopressor therapy as defined by the individual institution); (6) renal failure or oliguria defined as urine flow rate <0.5 mL/kg/h in the 8 hours prior to randomization (anuria was acceptable if infant was within first 24 hours of life; (7) platelet count $<75{,}000/\text{mm}^3$; (8) clinical bleeding tendency (i.e., oozing from puncture sites); (9) expected survival <48 hours in the opinion of the attending neonatologist; and (10) participation in other clinical intervention trials unless approved by the medical director or study coordinator. For multiple births, no more than two of the infants could be enrolled.

Sample Size, Randomization, and Drug Dosing

Based on the assumptions of a 50% reduction in rescue rate in neonates with symptomatic PDA from 70% in the placebo group to 35% in the ibuprofen group, 120 evaluable infants ($n=60$ per treatment group) were required to detect this difference with 90% power and α of 0.01. Subjects were stratified into two birth weight categories: 500 to 750 g and 751 to 1000 g. Following echocardiogram confirmation of a PDA, infants were randomized into two groups to receive either ibuprofen (L-lysine formulation) or placebo (normal saline) within 72 hours of birth. The coded vials of study drug or placebo contained indistinguishable colorless solutions dispensed by the blinded research pharmacists of the participating sites. Central randomization (ClinPhone Plc., Nottingham, UK) was implemented using a dynamic allocation method of biased coin randomization,[31] balancing within birth weight, within each site, and in the study overall. Placebo or ibuprofen (10 mg/mL) was given intravenously for 10 minutes using 10 mg/kg loading dose followed by 5 mg/kg/d on the second and third study days, using umbilical venous catheter or peripheral IV site.

Outcome Assessments and Procedures

Outcome assessments were collected from enrollment through study day 14. Follow-up outcomes were collected at 36 weeks postconceptional age (± 7 days) or at transfer from facility. Adverse events were collected through 30 days after the last administration of study drug.

The primary outcome was the presence of a symptomatic PDA requiring rescue with indomethacin or surgery as determined by the attending neonatologist and staff. This endpoint was selected based on the assumption that a clinically significant PDA requires intervention with indomethacin or surgery and is in accord with the Food and Drug Administration (FDA) regulatory requirement of providing a clinically significant outcome beyond ductal closure for this placebo-controlled study. As this study involved an intent-to-treat analysis, all dropouts and deaths were included as part of this primary endpoint.

The presence of a clinically significant PDA was determined by three or more clinical and physical findings of symptomatic ductus (bounding pulses, hyperdynamic precordium, pulmonary edema, increased radiographic cardiac silhouette, systolic murmur), confirmed by an echocardiogram, and requiring intervention.

Echocardiograms were done within the first 72 hours of age, prerandomization, and at study day 14 (± 1 day). Additional echocardiogram(s) were performed if rescue therapy was considered for symptomatic PDA. Echocardiography using color Doppler echocardiography (Sonos 5500 or Sonos 1500 imaging system; Hewlett–Packard, Andover, MA, or Ultramark 4 Plus; Advanced Technology Laboratories, Bothell, WA with a 7.5-MHz or 10-MHz transducer) was performed by cardiologists unaware of infants' treatment. The purpose of the echocardiography was to evaluate patency of the ductus and shunting at the time of inclusion, at anytime rescue therapy with indomethacin or surgery was considered, and at study day 14. M mode was used to calculate the shortening fraction and to measure left ventricular internal diameter in diastole (left ventricle [LV]). A two-dimensional parasternal long-axis view was obtained for assessment of the diameter of the left atrium (LA) in systole and aortic root diameter (AO). Ratios of LA/AO and LV/AO were calculated off-line from these diameters. A two-dimensional ductal view with color Doppler was performed to assess the ductal shunting and minimum diameter of the PDA.

The guideline for a hemodynamically significant PDA was the presence of at least two of the following three parameters: (1) LA/AO ratio of $>1.4{:}1$; (2) LV/AO ratio of $>2.1{:}1$; and/or (3) narrowest ductal diameter >1.5 mm. Cardiac echocardiogram provides more accurate assessment of PDA; however, a clinically based decision by the neonatologist was deemed more practical in the clinical setting using criteria noted above.

Safety Considerations and Assessments

Subjects with symptomatic PDA at any time during the study could receive rescue treatment at the discretion of the investigator/attending neonatologist, provided the infant met criteria for medical or surgical intervention. No data on potential synergistic interactions of ibuprofen and indomethacin in newborns were known; therefore, if rescue therapy with indomethacin was indicated, it was administered at least 24 hours from last dose of study drug, based on plasma ibuprofen half-life of ~23 hours.[32]

Secondary outcomes were related to safety. NEC was graded using Bell's classification.[33] Retinopathy of prematurity (ROP) was evaluated as per standard of care.

Respiratory effects were closely monitored and evaluated. Pulmonary hemorrhage and persistent pulmonary hypertension in newborns (PPHN) were tracked at study day 14. PPHN was diagnosed after severe hypoxemia was observed. This was defined as hypoxic respiratory failure with an oxygenation index (mean airway pressure $\times$ FiO_2 $\times$ 100/PaO_2) (OI) $\geq$ 15 on two arterial gases at least 15 minutes apart and $\leq$ 12 hours apart. Because of the brief duration of these hypoxemic episodes (20 min)[34] and their good response to inhaled nitric oxide, no echocardiograms were obtained for PPHN diagnosis. Respiratory data, including FiO_2 (inspired oxygen) and method of ventilatory support, were collected at baseline and study days 4 and 14. BPD was the need for supplemental oxygen at 28 postnatal days or 36 weeks postconceptional age.

IVH was a secondary outcome for safety and was not an exclusion criteria for the study. Although ibuprofen has been shown to improve CBF autoregulation in neonatal piglets,[35] at least two clinical trials showed no effect on the risk of IVH in preterm neonates.[24,36] Moreover, nonsteroidal anti-inflammatory drugs, like indomethacin, do not worsen or cause extension of an existing IVH.[37]

IVH was evaluated by cerebral ultrasounds. For study purposes, ultrasounds were performed as standard of care and were performed closest to study days 4 and 14. As such, these ranged from day of life 1 to 24. The lesions were classified as described by Papile et al.[38] All cranial ultrasounds were read by radiologists of participating centers. Periventricular leukomalacia (PVL) was graded by the characteristics of periventricular white matter on sonography.[39]

Serum laboratories and fluid status were monitored during the study period. Serum bilirubin, creatinine, electrolytes, and blood urea nitrogen were recorded daily from study days 1 through 6. Daily fluid intake and output for 24-hour intervals were recorded from birth through day 10 of life. Complete blood counts were collected at baseline and study day 4. Liver enzymes including serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and serum gamma glutamyl transferase (SGGT) were collected at baseline and at study day 14.

Plasma samples for ibuprofen concentrations were obtained at 1 hour ($\pm$ 30 minutes) after the first dose; at 24 hours ($\pm$ 1 hour) just prior to dose 2; at 48 hours (prior to dose 3), and at 120 hours. Plasma ibuprofen assays by high-pressure liquid chromatography were performed at the conclusion of the clinical trial when blinding was broken.

Data Analysis

Data were analyzed using the intent-to-treat principle. The primary endpoint comprised all subjects who died, dropped out, or required rescue. Analysis involved logistic regression with factors for treatment and site and utilized SAS® software and procedures (SAS Corporation, Cary, NC). Furthermore, a confirmatory analysis was performed using logistic regression with covariates: birth weight (500 to 750 g, 751 to 1000 g), gestational age ($<$ 28, $\geq$ 28 weeks), gender, use or nonuse of high-frequency oscillatory ventilation, and maximum weight loss during the first 7 days of life. Because this was a Phase III confirmatory trial, a p value of $<$ 0.01 for the primary outcome was designated as significant. Other statistical analyses of efficacy parameters included the Wilcoxon rank-sum tests or Cochran-Mantel-Haentzel tests stratified by site and repeated measures analyses. Kaplan-Meier survival curves were presented for survival data with statistical significance tested utilizing a log-rank test.

Adverse event data were evaluated via the Data Safety Monitoring Committee (DSMC), composed of experts in neonatology, pediatric cardiology, pharmacology, epidemiology, and biostatistics (Appendix 1). A mandatory review of adverse event data was conducted after 25%, 50%, and 75% of infant recruitment. Committee members received blinded summary data grouped by treatment codes. A formal summary of each safety review was written by the committee and incorporated in study file. Communications with DSMC was through a designated biostatistician for the study.

RESULTS

Subject Disposition and Characteristics

Nine hundred forty-four very low-birth-weight neonates were screened for the study. Of these infants, 749 were considered not eligible because of maternal tocolysis with indomethacin, enrollment in other studies, or parental refusal to give informed consent. From the remaining 195 subjects who gave informed consent, 59 failed to meet inclusion and/or exclusion criteria or did not have a patent ductus on the initial cardiac echocardiogram. Therefore, 136 preterm newborns

Table 1 Demographics

Variable	Ibuprofen* ($n=68$)	Placebo ($n=68$)
Birth weight (g), mean (SD)	798.5 (128.7)	797.3 (132.8)
Gestational age (wk), mean (SD)	26.1 (1.3)	26.2 (1.4)
Gender, *n* (%)		
Male	32 (47)	37 (54)
Female	36 (53)	31 (46)
Ethnicity, *n* (%)		
Caucasian	23 (34)	18 (26.5)
Black	17 (25)	18 (26.5)
Hispanic	21 (31)	28 (41)
Asian/Pacific Islander	1 (1.5)	2 (3)
Other	6 (9)	2 (3)
Apgar score, 1 minute (median, IQR)	4.0 (2.0), $n=67$	4.0 (2.0), $n=67$
Apgar score, 5 minutes (median, IQR)	7.0 (2.0), $n=67$	7.0 (2.0), $n=68$
Maternal age, mean (SD)	28.0 (6.6)	27.8 (6.6)
Maternal steroid use, *n*/*N* (%)	51/67 (76.1)	48/68 (70.6)
Age of first dose of study drug, mean (SD)	1.5 (0.74)	1.4 (0.73)
Baseline neurological exam abnormal, *n*/*N* (%)	6/68 (8.8)	4/68 (5.9)
Baseline apnea, *n*/*N* (%)†	15/68 (22)	13/68 (19)
Mechanical ventilation, *n*/*N* (%)	47/68 (69)	46/68 (67)

*No significant difference between treatment and placebo: $p>0.05$.
†Defined as no respiratory effort >15 s, with bradycardia (heart rate <100 beats/min).
SD, standard deviation; IQR, interquartile range.

were enrolled and randomized to receive either placebo or study drug.

Placebo- and ibuprofen-treated groups were similar in demographic characteristics, including birth weight, gestational age, ethnicity (Table 1). Subjects were enrolled within 72 hours after birth, and mean ages and standard deviation of the first dose were 1.5 (0.74) and 1.4 (0.73) days for ibuprofen and placebo group, respectively.

Efficacy Analysis

In this study of early closure of nonsymptomatic PDA within 72 hours of birth in ELBW infants, efficacy outcomes have been depicted in Figs. 1 and 2. Based upon the intent-to-treat analysis of the primary endpoint, the ibuprofen group had a significantly lower proportion of infants who died, dropped out, or required rescue (21/68; 30.9%) as compared with the placebo group (36/68; 52.9%; $p=0.005$) for symptomatic PDA on or before study day 14 as depicted in Fig. 1. This significant difference was even more pronounced when adjusted for covariates ($p=0.0014$), including birth weight, gestational age, gender, maximum weight loss, use of oscillatory ventilation, and site.

Excluding those who died before study day 14, a significantly lower proportion of infants needed rescue (Fig. 2) in the ibuprofen group compared with the placebo group (25.0% versus 48.5%, $p=0.003$). In addition, the mean (SD) age of first rescue treatment was 8.7 (3.8) versus 6.9 (3.2) days for ibuprofen and placebo, respectively. Interestingly, the proportion of infants requiring rescue with indomethacin on or prior to study day 14 who were surgically ligated (Fig. 2) was not significantly different between the ibuprofen (8/17; 47.1%) and the placebo group (9/33; 27.3%).

With respect to rescue after study day 14, 5 (7.4%) ibuprofen infants and 4 (5.9%) placebo patients were rescued. The mean ages were 19 and 18 days in the

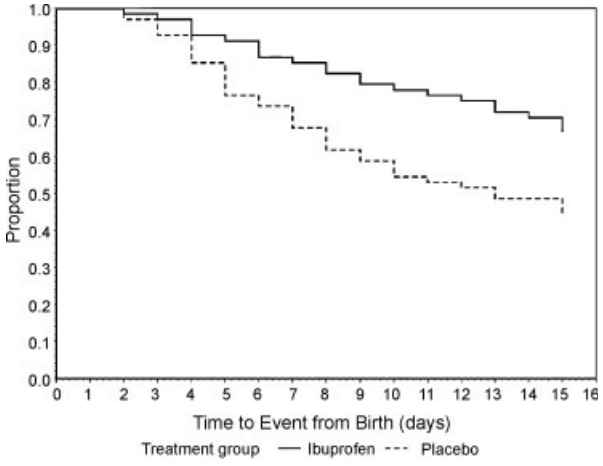

Figure 1 Kaplan-Meier curve showing the proportions of study participants who did not have any intervention, who dropped out, or who died. Broken line represents the placebo group; solid line represents the ibuprofen group. Log rank-sum test p value $=0.006$.

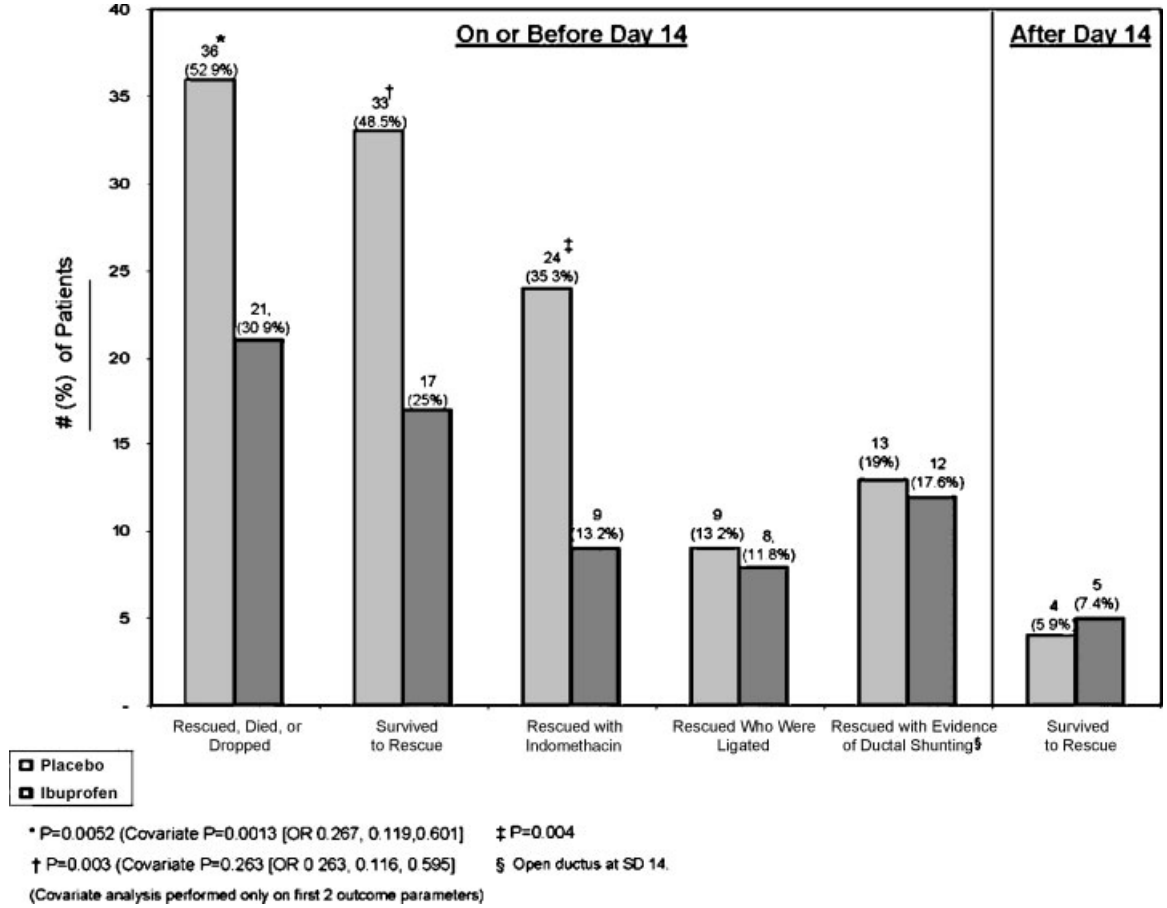

Figure 2 Summary of efficacy outcomes.

ibuprofen and placebo groups, respectively. Of these patients, three ibuprofen patients and one placebo patient subsequently underwent surgery, and one patient in each group died due to NEC. Neither gestational age nor birth weight was related to the rates of rescue (Table 2). Placebo treatment was the only factor statistically associated with an increased rescue outcome (Table 2).

Of the 30 infants (40%) in the placebo group who were not accounted for as either deaths, dropouts, or rescued patients either before, on, or after study day 14, 20 (29%) did not present with evidence of ductal shunting and, hence, were identified as having undergone spontaneous closure.

Safety Analysis and Serum Drug Concentrations

Safety endpoints have been summarized in Table 3. Higher urine flow rate was noted in the ibuprofen group at day 9, reflecting the effect of indomethacin rescue in a greater proportion of infant in the placebo group (Fig. 3A). Mean serum creatinine, within upper normal range in both groups, was significantly higher in the ibuprofen group on study days 3 and 4 (Fig. 3B); however, when adjusted for baseline, these differences disappear. Blood urea nitrogen was not significantly different between the placebo and ibuprofen groups (Fig. 3C) at any time point. Fluid intakes were also similar in both groups (Fig. 3D).

Table 2 Factors Associated with Rescue in Preterm Newborns with Patent Ductus Arteriosus

Effect	Adjusted Odds Ratio	95% Confidence Interval	*p* Value
Treatment: ibuprofen vs. placebo	0.27	(0.12, 0.60)	0.001
Birth weight: 500–750 vs. 751–1015	0.90	(0.38, 2.17)	0.817
Gestational age: <28 vs. ≥ 28	2.38	(0.66, 8.58)	0.187
Sex	1.05	(0.47, 2.36)	0.904
High-frequency oscillatory ventilation use: no vs. yes	0.40	(0.15, 1.06)	0.065
Maximum weight loss during the first 7 d of life (per 100-g loss)	0.49	(0.22, 1.08)	0.076

Table 3 Safety Outcomes and Adverse Events

Safety Outcomes and Adverse Events*	Ibuprofen, *n/N* (%)	Placebo, *n/N* (%)
NEC	9/65 (13.8)	9/65 (13.8)
Stages of NEC (highest identified from all sources)		
None	56/65 (86.2)	56/65 (86.2)
Pre-NEC	2/65 (3.1)	2/65 (3.1)
Definite	3/65 (4.6)	1/65 (1.5)
Advanced	4/65 (6.2)	6/65 (9.2)
IVH	25/67 (37.3)	25/67 (37.3)
Worst reported IVH grade		
None	42/67 (62.7)	42/67 (62.7)
Grade I	6/67 (9.0)	7/67 (10.4)
Grade II	8/67 (11.9)	7/67 (10.4)
Grade III	8/67 (11.9)	8/67 (11.9)
Grade IV	3/67 (4.5)	3/67 (4.5)
Pulmonary hemorrhage	1/68 (1.5)	4/68 (5.9)
Pulmonary hypertension	2/68 (2.9)	1/68 (1.5)
ROP	40/65 (61.5)	33/64 (51.6)
Stages of ROP		
None	25/65 (38.5)	31/64 (48.4)
Stage 1 or 2	34/65 (52.3)	28/64 (43.8)
Stage 3 or 4 (no stage 4 were observed)	6/65 (9.2)	5/64 (7.8)
ROP plus disease	4/65 (6.2)	3/64 (4.7)
BPD		
O_2 need at 28 d	58/65 (89.2)	53/65 (81.5)
O_2 need at 36 wk corrected age	42/46 (91.3)	48/52 (92.3)
PVL	0/65 (0.0)†	4/65 (6.2)
Death	8/68 (11.8)	10/68 (14.7)

*Chi-square test based on logistic regression controlling for sites.
†$p = 0.0587$.
NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia.

With respect to complications and adverse events, there were no differences in the proportion of babies who developed IVH, NEC, BPD, PPHN, or ROP between groups. None of the ibuprofen-treated infants had PVL, whereas four newborns in the placebo group had PVL diagnosed by head ultrasound at 36 weeks or prior to discharge ($p = 0.059$).

BPD at 28 days or at 36 weeks corrected age was higher than the usual average rates of ~40%. The high rate of oxygen use in both groups reported in this trial is likely explained by the broad definition of oxygen use and the low weight and gestational age of the population. Ventilator use was high in both groups on study day 1 (~80%) but decreased to ~57% in both groups by study day 14. Many of the infants continued to require supplemental inspired oxygen, albeit of low concentrations via nasal cannula (e.g., 22% inspired oxygen).

Liver function tests were evaluated for both groups. SGPT values did not vary between ibuprofen and placebo, respectively, at baseline (15.8 U/L versus 14.3 U/L) and study day 14 (14.9 versus 15.2). However, SGGT decreased from baseline to study day 14 for both ibuprofen (91.8 U/L to 51.0 U/L) and placebo (103.0 U/L to 47.9 U/L). SGOT also decreased for both Ibuprofen (54.4 U/L to 27.6 U/L) and placebo (55.9 U/L to 27.9 U/L). Changes from baseline and difference between treatments were not deemed to be significant.

Mean plasma concentrations ($\pm$ SD) of ibuprofen at 1, 24, 48, and 120 hours after the first dose were: 34.7 (9.0), 24.2 (7.6), 27.3 (14.2), and 13.2 (11.5) mg/L, respectively. There were no correlations between plasma concentration and primary outcome, PDA closure, or adverse effects.

DISCUSSION

The purpose of this study was to evaluate the effectiveness and safety of early closure of nonsymptomatic PDA within 72 hours of birth in ELBW infants with evidence of ductal shunting by echocardiogram with IV ibuprofen. In contrast to other ibuprofen studies that used ductal closure as the primary endpoint, this study was unique in its design to address the specific question as to whether treatment versus no treatment (placebo) during the early preterm setting (< 72 hours of birth) imparted a clinically meaningful and statistically significant benefit, preventing the need for rescue with surgery or indomethacin.

This was the first study in the United States conducted with ibuprofen L-lysine. This is important because birth weights and gestational ages tend to be lower in infants than in other countries. In this study, the mean birth weight was ~798 g and gestational age was ~26 weeks. This contrasts infant characteristics observed in other studies with ibuprofen conducted internationally where the mean weights ranged from 900 to 1200 g and gestational ages were ~29 weeks. These characteristics represent important population differences that have significant clinical implications. It is important to recognize that the rate of spontaneous closure of the ductus without treatment is inversely related to birth weight and gestational age, especially in infants under the age of 28 weeks versus those over 29 weeks.[27,28]

Placebo, rather than indomethacin, was used for comparison to address the specific question: does ibuprofen reduce the need for rescue therapy by early recognition and treatment of an asymptomatic, but early identifiable PDA? This study also met an FDA regulatory requirement for a placebo-controlled study that was ethical and allowed for the evaluation of a clinically meaningful endpoint beyond ductal closure such as rescue rates. Furthermore, this study was designed to

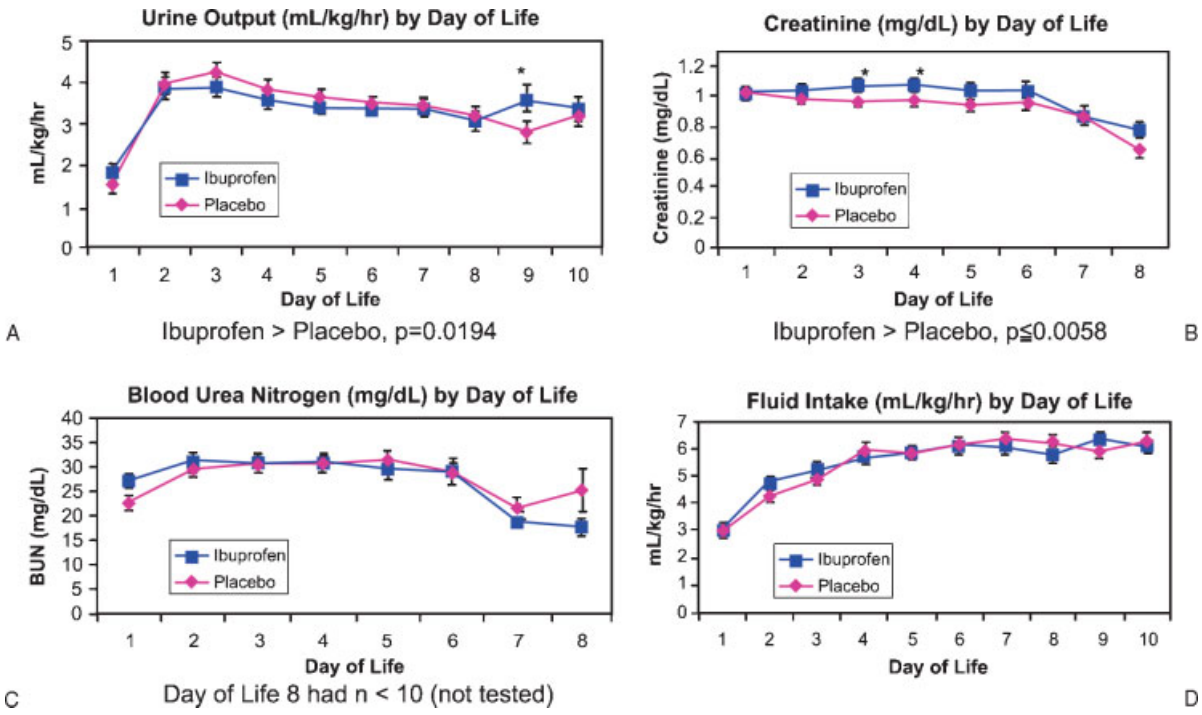

Figure 3 Renal effects of ibuprofen. (A) Effect on urine output. There was a significantly lower urine output at day 9 in the placebo group ($p < 0.02$) compared with the ibuprofen group. More subjects received indomethacin in the placebo group, which may have been associated with this lower renal output. (B) Effect on serum creatinine. Mean serum creatinine levels were below 1.1 mg/dL in both groups. A significantly higher serum creatinine level was noted in the ibuprofen group ($p < 0.05$) at days 3 and 4; however, these differences disappeared when corrected for baseline values. (C) Effect on blood urea nitrogen. No differences were noted except at day 8 when values in ibuprofen group were lower than placebo. (D) Fluid intake of the placebo- and ibuprofen-treated groups. No differences were noted between the two groups.

answer questions from some practitioners who believe spontaneous closure will occur and will wait on active treatment until clinical symptoms present. Results from this trial indicate that, in this ELBW population, spontaneous closure rates were no $\leq 30\%$. Moreover, closure of early asymptomatic PDA, outside of the prophylactic setting with indomethacin, has not been robustly evaluated and remains a matter of debate as it is also associated with a failure rate between 30% and 35%, requiring retreatment or surgical closure of the ductus arteriosus.[9] This is the subject of a currently ongoing large clinical trial in Australia (DETECT Trial) with indomethacin targeting asymptomatic patients who are between 6 and 12 hours of age and present with an open ductus.[30] Thus, the need for a placebo control and the endpoint of rescue were determined to be real and clinically relevant.

Ibuprofen has been extensively studied. Previous trials that compared the clinical effects of ibuprofen versus an active treatment, indomethacin,[17,25,40] have shown that ibuprofen is effective in PDA closure. Many of these studies, however, have evaluated treatment in different populations (prophylaxis, >72 hours after birth, different gestational age and birth weight profiles) or have been direct comparison versus an active treatment. No study has been published previously that specifically addressed the question regarding the clinical benefit of early medical therapy with a cyclooxygenase inhibitor versus placebo.

The efficacy results from this trial demonstrated that early treatment with ibuprofen of a confirmed PDA in infants <72 hours of birth can significantly decrease the need for further pharmacological or surgical intervention as compared with placebo. In addition to the significant reduction in the primary outcome, there was also a significant difference in the number of infants who had a completely closed ductus (0 mm) in the ibuprofen group versus placebo by study day 14 (69% versus 33%, $p = 0.046$), indicating that early therapy with ibuprofen versus placebo produces a meaningful clinical benefit in the treatment of a medically identifiable, but asymptomatic PDA. From a safety vantage point, the ibuprofen and the placebo groups did not significantly differ in rates of neonatal morbidities, including IVH, NEC, BPD, PPHN, and ROP.

Ibuprofen plasma concentrations were evaluated at 1, 24, 48, and 120 hours after the first dose to determine any correlation with efficacy outcome or adverse events. The highest mean concentration ($\pm$ SD) was 34.7 mg/L (0.9), which was 1 hour after dosing and was significantly below levels deemed to be of clinical concern. There was no correlation of mean blood

level versus resultant outcomes or appearance of adverse events; further work is planned to evaluate the pharmacokinetic profile of ibuprofen dosing from this study.

The data from this study are consistent with previous studies[16] and others[25,36,41] that ibuprofen L-lysine, given during the first 3 days of life, significantly increases PDA closure. In addition, our study supports others that IV ibuprofen decreases PDA with minimal effect on renal function.[16,25,41] However, a placebo-controlled PDA prevention study utilizing a different formulation (ibuprofen trishydroxymethylaminomethane) noted an increased risk of NEC, gastrointestinal perforation, PPHN, and a higher proportion of neonates with elevated creatinine with IV ibuprofen, when given within 6 hours of birth.[34,42] It should be noted that this study population was not screened for the presence of a PDA prior to therapy, and therefore, some patients were likely exposed to drug when they did not need it. Indeed, two of the three patients reported to have experienced PPHN in the trial by Gournay and colleagues[42] were found to have a constricted ductus and no shunt. These authors recommended an "early curative ibuprofen" regimen, which is similar to, and supportive of, the conclusions from the trial reported here.

In the present study, there were no differences noted in the incidence of NEC, gastrointestinal perforation, or PPHN between the ibuprofen and placebo groups. Feeding practices, not controlled in this study, differed between participating centers; some babies had no enteral feedings, although ~80% of others were given trophic or feeding as per institutional standard of care practice. Studies on ibuprofen and indomethacin effects on mesenteric and renal blood flow show that ibuprofen does not alter blood flow 30 minutes after treatment, but increases it 120 minutes after treatment.[22] In contrast, indomethacin has been shown to significantly reduce mesenteric and renal blood flow velocity 30 minutes after administration, without returning to pretreatment values within 120 minutes. This suggests that continued feeding may be acceptable with ibuprofen, although further controlled studies are needed to clarify this issue.

The minimal effects upon renal function, shown in this trial and others,[24,25] are a reflection of ibuprofen's mild effect on renal prostaglandins. Ibuprofen treatment of neonatal rats in the first 3 postnatal days had minimal effects on renal prostaglandin E, F2a, 6 keto-prostaglandinGF1a, and thromboxane B2.[43]

There was a trend toward a decrease in PVL by head ultrasounds at 36 weeks, which has not been noted in previous studies.[24] This observation is intriguing and bears further scrutiny as few pharmacologic agents with the exception of inhaled nitric oxide and caffeine have been shown to decrease PVL in preterm newborns.[44,45] In previous studies, ibuprofen showed no effect on cerebral CO_2 vasoreactivity, CBF velocities, and cytochrome c reductase levels,[18,21] but the role of inflammation on the pathogenesis of brain injury has been recognized recently.[46,47]

CONCLUSION

In summary, in this study of early closure of nonsymptomatic PDA within 72 hours of birth in ELBW infants, the treatment of echocardiogram-confirmed but asymptomatic PDA with IV ibuprofen L-lysine can significantly decrease the need for further pharmacological or surgical intervention as compared with placebo. In this study, IV ibuprofen L-lysine was associated with significantly lower rates of rescue, death, and dropouts, as compared with placebo. Furthermore, there was no difference in complications including IVH, NEC, BPD, ROP, or PPHN, indicating safety and efficacy of ibuprofen for early closure of PDA. Moreover, ibuprofen L-lysine had minimal effect on renal function and did not unduly decrease urine flow rate. The intriguing trend toward reduction of PVL with ibuprofen L-lysine requires further examination.

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DISCLOSURES

Jacob V. Aranda, M.D., received honoraria for serving as educational consultant for Ross Abbott (December 2005) and Ovation Laboratories (2006–2008). He also served as unpaid (pro bono) and paid consultant (honoraria) on pediatric drug development for various pharmaceutical companies and clinical drug trials performed with the NICHD Pediatric Pharmacology Research Unit Network including Aventis, Merck, Purdue, Johnson and Johnson, Farmacon, Pfizer, and Bristol Myers Squibb-Mead Johnson.

Robert M. Ward, M.D., received an honorarium for serving as educational consultant for Ovation

Laboratories in 2007. He has also served as an unpaid and paid consultant on pediatric drug development for various pharmaceutical companies including Wyeth Pharmaceuticals, Abbott Laboratories, Farmacon, McNeil Consumer Group, and Johnson & Johnson during 2005.

Robert Shalwitz, M.D., was the Medical Director of Abbott Nutritionals during the trial.

Geraldine Baggs, Ph.D., and Anand Seth, Ph.D., are senior clinical research scientists at Abbott Nutritionals.

L. Darko, Ph.D. (deceased), was the CEO of Farmacon IL, Inc.

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APPENDIX 1

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- Data Safety Monitoring Committee: Ronald Clyman, M.D. (UCSF), Yvette Johnson, M.D., M.P.H. (Baylor) (Chair), Leonard Weissman, M.D. (Baylor); Stanley Lemeshow, Ph.D. (OSU)

The NICHD Pediatric Pharmacology Research Unit Network (NICHD PPRU), Children's Hospital of Michigan and Wayne State University, Detroit, MI, and the Intravenous Ibuprofen Clinical Trial Group.