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ARTICLE

Comparison of standard versus high-dose ibuprofen for the treatment of hemodynamically significant patent ductus arteriosus in preterm infants

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Abstract

Objective To evaluate the effectiveness and safety of standard vs. high-dose ibuprofen for the treatment of hemodynamically significant patent ductus arteriosus(hs-PDA).

Study design A retrospective study of preterm infants who received either standard (10–5–5 mg/kg/day) or high (postnatal age 1–3 days: 10–5–5 mg/kg/day; 3–5 days: 15–7.5–7.5 mg/kg/day; >5 days: 20–10–10 mg/kg/day) dose ibuprofen for hs-PDA was conducted.

Result Sixty preterm infants with a mean birthweight of 898.2 (±262.6) g and mean gestational age of 26.3 (±0.6) weeks were included. High-dose ibuprofen was associated with a 21%(95% CI, −1.87 to 39.06%; $p = 0.07$) absolute reduction in PDA ligation compared to standard-dose ibuprofen. On adjusted analysis, receipt of standard-dose ibuprofen (OR 7.37, 95% CI, 1.2–45.27; $p = 0.03$) independently predicted increased PDA ligation risk. There were no differences in oliguria, NEC, or BPD between groups.

Conclusion High-dose ibuprofen may significantly reduce PDA ligations. No difference in the safety profile with high-dose ibuprofen as compared to the standard-dose regimen was demonstrated.

Background

Hemodynamically significant patent ductus arteriosus (hs-PDA) is a cardiovascular condition that occurs in preterm infants. Its incidence is inversely related to gestational age (GA) and birthweight (BW), occurring most frequently in infants born less than 28 weeks GA or weighing less than 1000 g [1, 2]. Resultant persistent ductal shunting secondary to a PDA can lead to detrimental health outcomes related to both pulmonary over-circulation (e.g., BPD) and systemic hypoperfusion (e.g., NEC, intraventricular hemorrhage, gastrointestinal bleeding, renal failure, and mortality) [1–4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the standard first-line treatment to facilitate PDA closure, thus playing a vital role in mitigating risks associated with PDA-induced cardiopulmonary instability, including the need for PDA ligation [1, 2, 5–9]. The two most commonly used NSAIDs for PDA treatment are ibuprofen and indomethacin. Recent Cochrane systematic reviews have shown therapies to be comparable in terms of efficacy; however, ibuprofen's superior safety profile makes it the NSAID of choice for the treatment of PDA given its associated reduction in NEC and transient renal insufficiency when compared to indomethacin [1, 8, 10].

A comprehensive systematic review and Bayesian network meta-analysis performed by Mitra et al. reviewed all of the commonly used pharmacologic interventions for hs-PDA, including NSAIDs, in an effort to rank each in terms of safety and efficacy [1]. This review revealed that both

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high-dose oral and intravenous ibuprofen (20–10–10 mg/kg/day; 15–7.5–7.5 mg/kg/day) were significantly more likely to result in PDA closure when compared to the more commonly used standard-dose intravenous ibuprofen (10–5–5 mg/kg/day) pharmacotherapy regimen. These results were in keeping with prior pharmacokinetic data which demonstrated higher doses of ibuprofen were required to account for neonatal development and secondary increasing hepatic enzyme metabolism capacity [11, 12]. In addition, the Mitra et al. study showed no significant increase in the odds of mortality, NEC, or intraventricular hemorrhage with high-dose ibuprofen when compared to all other treatment modalities [1].

Despite the presence of new evidence, hesitation to implement a high-dose ibuprofen regimen exists amongst clinicians due to the lack of clinical practice data and a fear of placing these infants at risk for more frequent adverse effects [1]. However, based on the results of the network meta-analysis by Mitra et al. as well as supporting pharmacokinetic data [11] the IWK Health Centre neonatal intensive care unit (NICU) (Nova Scotia, Canada) updated their drug dosing guidelines in June 2017 from using standard-dose ibuprofen irrespective of postnatal age, to using progressively higher doses of ibuprofen with increasing postnatal age. Infants aged 0–3 days received 10 mg/kg on day 1 of treatment, followed by 5 mg/kg on days 2 and 3. Infants aged 3–5 days received 15 mg/kg on day 1 of treatment, followed by 7.5 mg/kg on days 2 and 3. Infants aged greater than 5 days received 20 mg/kg on day 1 of treatment, followed by 10 mg/kg on days 2 and 3. The objectives of this study were to determine if (1) high-dose ibuprofen is more effective for the treatment of PDA vs. standard-dose ibuprofen when implemented into a clinical practice setting, and (2) if high-dose ibuprofen is associated with no worse of an adverse effect profile vs. standard-dose ibuprofen when implemented into a clinical practice setting. To our knowledge, this is the first study comparing high-dose (oral, intravenous) vs. standard-dose (intravenous) ibuprofen in a real-world practice setting.

Methods

This single-centre retrospective observational cohort study of preterm infants who received ibuprofen for treatment of hs-PDA was conducted in a tertiary care NICU at the IWK Health Centre in Halifax, Nova Scotia, Canada. The study was approved by the IWK Health Centre Research Ethics Board (IWK-REB project #: 1023920).

Eligibility criteria

The study cohort was a convenience sample that included all preterm infants who were born in or admitted to the IWK

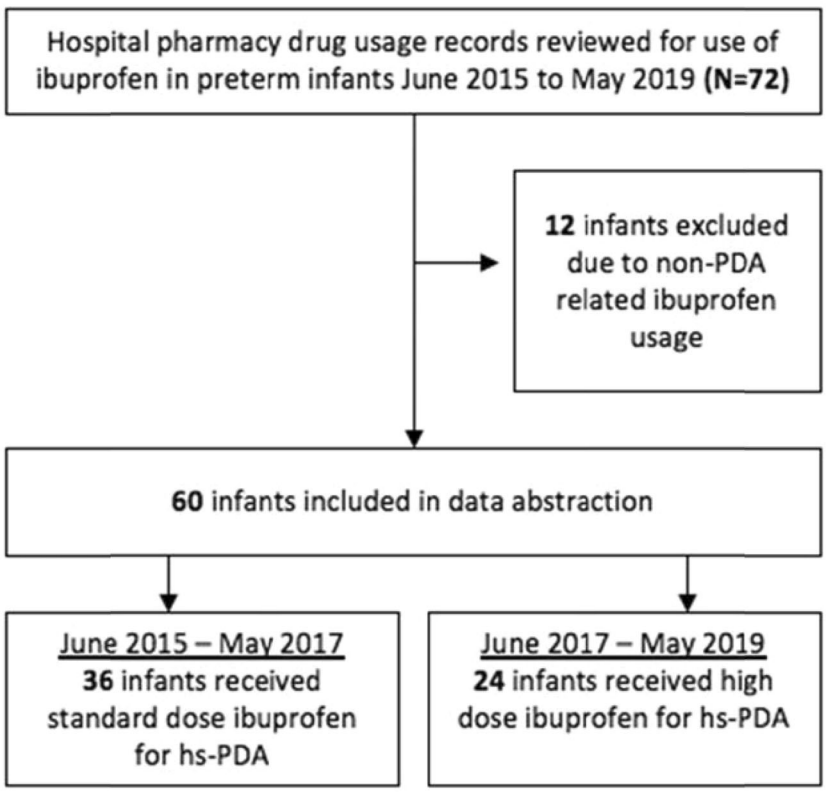

Fig. 1 PDA: Patent ductus arteriosus; hs-PDA: Hemodynamically signficant patent ductus arteriosus. Study flow chart of included preterm infants with hs-PDA throughout the study period.

Health Centre NICU with a GA younger than 37 weeks at birth and were treated with either intravenous or oral ibuprofen for a hs-PDA confirmed on echocardiogram. Hs-PDA on echocardiogram was defined as documentation of a moderate-to-large sized PDA (or PDA size ≥1.5 mm) with documentation of dilated left atrium (or left atrium to aortic root ratio ≥1.5). The echocardiograms were performed by pediatric cardiology services or by neonatologists trained in targeted neonatal echocardiography based on availability. The infants were excluded if they had known structural heart defect, chromosomal abnormality or if they had no documented echocardiographic evidence of a hs-PDA. All eligible preterm infants were identified through the generation of electronic drug usage reports on ibuprofen (using Meditech®) specific to the study centre. The included preterm infants were divided into two separate 2-year time epochs (June 2015 to May 2017; June 2017 to May 2019) reflecting the timeline and changes to the centre-wide ibuprofen dosing protocol (Fig. 1).

Standard vs. high-dose ibuprofen protocols

The standard-dose ibuprofen regimen for hs-PDA was administered intravenously once daily for 3 consecutive days (10–5–5 mg/kg/day). The newly implemented (June 2017) high-dose ibuprofen regimen for the treatment of hs-PDA was administered orally or intravenously once daily for 3 consecutive days at progressively higher dosages based on postnatal age (Postnatal age of 1–3 days: 10–5–5 mg/kg/day; Postnatal age of 3–5 days: 15–7.5–7.5 mg/kg/day; Postnatal age of >5 days: 20–10–10 mg/kg/day). Route of administration was chosen at the discretion of the treating clinician. Preference was given to oral administration over intravenous if infants were tolerating enteral feeds.

Primary and secondary outcomes

Nine outcomes were defined a priori, which included two effectiveness outcomes and seven adverse event outcomes. The primary outcome was surgical PDA ligation secondary to an inadequate pharmacotherapy response as was determined clinically (persistent requirement of invasive ventilatory support, need for inotropic support for systemic hypotension and inability to progress enteral feeds due to feeding intolerance or NEC) and confirmed by an echocardiogram (PDA remains hemodynamically significant, as defined previously in the eligibility criteria) in spite of multiple (at least two) pharmacotherapy courses. The other effectiveness outcome was receipt of repeat pharmacotherapy secondary to a failed initial course. Adverse event outcomes included were all-cause mortality, NEC (stage 2 or greater as per modified Bell's criteria), BPD (defined as oxygen use at corrected GA of 36 weeks), intraventricular hemorrhage (defined as any new intraventricular bleed or worsening of existing intraventricular bleed on cerebral ultrasounds postibuprofen therapy), gastrointestinal bleeding (defined as bleeding occurring during or up to 3 days post treatment), oliguria (defined as urine output <1 mL/kg/h during treatment), and retinopathy of prematurity (defined as ≥Stage 3 according to the international classification of retinopathy of prematurity) [13–15]. Concomitant use of medications that may influence study safety outcomes, such as vancomycin, aminoglycosides, furosemide, prophylactic indomethacin, and caffeine were recorded in each group.

Statistical analysis

Baseline variables and outcome data of infants with hemodynamically significant PDA as defined above were compared for univariate analysis. All categorical data were analyzed using χ^2 or Fisher's exact tests. Continuous data were tested for normality using the normal probability plots (q–q plots) and the Kolmogorov–Smirnov test for normality. Student's t test (unpaired) was used for analysis of continuous variables with normal distribution while the Mann–Whitney U test was used for analysis of variables with skewed distribution. The results were reported as risk ratio for binary outcomes or means and standard deviations for continuous outcomes, with corresponding 95% confidence interval and associated p values. Significance level for all analyses was set at a two-sided α of 0.05. Following the univariate analysis, a multivariable logistic regression analysis was conducted controlling for potential confounders (such as GA, BW, receipt of antenatal steroids, use of prophylactic indomethacin, timing of initiation of pharmacotherapy, and use of standard vs. higher doses of ibuprofen) to find out independent risk factors for the primary outcome. Statistical analysis was performed using SPSS, version 25.0 software©.

Results

A total of 60 preterm infants received oral or intravenous ibuprofen during the study period for treatment of hs-PDA (Fig. 1). Overall the infants included had a mean BW of 898.2 (±262.6) g, mean GA of 26.3 (±0.6) weeks, and time to ibuprofen initiation of 8.1 (±1.4) days. There were 36 preterm infants in Epoch 1 who received standard-dose ibuprofen, and 24 preterm infants in Epoch 2 who received high-dose ibuprofen.

The demographic and clinical characteristics of both groups are shown in Table 1. There were no statistically significant differences in baseline characteristics between the standard and high-dose groups, except for the ibuprofen route of administration. The standard-dose group had more

Table 1 Demographic and clinical characteristics.

	Standard-dose ibuprofen ($n = 36$)	High-dose ibuprofen ($n = 24$)	*P* value
Gestational age, weeks [Mean (SD)]	26.3 (2.5)	26.3 (2.3)	0.95
Birthweight, grams [Mean (SD)]	901 (278)	893 (243)	0.89
Apgar score: 1 min(s) [median (IQR)]	4 (2–6)	4 (1–5)	0.73
Apgar score: 5 min(s) [median (IQR)]	7 (5–8)	6 (5–7)	0.37
Caesarean section (%)	23 (63.9)	18 (75)	0.37
Prolonged rupture of membranes (%)	9 (25)	6 (25)	1.00
Received antenatal steroids (%)	24 (66.7)	15 (62.5)	0.74
Maternal chorioamnionitis (%)	7 (19.4)	5 (20.8)	0.90
Enteral feeding started at the time of PDA treatment [including MEN feeds (%)]	29 (80.6)	23 (95.8)	0.09
Pretreatment PDA size, mm [Mean (SD)]	2.4 (0.4)	2.1 (0.6)	0.06
Time to first ibuprofen dose, days [median (IQR)]	6 (3–9)	8 (5–11)	0.09
Route of administration: ibuprofen			
Oral (%)	0 (0)	12 (50)	0.0001
Intravenous (%)	36 (100)	12 (50)	0.0001
Time to PDA ligation, days [Median (IQR)]	23.5 (19–40)	24 (23–49)	0.60
Culture positive sepsis (%)	10 (27.8)	7 (29.2)	0.91
RDS requiring surfactant (%)	32 (88.9)	19 (79.2)	0.31
Caffeine use (%)	34 (94.4)	23 (95.8)	0.81
Furosemide use (%)	4 (11.1)	7 (29.2)	0.07
Aminoglycoside use (%)	33 (91.6)	20 (83.3)	0.33
Vancomycin use (%)	4 (11.1)	5 (20.8)	0.31
Prophylactic indomethacin use (%)	3 (8.33)	3 (12.5)	0.60

SD standard deviation, *IQR* interquartile range, *MEN* minimal enteral nutrition, *RDS* respiratory distress syndrome.

Table 2 Effectiveness and safety outcomes for standard versus high ibuprofen treatment.

	Standard-dose ibuprofen ($n = 36$)	High-dose ibuprofen ($n = 24$)	*P* value
Effectiveness outcomes			
PDA ligations total (%)	12 (33.3)	3 (12.5)	0.07
Repeat pharmacotherapy (%)	21 (58.3)	13 (54.2)	0.75
Administered as:			
Ibuprofen (%)	17 (80.9)	11 (84.6)	0.79
Indomethacin (%)	2 (11.8)	0 (0)	–
Acetaminophen (%)	2 (11.8)	2 (15.4)	0.77
Safety outcomes			
Necrotizing enterocolitis (%)	3 (8.3)	3 (12.5)	0.60
Bronchopulmonary dysplasia (%)	28 (77.8)	13 (65)[a]	0.30
Oliguria (%)	2 (5.6)	2 (8.3)	0.69
Retinopathy of prematurity (%)	11 (30.6)	4 (16.7)	0.22
Gastrointestinal bleed (%)	1 (2.8)	0 (0)	–
Intraventricular hemorrhage: new or progressed	1 (2.8)	0 (0)	–
All-cause mortality (%)	1 (2.7)	3 (12.5)	0.14

PDA patent ductus arteriosus.

[a]Bronchopulmonary dysplasia data do not include preterm infants who expired prior to 36 weeks of age.

intravenous administrations than the high-dose group (100% vs. 50%, $P < 0.001$), and had no oral administration.

Effectiveness outcomes

Use of high-dose ibuprofen in epoch 2 was associated with a 21% (95% CI: −1.87 to 39.06%) absolute reduction in PDA ligation compared to the use of standard-dose ibuprofen in epoch 1 (33.3% vs. 12.5%, $P = 0.07$) (Table 2). This finding was consistent following a multivariable logistic regression analysis which demonstrated statistical significance when neonatal and perinatal hs-PDA risk factors, such as GA, time-to-first ibuprofen dose, receipt of prophylactic indomethacin, and antenatal steroids were accounted for. Lack of receipt of antenatal steroids (odds ratio [OR] 9.46, 95% CI 1.40–63.83; $p = 0.02$) and receipt of standard-dose ibuprofen (OR 7.37, 95% CI 1.2–45.27; $p = 0.03$) independently predicted increased PDA ligation in this cohort (Table 3). There were no statistically significant differences in the frequency of repeat pharmacotherapy (58% vs. 54%, $p = 0.75$) or the time to PDA ligation (23.5 days vs. 24 days, $p = 0.60$) between the standard and high-dose ibuprofen groups. Use of acetaminophen also did not significantly differ between the two groups ($p = 0.77$) (Table 2).

Safety outcomes

There were no statistically significant differences between infants in the standard-dose vs. high-dose ibuprofen groups for NEC, BPD, oliguria, and retinopathy of prematurity (Table 2). Mortality rates were not significantly different between groups.

Sensitivity analyses and post hoc power calculation

Out of the three infants who had PDA ligation in the second epoch, one infant had received high-dose oral ibuprofen and two infants had received high-dose IV ibuprofen. A sensitivity analysis comparing standard-dose IV vs. high-dose IV ($p = 0.27$), standard-dose IV vs. high-dose oral ($p = 0.09$), and high-dose IV vs. high-dose oral ibuprofen ($p = 0.53$) did not show any statistically significant differences for the primary outcome of PDA ligation.

Post hoc calculation of statistical power demonstrated that assuming α of 0.05, our study had a power of 78% to detect the observed 21% difference in the rate of our primary outcome (PDA ligation) between the two epochs.

Table 3 Multivariable logistic regression analysis for the outcome of PDA ligation.

Variable	*P* value	OR (adjusted)	95% CI
Gestational age (weeks at birth) (Δ1 week)	0.62	0.82	0.38, 1.79
Lack of antenatal steroids	0.02	9.46	1.40, 63.83
Indomethacin prophylaxis	0.38	3.35	0.22, 50.21
Ibuprofen dose (standard vs. high)	0.03	7.37	1.20, 45.27
Time to first ibuprofen dose	0.85	0.99	0.89, 1.10
Birthweight (g) (Δ1 g)	0.26	1.00	0.99, 1.01

Discussion

This single-centre retrospective observational study in preterm infants treated with standard vs. high-dose ibuprofen for hs-PDA demonstrated that use of a high-dose ibuprofen regimen was associated with a 21% absolute reduction in PDA ligation rates when compared to using standard-dose ibuprofen (Table 3). Logistic regression analysis controlling for relevant perinatal and neonatal confounders confirmed use of standard-dose ibuprofen as an independent predictor for increased PDA ligation, along with lack of exposure to antenatal corticosteroids. To our knowledge, this is the first report on the use of high-dose ibuprofen for PDA treatment in preterm infants from any NICU in North America.

Our study's conclusion regarding high-dose ibuprofen superiority was congruent with a recent Cochrane Review on the use of ibuprofen for the treatment of PDA in preterm infants [8]. This review included data from three studies to compare how frequently high-dose ibuprofen (20–10–10 mg/kg/day or 15–7.5–7.5 mg/kg/day) compared to standard-dose ibuprofen (10–5–5 mg/kg/day) in infants with echo diagnosed hs-PDA resulted in failure to close PDA [16–18]. The studies included in the analysis were a 2-year randomized controlled trial by Dani et al. of 70 preterm infants being treated with intravenous ibuprofen, a 1-year randomized clinical trial by Pourarian et al. of 60 preterm infants with oral ibuprofen, and a 2-year randomized controlled clinical trial by Fesharaki et al. of 60 preterm infants being treated with oral ibuprofen. The resulting analysis demonstrated that preterm infants with hs-PDA who were treated with standard-dose ibuprofen were on average 63% more likely to experience failed PDA closure than those treated with high-dose ibuprofen (RR 0.37 [95% CI: 0.22–0.61]). A differentiating factor of our study results from those of prior literature was that of our primary outcome. Most often, echocardiographic evidence of PDA closure has been used as surrogate outcome for treatment success. At present, there has not yet been a randomized controlled trial to demonstrate that complete echocardiographic PDA closure leads to improved clinical outcomes. As a result, we chose PDA ligation as our primary outcome due to its clinical and logistical implications compared to the surrogate outcome of PDA closure with unknown

clinical significance. Our results are further supported by a recent randomized, double-blind, placebo-controlled, non-inferiority trial completed by Sung et al. In their study, it was demonstrated that among 142 preterm infants with hs-PDA, non-intervention was noninferior to standard-dose ibuprofen in achieving PDA closure, reducing device closure of PDA or reducing the composite outcome of BPD or death. This new study calls into question the efficacy of standard-dose ibuprofen in treating hs-PDA given the high rates of death or BPD in both the groups (44% in the non-intervention group vs. 50% in the ibuprofen group; $p = 0.51$) . The results of the Sung et al. noninferiority trial has important implications for our study in that it provides further support that the reduction in PDA ligation rates seen in our study's high-dose ibuprofen group may likely be attributed to the increased dosage alone [19].

The median time to PDA ligation in our cohort was similar between groups (Table 1). This finding strengthens our overall conclusion regarding high-dose ibuprofen efficacy because the reduction in PDA ligations seen in the high-dose group may be accredited to the change in dosing regimen, rather than the recent shift in practice towards delaying PDA ligation procedures to allow time for possible spontaneous closure [1].

We found no difference in need for repeat pharmacotherapy between the high and standard-dose ibuprofen groups. This finding may suggest that while the high-dose ibuprofen regimen demonstrated a clinically meaningful reduction in PDA ligations, it does not appear to have reduced the need for, or exposure to, subsequent treatment courses over the standard-dose ibuprofen regimen. Previous studies by Dani et al., Pourarian et al., and Richard et al. also demonstrated that a second course of therapy was often required in both the standard and high-dose ibuprofen groups [16, 17, 20]. Importantly, these studies also showed that a second course of the high-dose regimen led to a greater proportion of PDA closures and less PDA ligations than a second course of standard-dose regimen. These findings in combination with our study further support the superiority of high-dose ibuprofen in achieving hs-PDA closure.

While infrequent, there were instances in our study whereby the treating physician chose to use acetaminophen (15 mg/kg every 6 h for 3–7 days) as the agent of choice for subsequent pharmacotherapy course(s). There is a growing body of literature to support the use of acetaminophen as an effective pharmacotherapeutic treatment option for hs-PDA [21]. Interpreting our results in this context is important, however the use of acetaminophen was similar for both epochs and therefore its use is unlikely to have affected our overall results (Table 2).

In this study, we were unable to demonstrate a statistically significant difference in the rate of BPD between the high and standard-dose ibuprofen groups. While this statistical insignificance is congruent with prior studies, our study presented a novel clinical finding in that the babies treated with high-dose ibuprofen group experienced a 12.8% absolute reduction in BPD. However, we refrain from attributing causality due to the retrospective nature of the study [22–24].

With regards to safety of high-dose ibuprofen, it is important to note here that previous randomized trials that used higher doses of ibuprofen mostly enrolled more mature preterm infants with a mean GA of 30 weeks or more [17, 18]. This is possibly a reason that has precluded widespread uptake of high-dose ibuprofen in the extremely preterm population in spite of its better efficacy profile due to fears of adverse effects, such as NEC. In our cohort of extremely preterm infants (mean GA of 26 completed weeks), we were unable to demonstrate any difference in safety outcomes, such as NEC and oliguria between the high-dose and standard-dose ibuprofen regimens. However we acknowledge that existing evidence on the incidence of NEC and oliguria when comparing high vs. standard-dose ibuprofen is still inconclusive [1, 18, 25, 26]. A larger study with a greater sample size is needed to generate adequate power and would allow one to draw more definitive conclusions regarding these safety outcomes [27].

Our study's main limitation was that it was a single-centre retrospective cohort study. Therefore, due to the non-randomized nature of the study, associated perinatal and neonatal clinical variables theoretically could have confounded the results. This design limitation was partially mitigated through identification, collection, and analysis of relevant confounders which were adjusted for in the regression analysis allowing quantification of their impact on overall results. However, the possibility of residual confounding cannot be ruled out.

The results of our study support the implementation of a high-dose ibuprofen regimen as the first-line therapy for hs-PDA. In keeping with previous literature, high-dose ibuprofen was shown to be more efficacious in reducing PDA ligation; furthermore, we were unable to demonstrate any difference in the safety profile as compared to the standard-dose ibuprofen regimen. Given the growing body of data in support of high-dose ibuprofen, adequately powered comparisons of high-dose vs. standard-dose ibuprofen and more specifically high-dose intravenous vs. high-dose oral ibuprofen regimens compared against each other and/or no treatment in extremely preterm infants at the highest risk of PDA attributable morbidities are essential areas for future research.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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