

# Impact of Oral versus Intravenous Ibuprofen on Neurodevelopmental Outcome: A Randomized Controlled Parallel Study

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## Abstract

**Objective** Although neurodevelopmental outcomes related to the management of patent ductus arteriosus with intravenous indomethacin and ibuprofen are known, little data on the long-term effects of oral ibuprofen can be found in the literature.

**Method** A follow-up study of 99 infants with birth weight  $\leq$  1,500 g and gestational age  $\leq$  32 weeks who received either oral or intravenous ibuprofen for patent ductus arteriosus was conducted to assess at 18 to 24 months (corrected age), abnormal neurological, neurosensory, and cognitive impairment were defined as follows: neurological outcomes included moderate/severe cerebral palsy, neurosensory outcomes included bilateral hearing loss and blindness in either eye, and cognitive impairment included mental developmental index score  $<$ 70.

**Results** The 18- to 24-month (corrected age) long-term outcomes of 30 subjects who received oral ibuprofen were compared with 27 subjects who received intravenous ibuprofen by certified and experienced examiners who were blind to the definitions of the groups. The results revealed that the long-term outcomes of the treatment regimens did not significantly differ.

**Conclusions** Preterm infants who were treated with oral ibuprofen for patent ductus arteriosus had similar neurological, neurosensory, and cognitive outcomes to patients who received intravenous ibuprofen at 2 years of age.

## Keywords

- ▶ ibuprofen
- ▶ long-term outcome
- ▶ neurodevelopmental outcome
- ▶ preterm
- ▶ very low birth weight

A hemodynamically significant patent ductus arteriosus (PDA) in preterm infants can cause cardiovascular instability, exacerbate respiratory distress, prolong the need for assisted ventilation, and increase risks of chronic lung disease (CLD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and death.<sup>1–5</sup>

Pharmacological therapy for ductal closure includes cyclooxygenase inhibitors, such as ibuprofen and indomethacin.<sup>6</sup>

In many clinical trials, it has been established that intravenous (IV) ibuprofen had fewer side effects than and similar efficacy to indomethacin. Recent studies have shown that oral ibuprofen was effective and well tolerated for early curative closure of PDA in very premature infants.<sup>2,7,8</sup> Because IV ibuprofen is not available in many developing countries and is more expensive than the oral form, many clinicians prefer oral ibuprofen in the medical management of PDA.<sup>2,7–9</sup>

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Several studies have evaluated the long-term outcomes of treatment strategies, such as indomethacin, ibuprofen, and surgical ligation, for PDA. Rheinlaender et al demonstrated that use of either IV ibuprofen or indomethacin for ductal closure did not influence 2-year neurodevelopmental outcomes of very low-birth-weight (VLBW) infants.<sup>10</sup> On the other hand, many studies have reported that surgical ligation was associated with neurodevelopmental impairment in preterm infants.<sup>10–16</sup>

Our previous randomized controlled trial, which compared oral ibuprofen versus IV ibuprofen for closure of PDA in preterm infants with gestational age  $\leq 32$  weeks, birth weight  $\leq 1,500$  g, and postnatal age 48 to 96 hours who had hemodynamically significant PDA, demonstrated that oral ibuprofen was more effective for closure of PDA. Patients were assigned randomly to treatment groups using cards in sealed opaque envelopes, and 102 patients (52 in the oral group and 50 in the IV group) completed the study protocol. Each enrolled patient received IV ibuprofen (Pedeia, Orphan Europe, Paris, France) or oral ibuprofen (Pedifen, Atafarm, Istanbul, Turkey) at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 hours and 48 hours.<sup>8</sup>

The impact on infant neurodevelopmental outcomes of treating PDA with oral versus IV ibuprofen is unknown. The higher closure rates observed in oral versus IV ibuprofen groups reported in previous studies<sup>2,7,8</sup> led us to hypothesize that better long-term neurodevelopmental outcomes would be observed in the former. Thus, we designed a study to compare the long-term effects of the two treatment regimes on neurodevelopmental outcomes at 18 to 24 months' corrected age (CA) in a cohort of VLBW preterm infants who were enrolled in our previous published study and survived.<sup>8</sup>

## Methods

We performed a controlled study using data collected for our previous study to test the hypothesis that the neurodevelopmental outcomes of PDA closure would be better following treatment with oral versus IV ibuprofen.

Neurodevelopmental follow-up was conducted by a neonatologist, a pediatrician, an audiologist, and an ophthalmologist. All data were collected by the researchers. The primary outcome measure of the current study was calculated by comparing the neurological, neurosensory, and cognitive impairment in the two groups. A comprehensive assessment was performed at 18 to 24 months' CA in our developmental behavioral pediatrics unit by certified and experienced examiners who were blind to the previous assignment of infants to oral or IV ibuprofen groups.

A physical examination, neurological examination, and developmental assessment were performed for all infants. Developmental assessments were performed with the Bayley Scales of Infant Development II for subjects up to 42 months.<sup>17</sup> The Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were determined. Abnormal neurological, neurosensory, and cognitive outcomes were defined as follows: neurological outcomes included moderate/severe cerebral palsy (CP; hypotonic, spastic diplegia, hemi-

plegia, or quadriplegia) with functional deficits that required rehabilitative services, neurosensory outcomes included bilateral hearing loss (requiring amplification) and blindness in either eye, and cognitive outcomes included MDI  $< 70$ . MDI and PDI scores were deemed to be 49 when the child could not be tested because of severe developmental delay.

Written informed consent for the long-term neurological and developmental evaluation at 18 to 24 months' CA was obtained from a parent or guardian of each infant. The study protocol was approved by the local ethics committee.

## Statistical Analyses

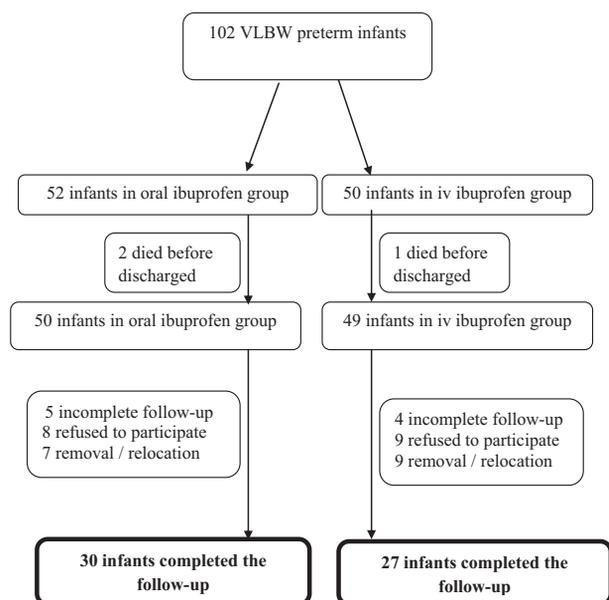
Statistical analyses were performed using SPSS software (version 16.0). Differences between oral and IV ibuprofen groups were analyzed for statistical significance using a *t* test for normally distributed data, a Mann–Whitney *U* test for nonnormally distributed data (MDI and PDI scores), and a chi-square analysis for frequencies. Multinomial logistic regression analysis was used to represent the effects of risk factors, such as gestational age, birth weight, respiratory distress syndrome (RDS), NEC, sepsis, pneumothorax, grade 3 to 4 IVH, CLD, retinopathy of prematurity (ROP), and application route of ibuprofen on CP and cognitive impairment. A *p* value of  $< 0.05$  was deemed to indicate statistical significance.

## Results

In total, 102 VLBW preterm infants born  $\leq 1,500$  g and  $\leq 32$  weeks' gestational age had completed our previous study. Of these, 52 were in the oral ibuprofen treatment group and 50 were in the IV ibuprofen group. During the neonatal intensive care unit stay 2 (3.8%) infants in the oral group and 1 (2.0%) infant in the IV group died, and 99 (94.2%) infants were discharged from the hospital. Twenty (40.0%) of 50 infants in the oral group and 22 (55.1%) of 49 infants in the IV group were excluded because of incomplete follow-up, refusal to participate, and relocation. At 18 to 24 months' CA 30 infants in the oral group and 27 infants in the IV group were assessed for the long-term outcome (**Fig. 1**).

The mean birth weight and gestational age did not differ between the groups ( $p = 0.25$  and  $p = 0.15$ ). **Table 1** shows perinatal characteristics of the study infants. No significant differences in variables such as RDS, NEC, sepsis, pneumothorax, CLD, or ROP were found between the groups. Although the rates of grade 3 to 4 IVH was higher in the oral group compared with the IV group, this was not statistically significant. Clinical characteristics such as RDS, NEC, sepsis, pneumothorax, grade 3 to 4 IVH, and CLD, which might affect the long-term outcomes of patients who were excluded, did not differ between the groups (56.4% versus 61.8%, 4.5% versus 4.3%, 63.6% versus 60.8%, 4.5% versus 8.6%, 9% versus 13.0%, and 18.8% versus 21.7% for the oral and IV ibuprofen groups, respectively;  $p > 0.05$ ).

Thirty (60.0%) of 50 subjects who received oral ibuprofen were compared with 27 (55.1%) of 49 who received IV ibuprofen for the long-term outcomes. The infants were assessed at a mean age of  $20.8 \pm 1.2$  months' CA. The median MDI score was 85 (49 to 126, interquartile range: 24) in the

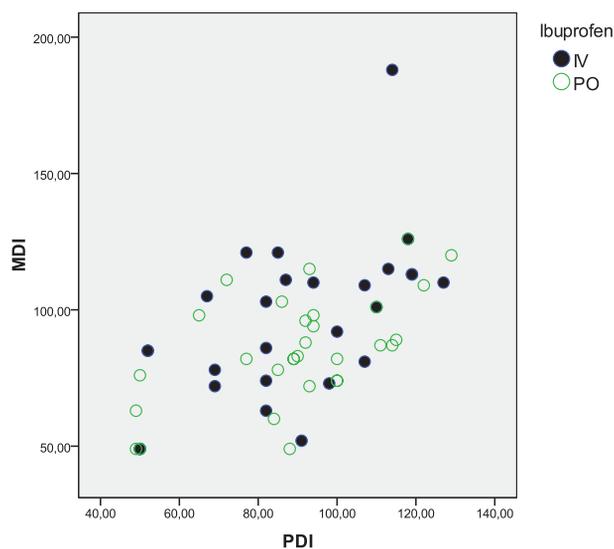


**Fig. 1** Flowchart of the study group. Abbreviations: iv, intravenous; VLBW, very low birth weight.

oral group and 94 (49 to 189, interquartile range: 39) in the IV group ( $p = 0.14$ ). The median PDI score was 92 (49 to 129; interquartile range: 20) in the oral group and 87 (50 to 127; interquartile range: 41) in the IV group ( $p = 0.86$ ). No significant difference was found between the group among median MDI and PDI scores. Scatter plots of MDI and PDI scores are shown in ►Figs. 2, 3, and 4.

The neurological, neurosensory, and cognitive outcomes in both groups at 18 to 24 months' CA are shown in ►Table 2. Three (10.0%) of 30 infants in the oral ibuprofen group had moderate/severe CP compared with 2 (7.4%) of the 27 infants in the IV ibuprofen group. The CP rates did not differ between the groups ( $p = 0.73$ ). No infant in the cohort was diagnosed as blind or deaf.

Five (16.7%) infants in the oral group and 4 (14.8%) in the IV group had MDI scores < 70 and cognitive impairment. Six (20.0%) infants in the oral group and eight (29.6%) in the IV



**Fig. 2** Scatter plot of mental developmental index and psychomotor developmental index scores. Abbreviations: IV, intravenous; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; PO, oral.

group had PDI scores < 70. We found no significant differences between the groups in terms of MDI or PDI scores < 70 ( $p = 0.48$  and  $p = 0.39$ , respectively).

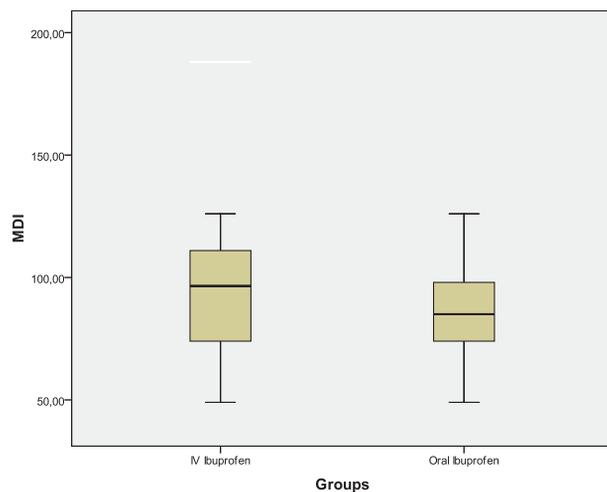
There were no significant differences between girls and boys among MDI < 70 and PDI < 70 both in oral and IV groups. According to the results of a multinomial logistic regression analysis, the risk factors of gestational age, birth weight, RDS, NEC, sepsis, pneumothorax, grade 3 to 4 IVH, CLD, ROP, and application route of ibuprofen had no effect on CP or cognitive impairment ( $p > 0.05$ ).

## Discussion

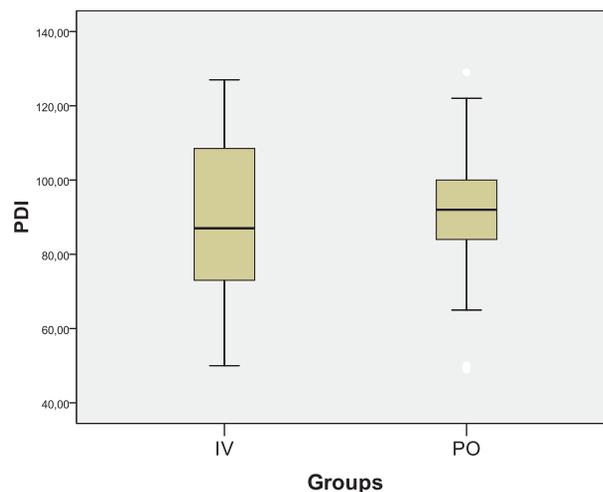
In our cohort of VLBW preterm infants, we found that infants treated with oral ibuprofen had similar, but not better, neurological, neurosensory, and cognitive outcomes at 18 to 24 months' CA compared with infants whose PDA was

**Table 1** Perinatal characteristics of study infants

Variables	Oral ibuprofen group (n = 30)	Intravenous ibuprofen group (n = 27)	p
Gestational age	28.2 ± 1.9	27.5 ± 1.3	0.15
Birth weight	1,110 ± 268	1,035 ± 222	0.25
Respiratory distress syndrome, n (%)	20 (66.7)	19 (70.4)	0.76
Necrotizing enterocolitis, n (%)	1 (3.3)	0 (0)	0.34
Sepsis, n (%)	23 (76.6)	21 (77.7)	0.92
Pneumothorax, n (%)	0 (0)	2 (7.4)	0.12
Intraventricular hemorrhage grade 3–4, n (%)	6 (20.0)	2 (7.4)	0.068
Chronic lung disease, n (%)	9 (30.0)	8 (29.6)	0.97
Retinopathy of prematurity, n (%)	17 (56.7)	21 (77.7)	0.15
Retinopathy with laser, n (%)	2 (6.7)	5 (18.5)	0.14



**Fig. 3** Scatter plot of mental developmental index scores. Abbreviations: IV, intravenous; MDI, Mental Developmental Index.



**Fig. 4** Scatter plot of psychomotor developmental index scores. Abbreviations: IV, intravenous; PDI, Psychomotor Developmental Index; PO, oral.

treated with IV ibuprofen. To our knowledge, no data comparing the neurodevelopmental outcomes of infants treated with oral versus IV ibuprofen for PDA have been reported in previous clinical studies. We found other studies about other treatment regimes, such as IV ibuprofen, indomethacin, and surgical ligation. Rheinlaender<sup>10</sup> et al evaluated outcome parameters in VLBW with PDA; 89 of the patients in this study were treated with indomethacin and 93 with IV ibuprofen. Eight (11%) infants treated with indomethacin and 6 (9%) infants treated with IV ibuprofen had CP. Twenty-three (32%) of 71 infants treated with indomethacin and 15 (22%) of 70 treated with IV ibuprofen had Bayley MDI < 70. They reported that use of IV ibuprofen or indomethacin for closure of PDA did not influence 2-year neurodevelopmental outcomes in VLBW infants.<sup>10</sup> Moreover, studies evaluating surgical ligation reported different results with regard to neurodevelopmental outcomes. Kabra et al studied 426 infants with PDA; 110 of these infants underwent PDA ligation, and 316 received medical therapy only. The infants were assessed at 18 months' CA. Of 95 infants who survived after PDA ligation, 50 (53%) had neurosensory impairment compared with 84 of the 245 infants (34%) who survived after receiving only medical therapy ( $p = 0.0093$ ). The authors

concluded that PDA ligation might be associated with increased risks of neurosensory impairment in VLBW infants.<sup>14</sup> Madan et al studied infants born at 23 to 28 weeks' gestational age and < 1,000 g who were treated with either indomethacin alone or indomethacin followed by secondary surgical closure or primary surgery for PDA. They suggested that infants treated with primary or secondary surgery for PDA might be at increased risk for poor long-term outcomes compared with those treated with indomethacin (odds ratios: 1.89 and 1.39).<sup>15</sup> Chorne et al examined a total of 446 infants born after < 28 weeks' gestation to investigate the effects of indomethacin and surgical ligation on the incidence of neurodevelopmental impairment and reported that surgical ligation was significantly associated with poor outcome.<sup>12</sup>

Our study is the first reported research to compare the long-term outcomes of two treatment regimens, oral and IV ibuprofen, used for PDA in VLBW preterm infants. Although our findings did not show better neurological, neurosensory and developmental outcomes with oral ibuprofen, we found similar results with oral and IV ibuprofen. Although statistically insignificant, in the oral group, the mean MDI score was 10 points and the mean PDI score was 5 points lower than the IV group. Because this is a pilot study, the study size was quite

**Table 2** Long-term outcomes of study infants at 18–24 mo corrected age

Variables	Oral ibuprofen group (n = 30)	Intravenous ibuprofen group (n = 27)	p
Median Mental Developmental Index	85 (49–126)	94 (49–189)	0.14
Median Psychomotor Developmental Index	92 (49–129)	87 (50–127)	0.86
Moderate/ to severe cerebral palsy, n (%)	3 (10.0)	2 (7.4)	0.73
Blind, n (%)	0 (0)	0 (0)	–
Deaf, n (%)	0 (0)	0 (0)	–
Mental Developmental Index < 70, n (%)	5 (16.7)	4 (14.8)	0.48
Psychomotor Developmental Index < 70, n (%)	6 (20.0)	8 (29.6)	0.39
Neurosensory Impairment, n (%)	0	0	–

small, and that the study was not powered initially to look at long-term outcomes at all, we suggest that these differences may be clinically significant in practice and may even be statistically significant with a larger sample size.

As a pilot preliminary exploratory study, this research has several limitations. First, this study was not powered to show any effects on CP or cognitive impairment between groups initially. New studies with a power analysis are needed to evaluate long-term outcomes in the future. Additionally, we did not control for differences in variables that may have confounded the effects of the treatments on the neurodevelopmental outcomes. A larger sample size is required to control for various confounders such as NEC, IVH and CLD, which we could not define any correlation with CP or cognitive impairment. Beside, although insignificant difference was noticed in IVH rates, the tendency of a higher rate in oral ibuprofen should be evaluated in future studies with larger samples. Second, because this study was conducted at a referral hospital serving a large geographical area, we could not assess all surviving subjects, which should be considered in interpretations of our results.

## Conclusions

PDA is of significant clinical importance in VLBW preterm infants. Many treatment strategies (e.g., IV ibuprofen, indomethacin, surgical ligation) have been shown to be effective for closure of PDA. However, a reasonable question in this regard concerns which approach is more readily available, simpler, and less expensive. IV ibuprofen is not available in many developing countries and is more expensive than the oral form. In this preliminary pilot study evaluating approximately 50% of the subjects enrolled in our controlled trial of evaluating the “impact of oral versus IV ibuprofen on neurodevelopmental outcome,” we were not able to identify a statistically significant difference in NDI. As the size of the study was too small to see differences, future studies with sufficient power should be designed to outline the effects on NDI long term.

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Dr. Zeynep Eras had primary responsibility for protocol development, patient screening, enrollment, outcome assessment, preliminary data analysis, and writing the manuscript. Drs. Banu Mutlu Ozyurt and Tulin Gokmen participated in the development of the protocol and analytical framework for the study and contributed to the writing of the manuscript. Child Development Specialist Bagdagul Saridas was responsible for patient screening. Drs. Omer Erdevi and Ugur Dilmen supervised the design

and execution of the study, performed the final data analyses, and contributed to the writing of the manuscript.

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