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Safety and Effectiveness of Indomethacin versus Ibuprofen for Treatment of the Patent Ductus Arteriosus

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Abstract

Objective—Compare the rates of medical closure of the PDA and complications (renal dysfunction, necrotizing enterocolitis, spontaneous intestinal perforation, and intraventricular hemorrhage) between infants treated with indomethacin and ibuprofen.

Study Design—A retrospective comparative cohort study of infants treated with indomethacin or ibuprofen for symptomatic patent ductus arteriosus at Duke University Medical Center between November 2005 and November 2007.

Result—We identified 65 infants that received indomethacin and 57 that received ibuprofen. The rate of survival without surgical ductal ligation was 62% (40/65) in the indomethacin group and 58% (33/57) in the ibuprofen group, P=0.71. The rate of the composite of complications (death, necrotizing enterocolitis, or intestinal perforation) was 40% (26/65) in the indomethacin group and 32% (18/57) in the ibuprofen group, P=0.35. There was no significant difference between groups in elevation of serum creatinine during treatment.

Conclusion—In clinical practice, ibuprofen appears to be as effective as indomethacin for closure of patent ductus arteriosus with similar complication rates. The decision to use one agent over the other should be based on dose schedule preference and the currently published clinical trials until more safety and effectiveness data are available.

Keywords

Ibuprofen; Indomethacin; Patent Ductus Arteriosus; Neonates; Nonsteroidal antiinflammatory drug

INTRODUCTION

Historically, indomethacin has long been the sole agent available for treatment of patent ductus arteriosus (PDA). In April 2006, Ibuprofen lysine (ibuprofen) was introduced as an alternative agent with U.S. Food and Drug Administration approval for closure of PDA in premature infants[1]. In well powered randomized controlled trials, ibuprofen was equally efficacious as indomethacin, for ductal closure and had less effect on renal, mesenteric, and cerebral perfusion2–9. However, few studies describe the safety and effectiveness of ibuprofen in clinical practice outside the context of randomized clinical trials. The current lack of difference in cost10 between the two agents further complicates the clinical decision and makes it difficult to choose one over the other.

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Based on comparable efficacy and the potential for improved safety reported in clinical trials[9, 11], the Neonatal Intensive Care Unit at Duke University Medical Center (DUMC) changed practice from indomethacin to ibuprofen as the first line agent for PDA closure in November 2006. However, efficacy is only a reflection of how an intervention is beneficial under ideal conditions (within the context of a well-designed clinical trial with strict inclusion criteria), and it is important to know whether or not efficacy translates into effectiveness (extent to which an intervention functions under real world clinical circumstances). The aim of this study is to review the effectiveness and safety of ibuprofen versus indomethacin by assessing rates of successful PDA closure and complications between infants treated with indomethacin and those treated with ibuprofen.

METHODS

This retrospective cohort study included all infants that received at least one treatment dose of indomethacin or ibuprofen at DUMC between November 2005 and November 2007. Clinical data and demographic information were collected by review of medical and pharmacy records of the identified patients. Age at treatment, birth weight, gestational age, and prophylactic indomethacin use were noted along with the incidence of surgical ligation of the PDA, necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), intraventricular hemorrhage (IVH), and death. Serum creatinine levels, pre- and post-treatment, were compared. Due to the differences in dosing schedule, the post-treatment creatinine was recorded 48 hours after initiation of indomethacin and 72 hours after initiation of ibuprofen. Data were analyzed using logistic regression analysis, Fisher's exact, Wilcoxon rank-sum, and t-tests where appropriate. STATA 10 (College Station, TX) was used for statistical analysis. This retrospective study was approved by the Duke University Institutional Review Board.

During the study period, prophylactic indomethacin (0.1 mg/kg/dose x 3 doses) was used for prevention of IVH in infants with a birth weight < 750 g or gestational age < 26 weeks. Routine echocardiographic screening of infants receiving indomethacin prophylaxis was not performed. Symptomatic infants with echocardiographic evidence of PDA were treated with indomethacin prior to November 2006 and with ibuprofen afterwards. Infants with increasing oxygen requirement, low blood pressure, metabolic acidosis, or evidence of renal dysfunction were considered symptomatic.

Ibuprofen was given in 3 doses of 10 mg/kg, 5 mg/kg, and 5 mg/kg at 24 hour intervals. Indomethacin was given in 3 doses at 12 hour intervals and the dose varied by age (< 48 hours of life, 0.2 mg/kg, 0.1 mg/kg, and 0.1 mg/kg; 2–7 days of life 0.2 mg/kg; and > 7 days of life, 0.2 mg/kg, 0.25 mg/kg, and 0.25 mg/kg). Contraindications to either agent included serum creatinine > 1.7 mg/dL or platelet count <70,000/mm^3. Unless limited by poor renal function, 2 courses (6 total doses) of either agent were used before surgical ligation was considered. Furthermore, enteral feeding was held during the treatment period for all infants included in the study.

RESULTS

Demographic data

We identified 65 infants who received indomethacin and 57 infants who received ibuprofen. The mean birth weight was 950 g (5%tile 95%tile; 500, 2030) in the indomethacin group and 910 g (489, 1640) in the ibuprofen group (Table 1), (P=0.58). The mean gestational age was 26 weeks for both groups (P=0.72). Indomethacin for IVH prophylaxis was administered to 32% (21/65) of the infants in the indomethacin group and 42% (24/57) of infants in the ibuprofen group (P = 0.35).

The mean age at which indomethacin treatment was initiated was 3.7 days of life vs. 6.0 for infants that received ibuprofen (P = 0.03). Two infants in the ibuprofen group were treated after the first month of life (day of life 37 and 41). When the two outliers in the ibuprofen group are excluded, the mean age at treatment initiation was 3.7 days for the indomethacin group vs. 4.9 days for the ibuprofen group (P = 0.10). There was no systematic practice difference in our approach to treatment of PDAs during the study period that would explain the difference in age at treatment initiation.

Similar proportions of infants in indomethacin and ibuprofen groups were treated with hydrocortisone (59% and 60% respectively, P= 0.99). 17% (11/65) of the infants in the indomethacin group and 28% (16/57) of the infants in ibuprofen group received hydrocortisone within 3 days of treatment initiation (P=0.19)

Effectiveness

Survival with successful pharmacological closure of the PDA occurred in 62% (40/65) of the infants in the indomethacin group and 58% (33/57) of the infants in the ibuprofen group (P=0.71). Among infants that received indomethacin prophylaxis for IVH, the rate of survival without PDA ligation was 33% (7/21) in the indomethacin group and 29% (7/24) in the ibuprofen group (P=0.99). Among infants not exposed to indomethacin prophylaxis, the rate of survival without PDA ligation was 75% (33/44) in the indomethacin group and 79% (26/33) in the ibuprofen group (P=0.79). Twenty-nine percent (19/65) of the infants in the indomethacin group and 28% (16/57) of the infants in the ibuprofen group underwent surgical PDA ligation (P=0.99). Twenty-six percent (17/65) of the infants that received treatment with indomethacin received a second course and 37% (21/57) of those treated with ibuprofen received a second course (P = 0.24).

Safety

The rate of a composite of complications (death, medical NEC, surgical NEC, or SIP) was 40% (26/65) in the indomethacin group and 32% (18/57) in the ibuprofen group (P=0.35). In addition, 17% (11/65) of the infants in the indomethacin and 11% (6/57) of the infants in the ibuprofen group were diagnosed with Grade III or Grade IV IVH (P = 0.43). The mortality rate was 9% (6/65) in the indomethacin group and 18% (10/57) in the ibuprofen group (P=0.19). After adjusting for birth weight, we did not note any significant differences in outcomes between the two groups (Table 2). Among infants that received indomethacin prophylaxis for IVH, the rate of complications (death, NEC, or SIP) was 62% (13/21) in the indomethacin group and 46% (11/24) in the ibuprofen group (P=0.37). Among infants not exposed to indomethacin prophylaxis, the rate of complications was 30% (13/44) in the indomethacin group and 21% (7/33) in the ibuprofen group (P=0.44).

Serum creatinine increased 0.20 mg/dL during treatment in the indomethacin group and 0.23 mg/dL in the ibuprofen group (P= 0.62). The mean serum creatinine before starting treatment was 1.09 mg/dL for both groups (P = 0.86). The mean serum creatinine at the end of the treatment was 1.29 mg/dL for the indomethacin group and 1.32mg/dL for the ibuprofen group (P = 0.74). There was no significant difference in the change in mean creatinine between the group that received indomethacin prophylaxis and the group that did not received indomethacin prophylaxis (indomethacin group: 0.21mg/dL and 0.19mg/dL, respectively; ibuprofen group: 0.13mg/dL and 0.30mg/dL, respectively, P= 0.27).

DISCUSSION

Our findings suggest that in this cohort that included a significant number of extremely low gestational age infants, there was no difference in effectiveness between ibuprofen and

indomethacin for PDA closure. In addition, there was no statistically significant difference in the rates of major complications between ibuprofen and indomethacin.

A recent Cochrane review involving 740 infants, from 15 randomized controlled trials, reported that there was no significant difference in failure rates of PDA closure between infants treated with indomethacin and ibuprofen [RR 0.99 (95% CI 0.78, 1.27); RD 0.00 (95% CI −0.06, 0.06)] [12]. Similarly, no difference was noted in outcomes such as Grade 3/Grade 4 IVH [4 studies, 312 infants, RR 1.19 (0.62,2.29), RD 0.02 (−0.05, 0.08)], NEC [10 studies, 586 infants, RR 0.63 (0.38,1.03), RD -0.04 (−0.08, 0.00)], and intestinal perforation [3 studies, 95 infants, RR 0.19 (0.02, 1.51), RD -0.10 (−0.20,0.01)] 12.

The rates of PDA closure following one course (3 doses) of treatment with indomethacin or ibuprofen observed in our study were lower than those reported in randomized controlled trials of similar size. Van Overmeire *et al* studied 148 infants and found ibuprofen to be as effective as indomethacin for treatment of PDA, with ductal closure rates of 66% in the indomethacin group and 70% in the ibuprofen group (P=0.41)9. Similar rates were reported in a prospective trial of 175 infants (69% closure in the indomethacin group and 73% in the ibuprofen group) 5. The lower rates of closure in our study (51% in the indomethacin group and 48% in the ibuprofen group, P =0.74) may be reflective of the lower birth weight and gestational age of the infants in our cohort. The mean gestational age and birth weight in our study is 26 weeks (both groups) and 950 g and 910 g (indomethacin and ibuprofen groups respectively), while it was 28–29 weeks and 1230 g–1260 g for infants in the previous two studies12. Overall medical closure rates in our cohort were higher for infants treated within the first four days of life compared to those treated later, 68% (50/74) vs. 49% (22/45), P=0.05. While infants of lower gestational age (≤26 weeks) have been found to be at increased risk for pharmacological treatment failure in previous studies9, a more recent trial, conducted in Taiwan, observed closure rates of 76% in indomethacin group and 75% in the ibuprofen group. Their cohort included 119 infants with a median gestational age of 25 weeks (both groups) and median birth weight of 762 g (indomethacin group) and 825 g (ibuprofen group) 8. Infants in this study were enrolled if they had a PDA by screening echocardiogram at <24 hours of life.

Variations in multiple other practice parameters and treatment strategies, including use of indomethacin prophylaxis for IVH, may be responsible for the differences in closure rates among trials and among centers. Among the infants treated within the first four days of life, there was no difference in the closure rates between infants treated with indomethacin and ibuprofen, 70% (32/46) vs. 64% (18/28), P=0.80. After the first 4 days of life, the closure rates were 38% (6/16) vs. 55% (16/29) for the indomethacin and ibuprofen groups, respectively (P=0.35).

Although we found no significant differences between the two groups in the rate of complications, the mortality rate in the ibuprofen group was twice that of indomethacin group (17.5% vs. 9.2%, P = 0.19). This trend in mortality has not been well described in the randomized trials published thus far. In the 2008 Cochrane review, out of 6 trials that reported rates of “all cause mortality,” only one had a slightly higher incidence of mortality in the ibuprofen group, without statistical significance [11.7% (11/94) in the ibuprofen group and 8.6% (7/81) in the indomethacin group] [12]. It is noteworthy that the incidence of complications such as medical NEC and grade III or grade IV IVH in our study were lower in the ibuprofen group (medical NEC, 19% in indomethacin group and 11% in ibuprofen group, P = 0.31; IVH, 17% and 11%, P = 0.43). We suspect that this difference in complication rates is secondary to the higher mortality rate observed in the ibuprofen group. The overall complication rate, including death, NEC, and SIP, was not significantly different between the groups (40% vs. 32%, P = 0.35).

Treatment with hydrocortisone, especially in conjunction with indomethacin, has been associated with SIP[13]. We found that concurrent use of indomethacin/ibuprofen and hydrocortisone more than doubled the combined incidence of NEC and SIP (8% vs. 21%, P = 0.13) within 10 days of treatment initiation but not the overall incidence of these complications (28% vs. 29%, P = 0.99). Since similar proportion of infants in each group (59% vs. 60%, P = 0.99) were treated with hydrocortisone, it is unlikely that hydrocortisone exposure contributed to the noted differences in outcomes between the two groups.

The similar change in the serum creatinine observed in this study during ibuprofen and indomethacin administration has not been noted in the majority of randomized controlled trials. In a Cochrane review, 4 out of the 6 studies reported serum creatinine level as an outcome and all of them noted statistically significantly lower serum creatinine levels 72 hours after initiation of treatment in the ibuprofen group compared with the indomethacin group12. However, the most recent randomized clinical trial comparing these agents, with treatment initiation in the first 24 hours of life, also noted lack of significant difference between the post-treatment serum creatinine between the treatment groups8. The timing of serum creatinine measures varies among trials. Pezzati et al measured creatinine on day 3 of treatment, Plavka et al measured creatinine trend over the first 96 hours of treatment, and Van Overmeire et al measured the trend over the first week after treatment initiation[12]. We measured the creatinine levels before and after the treatment course (48 hours after initiation of treatment for the indomethacin group and 72 hours after initiation of treatment for the ibuprofen group).

Our study is limited by its sample size and retrospective design. However, based on our sample size, we would have over 80% power to detect an absolute difference of 27% between the effectiveness of two agents.

This study is one of the first to report on effectiveness of ibuprofen in extremely preterm infants.. While there are numerous randomized controlled trials comparing indomethacin and ibuprofen, the generalizability (external validity) of these study results are limited. In the two largest European trials, the mean birth weight was over 1200 g, and the randomized treatment was limited to between days 2 and 49, 11. In the pivotal US trial by Aranda et al., the PDA had to be non-symptomatic and study treatment (or placebo) had to be initiated in the first 2–4 postnatal days2. The least mature infants, those whose first treatment with non-steroidals for a PDA occurred after the first four days, and those who are treated with indomethacin prophylaxis are not well represented in these studies.

Although the patients in our study were not randomized, the characteristics of the infants in the two groups are similar. One baseline characteristic that was statistically significantly different between the two groups is age at initiation of the treatment. No changes in management policy of premature infants or the practice parameters for treating PDAs occurred during the study period that can explain this difference.

A notable difference between the two drugs is the dosing schedule. Indomethacin is typically given in 3 doses, 12 hours apart while ibuprofen is typically given in 3 doses, 24 hours apart. Since the two agents seem to be similar in effectiveness, many clinicians choose one agent over the other based on the presumed renal protection provided by ibuprofen[14]. However, in clinical practice this may not be a significant advantage. Long-term surveillance and reporting of outcomes of more infants is needed to assess significant differences in effectiveness and safety between the two agents.

At our center, ibuprofen appears to be as effective as indomethacin for medical closure of PDA with similar complication rates. These findings are consistent with previously reported randomized controlled trials. Continued surveillance of infants in much larger national cohorts is necessary to assess differences in effectiveness and safety. The decision to use one agent

over the other should be based on dose schedule preference and the currently published clinical trials until more safety and effectiveness data are available from larger populations.

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Abbreviations

PDA	patent ductus arteriosus
DUMC	duke university medical center
NEC	nectrotizing enterocolitis
SIP	spontaneous intestinal perforation
IVH	intraventricular hemorrhage

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Table 1

Baseline Characteristics of the infants

Characteristic	Indomethacin(n = 65)	Ibuprofen (n = 57)	P-value
Birth weight (g) – mean (5^{th}, 95^{th} %tile)	950 (500, 2030)	910 (489, 1640)	0.58
Gestational age (weeks) – mean (5^{th}, 95^{th} %tile)	26 (23, 34)	26 (23, 30)	0.72
Age at treatment initiation (days) – mean (5^{th}%, 95^{th}%tile)	3.7 (1, 11)	6.0 (1, 13)	0.03
Indomethacin prophylaxis	32%	42%	0.35
Hydrocortisone	59%	60%	0.99
Hydrocortisone within 3 days of treatment initiation	17%	28%	0.19
Maternal chorioamnionitis*	12%	12%	0.99
Antenatal steroids†	71%	58%	0.18

*Maternal chorioamnionitis diagnosed by clinical presentation or placental pathology

†Exposure to atleast one dose of antenatal steroids

Table 2

Complications

Outcome	Indomethacin (65)	Ibuprofen (57)	P- value	OR*
PDA ligation	29%	28%	0.99	0.92 [0.41, 2.06]
Received 2nd course of treatment	26%	37%	0.24	1.68 [0.77, 3.64]
Medical NEC	19%	11%	0.31	0.50 [0.17, 1.45]
Surgical NEC	9%	14%	0.57	1.58 [0.51, 4.93]
Spontaneous Intestinal Perforation	8%	5%	0.72	0.63 [0.14, 2.85]
Grade III/Grade IV IVH	17%	11%	0.43	0.55 [0.19, 1.63]
Mortality	9%	18%	0.19	2.21 [0.66, 7.39]
Death, NEC, or intestinal perforation	40%	32%	0.35	0.63 [0.28, 1.42]

*OR for use of ibuprofen vs. indomethacin adjusted for infant birth weight