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ORIGINAL ARTICLE

Indomethacin prophylaxis or expectant treatment of patent ductus arteriosus in extremely low birth weight infants?

L Cordero[1], CA Nankervis[1], D DeLooze[2] and PJ Giannone[1]

[1]Division of Neonatal-Perinatal Medicine, Department of Pediatrics, College of Medicine, The Ohio State University, Columbus, OH, USA and [2]Department of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland, OH, USA

Background: Indomethacin prophylaxis or expectant treatment are common strategies for the prevention or management of symptomatic patent ductus arteriosus (sPDA).

Objective: To compare the clinical responses of extremely low birth weight (ELBW) infants to indomethacin prophylaxis with hat of other infants who were managed expectantly by being treated with indomethacin or surgically only after an sPDA was detected.

Methods: Retrospective cohort investigation of 167 ELBW infants who received indomethacin prophylaxis (study) and 167 ELBW infants (control) treated expectantly who were matched by year of birth (1999 to 2006), birth weight, gestational age (GA) and gender.

Results: Mothers of the two groups of infants were comparable demographically and on the history of preterm labor, pre-eclampsia, antepartum steroids and cesarean delivery. Study and control infants were similar in birth weight, GA, low 5 min Apgar scores, surfactant administration, the need for arterial blood pressure control, bronchopulmonary dysplasia and neonatal mortality. Necrotizing enterocolitis, spontaneous intestinal perforations, intraventricular hemorrhage grade III to IV, periventricular leukomalacia and stage 3 to 5 retinopathy of prematurity occurred also with similar frequency in both groups of infants. In the indomethacin prophylaxis group, 29% of the infants developed sPDA, and of them 38% responded to indomethacin treatment. In the expectantly treated group, 37% developed sPDA, and of them 59% responded to indomethacin treatment. Overall, surgical ligation rate for sPDA was similar between both groups of patients.

Conclusion: In our experience, indomethacin prophylaxis does not show any advantages over expectant early treatment on the management of sPDA in ELBW infants. Although no deleterious effects were observed, prophylaxis exposed a significant number of infants who may have never developed sPDA, to potential indomethacin-related complications.

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Correspondence: Dr L Cordero, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, The Ohio State University Medical Center, N118 Doan Hall, 410 W, 10th Avenue, Columbus, OH 43210-1228, USA.
E-mail: Leandro.cordero@osumc.edu
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Introduction

The incidence of a symptomatic patent ductus arteriosus (sPDA) among extremely low birth weight (ELBW) infants is reported to be 55 to 70%.[1] A hemodynamically significant sPDA is associated with serious co-morbidities such as congestive heart failure, pulmonary hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia and retinopathy of prematurity.[1,2]

Although spontaneous closure of the ductus arteriosus can occur, the majority of ELBW infants with sPDA require pharmacological treatment or surgical ligation.[3–4] The responsiveness of the ductus arteriosus to pharmacological agents such as indomethacin, provides clinicians with the opportunity for postnatal treatment (early symptomatic) or for prevention.[1–2,4–5] The potential disadvantage of expectant management is that by the time a sPDA is recognized, it may be too late to prevent some of the co-morbidities described above. On the other hand, early indomethacin prophylaxis may expose a significant number of ELBW infants who may never have an sPDA to a medication known to have significant side effects.[1–2,4,6–9]

A multicenter double-blind randomized study involving ELBW infants showed that indomethacin prophylaxis decreased the severity of IVH but did not improve the neurodevelopmental outcomes at 2-year follow-up.[5] Germaine to our study, secondary outcomes showed a lower incidence of sPDA and of the need for surgical ligation among infants who received indomethacin prophylaxis as compared to infants who received placebo.[5] It has been estimated that 20 infants would need to be treated with prophylactic indomethacin to prevent one surgical ligation.[2] It is also known that the incidence of sPDA varies widely between different institutions.[1–3] In light of the above, some investigators

have questioned the use of early indomethacin prophylaxis in patient populations in which the incidence of severe intracranial hemorrhage, pulmonary hemorrhage, sPDA and the need for surgical ligation after indomethacin treatment are low.[1,4]

The purpose of the present investigation is to compare the effects of indomethacin prophylaxis with those of expectant management on the prevalence and treatment of sPDA and its associated co-morbidities.

Methods

We retrospectively reviewed the medical records of all infants with gestational age (GA) of $\leqslant$28 6/7 weeks and birth weights $\leqslant$1000 g born at The Ohio State University Medical Center between July 1999 and June 2006. This investigation was approved by the Institutional Review Board. One hundred and sixty-seven ELBW infants who received indomethacin prophylaxis and 167 other infants who received expectant management for PDA were matched by gender, GA, birth weight and by year of birth. Infants who died within the first 48 h from birth and those with major congenital malformations were excluded from this study.

In our institution, the academic neonatologists who practiced as a group, began prescribing indomethacin prophylaxis in late 2000. The preference for this type of management involved 10% of all ELBW infants in 2001, 40% in 2002 and 90% in 2005. Thus, the same group of neonatologists with similar management styles provided care for infants in either the expectantly managed or the prophylaxis group. Indomethacin (Indocin IV Merck, WestPoint, PA, USA) prophylaxis was initiated within 15 h from birth at a dose of 0.1 mg/kg i.v. (intravenously) over 40 min to be repeated at 24 and 48 h of life.

Expectant management consisted of close scrutiny of clinical signs of sPDA during the first week of life. A ductus arteriosus was considered symptomatic if clinical signs (murmur, wide arterial pulse pressure, hemodynamic or respiratory compromise attributable to PDA) were corroborated with echocardiographic evidence. Indomethacin treatment was started at a dose of 0.2 mg/kg i.v. over 40 min to be repeated at 12 and 24 h. The failure to prevent by prophylaxis or to successfully treat sPDA with indomethacin, prompted a second indomethacin course or surgical ligation.

Relative contraindications to postnatal indomethacin use included active bleeding, low platelet count ($\leqslant$60 000/mm^3), oliguria ($\leqslant$0.5 ml/kg/h), elevated serum creatinine ($\geqslant$1.5 mg/dl) and active or suspected necrotizing enterocolitis (NEC).

In our institution, indomethacin is used in expectant mothers of no more than 32 weeks of gestation as a tocolytic agent only after magnesium sulfate and/or terbutaline fail to stop premature labor. Our standard protocol consists of a 50 mg oral dose followed by 25 mg every 6 h for 48 h (cumulative dose of 225 mg).[10]

GA was determined by first trimester ultrasound, by obstetrical dating of the pregnancy and/or by examination of the infant after birth. Upon admission to the NICU, all ELBW infants were treated empirically with ampicillin (100 mg/kg/day i.v. divided into two doses every 12 h) and gentamicin (5 mg/kg/day i.v. given every 48 h), and were discontinued after 2 days if blood cultures were negative. Mechanical ventilation was performed with a neonatal pressure-limited time-cycled ventilator and, when indicated, with high-frequency ventilation. Umbilical arterial catheterization was performed for blood pressure and blood gas monitoring, and umbilical or central venous catheters were used for long-term parenteral nutrition. Exogenous surfactant (Survanta Ross Products Division, Abbott Laboratories, Columbus, OH, USA) was given at the manufacturer's recommended dosage (4 ml/kg).

Renal function was evaluated by urinary output and by serum creatinine levels. Intraventricular hemorrhage (IVH) was documented by head ultrasound and was graded accordingly.[11] NEC was diagnosed by clinical signs confirmed by the radiographic presence of pneumatosis intestinalis or portal air. Retinopathy of prematurity (ROP) was staged according to international classifications and was diagnosed by a pediatric ophthalmologist who participated in the NIH CRYO, STOP and ET-ROP investigations. Considering the severity of these morbidities, ROP stages 3, 4 and 5 were grouped and analyzed together.

Statistical analysis

The indomethacin prophylaxis and the expectantly treated group were compared for obstetrical information, neonatal characteristics and outcomes. Student's *t*-test was used for continuous variables and χ^2 tests (with Yate's correction) or Fisher's exact tests were used for categorical variables. Multivariate analyses were conducted to further determine the effect of prophylaxis on outcomes. Logistic regression analyses were conducted for each of the outcomes. Seventeen potential demographic and clinical confounding variables were considered. Any of the 17 with a univariate association ($P<0.15$) was entered as a block into the logistic regression equation. Then the treatment variable was entered to determine if the effect was significant after controlling for the potential confounding variables. A $P<0.05$ was considered statistically significant.

Results

Our study population consisted of 167 ELBW infants who received indomethacin prophylaxis and 167 ELBW infants who were treated expectantly. Mothers in these two groups of infants were comparable in demographics, clinical characteristics and ethnic distribution (70% Caucasian, 23% African American, 3% Hispanic and 4% others). Antepartum complications of pregnancies for the two groups of mothers are shown in Table 1. Preterm labor with

Table 1 Obstetrical information

	Prophylaxis	*Expectant*	P
ELBW infants no.	167	167	
Preterm labor no. (%)	101 (60%)	102 (61%)	NS
Antepartum indomethacin tocolysis no. (%)	41 (25)	25 (15)	NS
Premature rupture of membranes no. (%)	56 (34)	49 (29)	NS
Chorioamnionitis no. (%)	25 (15)	32 (19)	NS
Fetal distress no. (%)	17 (10)	15 (9)	NS
Abruptio placenta no. (%)	19 (11)	26 (15)	NS
Preeclampsia no. (%)	48 (29)	44 (26)	NS
Antenatal steroids no. (%)	137 (82)	133 (80)	NS
Cesarean delivery no. (%)	111 (66)	119 (71)	NS

Abbreviation: ELBW, extremely low birth weight.

Table 2 Neonatal outcomes

	Prophylaxis	*Expectant*	P
ELBW infants no.	167	167	
Gestational age (weeks)	26±1	26±1	NS
Birth weight (g)	704±155	713±137	NS
Small for gestational age no. (%)	20 (12)	24 (14)	NS
Males no. (%)	78 (47)	78 (47)	NS
Apgar score $\leqslant$3 at 5 min. no. (%)	29 (17)	33 (20)	NS
Intratracheal epinephrine no. (%)	22 (13)	27 (16)	NS
Exogenous surfactant no. (%)	155 (93)	150 (90)	NS
Dopamine for BP treatment no. (%)	44 (26)	38 (23)	NS
On oxygen at 36 weeks PCA no. (%)	91 (54)	89 (53)	NS
Late onset sepsis no. (%)	63 (38)	60 (36)	NS
Neonatal deaths no. (%)	41 (25)	44 (26)	NS

Abbreviations: BP, blood pressure; ELBW, extremely low birth weight; PCA, post-conceptual age.

and without rupture of membranes was the predominant antepartum risk and pre-eclampsia was the most common reason for elective deliveries. Antepartum steroid treatment and cesarean delivery occurred with similar frequency in both groups.

Indomethacin tocolysis was given to 66 of the mothers in the study and control infants combined. Median duration of tocolysis was 2 days (range 1 to 5 days), whereas the median time from the last dose to delivery was 1 day (range 1 to 16 days). Median total indomethacin cumulative dose was 250 mg (range 75 to 600 mg). Analysis of the time from completion of indomethacin tocolysis to delivery showed that 10% of the patients delivered within 1 day, 90% delivered after 48 h and 50% delivered after 5 days.

Univariate comparisons of the data from the study and control ELBW infants shown in Tables 1–3 confirmed that none of the differences achieved statistical significance.

Table 3 Specific neonatal outcomes

	Prophylaxis	*Expectant*	P
ELBW infants no. (%)	167	167	
Necrotizing enterocolitis no.	12 (7)	14 (8)	NS
Spontaneous intestinal perforations no.	3 (2)	1 (0.6)	NS
Ultrasound examination no. infants (%)	167	164	
Normal no.	90 (54)	91 (55)	NS
IVH grade I–II no.	46 (28)	44 (27)	NS
IVH grade III–IV no.	21 (12)	19 (12)	NS
Periventricular leukomalacia no.	10 (6)	10 (6)	NS
Ophthalmological examination no. infants (%)	129	125	
Normal no.	42 (33)	53 (42)	NS
Stage 1–2 ROP no.	59 (46)	55 (44)	NS
Stage 3–5 ROP no.	28 (22)	17 (14)	NS

Abbreviations: ELBW, extremely low birth weight; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.

Neonatal outcomes

Neonatal outcomes for the 167 infants in the indomethacin prophylaxis group and their 167 matched controls are presented in Table 2. Study and control groups were similar in mean birth weight and GA. It should be noted that 72% of study and 71% of control infants were born at or before 26 weeks of gestation. Other similarities between study and control infants were low 5 min Apgar scores, the need for intratracheal epinephrine during resuscitation and dopamine administration for arterial blood pressure control during the first day of life.

All ELBW infants received exogenous surfactant at a median dose of two (range 1 to 4) whereas mechanical ventilation was used in both groups with comparable frequency for a median duration of 20 days (range 1 to 300 days).

During the first day of life, serum creatinines were similar between the two groups ($\leqslant$1.0 mg/dl: in 75 and 65%, 1.1 to 1.4 mg/dl in 22 and 30% and $\geqslant$1.5 mg/dl in 3 and 5% of the study and control infants, respectively). Serial serum creatinine levels during the first 3 weeks of life were also similar between the two groups of infants.

The incidence of late-onset sepsis, the need for prolonged mechanical ventilation and the incidence of chronic lung disease was comparable in both groups of patients. Neonatal deaths occurred in 26% of study and control ELBW infants.

Specific neonatal outcomes

Necrotizing enterocolitis was diagnosed in 7% of study and in 8% of control infants. Spontaneous intestinal perforation (SIP) occurred in three patients in the indomethacin prophylaxis group and in one of the control infants (Table 3).

Severe intraventricular hemorrhage (grade III to IV) and periventricular leukomalacia occurred with similar frequency in both groups of infants. ELBW infants who develop severe intraventricular hemorrhage and periventricular leukomalacia were of younger GA and of smaller birth weights than those who did not (data not shown).

Stage 3 to 5 ROP was found among 22% of infants in the indomethacin prophylaxis group and 14% of those in the control group. ELBW infants who develop retinopathy of prematurity were younger in GA than those who had normal ophthalmologic examination (25 and 26 weeks, respectively, $P = 0.001$). However, ELBW infants who developed Stage 1 to 2 ROP had similar GA and birth weight to those who developed Stage 3 to 5.

Additional comparisons of 118 infants from the prophylaxis group and 118 from the expectantly managed group who were born at $\leqslant 26$ weeks GA did not show any differences in the specific neonatal outcomes (data not shown).

Prevalence and treatment of sPDA

The clinical diagnosis of PDA was corroborated by echocardiography before treatment was initiated in 43 of the 48 (90%) sPDA in the prophylaxis group and in 58 of 61 (95%) of those in the control group.

The incidence of sPDA among ELBW infants who received indomethacin prophylaxis was similar to that of infants managed expectantly. Logistic regression analysis, however, showed that after controlling for confounding variables, sPDA occurred more often among expectantly treated infants than among study patients (RR 1.79 CI 95% (1.09 to 2.96) $P = 0.02$).

It was also noted that indomethacin antepartum tocolysis did not influence either the prevalence of sPDA or the response of the ELBW infants to indomethacin treatment.

Owing to severe oliguria and/or high serum creatinines, nine (19%) infants from the prophylaxis and six (10%) of the control group underwent surgical ligation (Table 4). The remaining infants received postnatal treatment at 5 ± 4 and 6 ± 4 postnatal days for indomethacin prophylaxis and expectant management group, respectively. Successful response to indomethacin treatment was observed in 38% of study and 59% of control infants. Logistic regression analysis showed that with the frequencies involved, indomethacin treatment for sPDA was more likely to be successful in the expectantly managed group of infants (RR 2.87 CI 95% (1.09 to 7.56) $P = 0.03$). The overall sPDA ligation rate was 20 and 17% for infants in the indomethacin prophylaxis and in the control group, respectively.

Table 4 Treatment for symptomatic PDA

	Prophylaxis	*Expectant*	P
Number of ELBW infants	167	167	
Symptomatic PDA no. (%)	48 (29)	62 (37)	NS
Surgical ligation only no. (%)	9 (19)	6 (10)	NS
Indomethacin treatment no. (%)	39 (81)	56 (90)	NS
Age at treatment (days)	5±4	6±4	NS
Successfully treated no. (%)	15 (38)	33 (59)	NS
Unsuccessful treatment and ligation no. (%)	24 (62)	23 (41)	NS
Overall surgical ligation rate no. (%)	33 (20)	29 (17)	NS

Abbreviations: ELBW, extremely low birth weight; PDA, patent ductus arteriosus.

Discussion

One of the goals of indomethacin prophylaxis is to reduce the incidence of sPDA and other co-morbidities in ELBW infants by facilitating the early and permanent closure of a ductus arteriosus.[1–2,4–5] The prevalence of sPDA as well as its responses to indomethacin treatment are influenced by numerous factors, namely GA and birth weight.[1,3,12] Spontaneous permanent closure of the ductus arteriosus occurred in less than 40% of infants born at $\leqslant 26$ weeks and in more than 70% of those born at $\geqslant 30$ weeks of gestation.[3,12] This wide variation in sPDA prevalence raises concern that unless a specific population of infants grouped by GA and birth weight are studied, the benefits of different management strategies will remain difficult to ascertain. For example, a recent meta-analysis that showed short-term benefits of prophylactic indomethacin included infants with birth weights of up to 1750 g and gestations of up to 36 weeks.[2]

A multicenter randomized study in infants of $\leqslant 1000$ g birth weight showed that indomethacin prophylaxis reduced the incidence of sPDA from 50% (placebo) to 24%.[5] The differences in rate of sPDA observed in our indomethacin prophylaxis group (29%) and in our expectantly managed group (37%) are not unexpected considering the well-established pharmacological effects of indomethacin on the ductus arteriosus.[1,4] Regardless of its potential benefits, indomethacin prophylaxis, although of benefit for some, exposed a significant number of infants who may never develop sPDA to a medication known to have significant side effects.[1–5]

The incidence of sPDA observed here for expectantly managed infants is lower than that reported by Schmidt *et al.*[5] but it is comparable to that noted by other investigators, for infants of similar GA.[12] Even if the incidence of sPDA among expectantly managed infants is higher than that of infants in the prophylaxis group, it is clear that a significant number of infants would have avoided exposure to indomethacin. The potential disadvantage of expectant management is that by the time of clinical or echocardiographic recognition of a sPDA it may be too late to prevent some of the associated co-morbidities.[1] The similar rates of co-morbidities between study and control group noted here made that possibility unlikely.

In our study, regardless of group assignment, an sPDA represents a failure of the ductus to close or maybe the consequence of the reopening of a previously closed ductus.[1] Antenatal use of indomethacin has been reported to increase not only the incidence of sPDA, but also to decrease its response to postnatal indomethacin treatment.[13,14] A recent study of 58 ELBW infants whose mothers received indomethacin tocolysis and 58 ELBW control infants showed that neither the incidence of sPDA nor the responses to postnatal indomethacin have been affected by the antenatal pharmacological exposure.[15]

Among the multiple factors known to decrease the response of the ductus arteriosus to postnatal indomethacin, GA and postnatal age at the time of treatment are the most relevant.[1–2,12] In humans, the ductus arteriosus constricts as early as 24-week GA, but that constriction is considered to be minimal at least until 31 weeks.[1,16] Postnatal indomethacin promotes constriction, ischemia and remodeling of the ductus arteriosus.[1,14,17] It is possible that in some preterm infants, whether spontaneously or indomethacin mediated, the ductus arteriosus frequently fails to develop the level of profound ischemia needed to cause remodeling, thus allowing the vessel to remain open, or if it is already closed, to reopen.[1,17,18] Satisfactory clinical responses to postnatal indomethacin treatment for sPDA are expected to be about 50% for infants at 24 to 25 weeks of GA and 60% or higher for those ELBW infants of older GA.[3,19] In the present study, successful indomethacin treatment of sPDA was noted in 38% of indomethacin prophylaxis infants and in 59% of those managed expectantly. It is possible that indomethacin prophylaxis, although failing to prevent an sPDA, may have preselected a group of infants that having failed once are predisposed to fail a second indomethacin treatment.

The association of indomethacin exposure and gastrointestinal complications in premature infants have been of great concern for many years.[8,9,20] In our study, NEC with and without intestinal perforation occurred with a low frequency similar to that reported by Schmidt *et al*.[5] for indomethacin prophylaxis and placebo group. Spontaneous intestinal perforation, now recognized as a clinical entity distinct from NEC, is strongly associated with early postnatal indomethacin exposure.[9] The low prevalence of SIP observed here in both groups of infants is similar to that published elsewhere.[5,9]

In our cohort of ELBW infants, the incidence of severe intraventricular hemorrhage and that of periventricular leukomalacia was not different between indomethacin prophylaxis and expectantly managed infants. This observation differs from that of Schmidt *et al*.,[5] who noted a small, but a statistically significant decrease in the incidence of severe intraventricular hemorrhage in infants who received indomethacin prophylaxis as compared with placebo-treated infants. The reason for this discrepancy is still unclear.

Another area of concern is the potential association between indomethacin exposure and retinopathy of prematurity.[6,21] We have not observed any differences in the incidence of severe ROP between study and control groups and more importantly, the occurrence of severe ROP is similar to that noted in populations of infants of comparable age.[5,20–21]

The potential selection bias inherent to retrospective studies had been partially minimized in our investigation by the case–control nature of the design. The present study, however, has the advantage of describing a clinical experience with a large group of ELBW infants born at a single institution during a recent period. Except for the introduction of indomethacin prophylaxis, all other neonatal practices (i.e. antepartum steroid, exogenous surfactant, fluid and arterial blood pressure control) were already established.

In summary, we have compared two commonly used strategies for the prevention and management of sPDA in ELBW infants. In our experience, indomethacin prophylaxis does not show any advantages over expectant management with early treatment for sPDA. Furthermore, prophylaxis exposed a significant number of infants who may have never developed sPDA to indomethacin, a pharmacological agent with potentially serious side effects.

The major contribution of our study is to encourage other investigators to evaluate their clinical experience before universally adopting or excluding new management strategies.

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