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Early surgical ligation versus a conservative approach for management of patent ductus arteriosus that fail to close after indomethacin treatment

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Abstract

Objective—To examine whether a more conservative approach to PDA treatment is associated with an increase or decrease in morbidity compared with an approach of early PDA ligation.

Study design—In 1/2005 we changed our approach to infants (≤ 27 weeks gestation) that failed indomethacin treatment. We changed from an early surgical approach (where feedings were stopped and all PDAs were ligated)(Period 1:1/99-12/04, n=216) to a more conservative approach (feedings continued and PDAs were ligated only if cardiopulmonary compromise developed) (Period 2:1/05-8/09, n=180). All infants in both periods received prophylactic indomethacin.

Results—The two periods had similar rates of perinatal/neonatal risk factors and indomethacin failures (24%); ventilator management and feeding advance protocols also were similar between the two periods. The conservative approach was associated with decreased rates of ductus ligation (72% versus 100%, $p < 0.05$). Even though infants were exposed to larger PDA shunts for longer durations in the conservative treatment period, the rates of BPD, Sepsis, ROP, Neurological Injury, and Death did not change; their overall rate of NEC was significantly lower.

Conclusions—These findings support the need for new controlled, randomized trials to reexamine the benefits and risks of different approaches to PDA treatment.

Keywords

surgery; ductus ligation; indomethacin; patent ductus arteriosus

A persistent patent ductus arteriosus (PDA) can produce alterations in renal, mesenteric and cerebral perfusion as well as pulmonary edema in preterm infants. Early indomethacin treatment was studied in numerous randomized controlled trials (RCTs) and decreased symptomatic PDA and to decrease the incidence of early severe pulmonary and intracranial hemorrhages (1-7). However, there is little information to guide neonatologists in what to do when the PDA fails to close after indomethacin treatment.

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Only two small RCTs, performed almost 30 years ago, were designed to examine the effects of a *persistent* symptomatic PDA on neonatal pulmonary morbidity (8,9). Both studies found that surgical closure of the PDA decreased the need for prolonged ventilatory support: significant pulmonary morbidity occurred in the group that did not have their PDA ligated when signs of congestive failure developed (8,9). Whether these findings are still applicable in the setting of modern neonatal treatment (including antenatal glucocorticoids, surfactant replacement therapies, etc) has become a matter of controversy among neonatologists (10). The relationship between a persistent PDA and necrotizing enterocolitis (NEC) is even more controversial. Although population-based studies reported an association between a PDA and NEC (11-13), there are no RCTs in the medical literature that examine the advisability of continuing or stopping enteral feeding in the presence of a PDA.

Surgical ligation produces definitive ductus arteriosus closure; however, it is associated with its own set of morbidities: thoracotomy, pneumothorax, chylothorax, post-operative hypotension, vocal cord paralysis, infection, and scoliosis (14-16) (17). In addition, several studies suggest that early surgical ligation may produce detrimental effects on lung function and growth and may even contribute to the development of bronchopulmonary dysplasia (18-21). This raises the possibility that ductus ligation may create problems that counteract any of the benefits derived from ductus closure (18,19).

Because preterm infants have a high rate of spontaneous PDA closure during the first 2 years after birth, early ligation may expose infants to a surgery they might not need. Currently there are significant differences of opinion in the neonatal community about whether it is better to treat the PDA “aggressively” (and proceed directly to surgical ligation if the PDA remains open after one or more courses of indomethacin treatment) or to treat it “more conservatively” (by continuing enteral feedings and ligating the PDA only if cardiopulmonary compromise ensues) (22). We examined whether a more conservative approach to PDA treatment (in infants delivered at $\leq 27^{6/7}$ weeks gestation, whose PDA had failed to close after indomethacin treatment) was associated with an increase or decrease in morbidity compared with an approach that used early surgical ligation.

Methods

This project was approved by the Institutional Review Board of the University of California San Francisco. Between January 1999 and July 2009, all infants $\leq 27^{6/7}$ weeks gestation, admitted to the William H. Tooley Nursery at University of California San Francisco, were treated with a course of prophylactic indomethacin starting within 15 hr of birth provided there were no contraindications. A full description of this approach has been published elsewhere (19). An echocardiogram was performed 24-36 hours after the last dose to determine the ductus' response to prophylactic indomethacin.

Following the prophylactic treatment, infants were examined daily for the appearance of clinical symptoms indicative of a PDA (systolic murmur, widened pulse pressure, hyperdynamic precordium). If any of these occurred, an echocardiogram was performed within 24 hours. If there was left-to-right flow through the PDA, the infant was considered to have a *symptomatic PDA*. When infants developed a symptomatic PDA they could be treated with a second course of indomethacin. The decision to use a second course of indomethacin was based mainly on the ductus' response to the initial prophylactic indomethacin course (23), not on the infant's medical condition. Infants whose ductus initially closed after prophylactic indomethacin were more likely to be treated with a second course of indomethacin, if symptoms developed because the likelihood of permanent closure was thought to be much greater than if the ductus had not completely closed after the initial treatment (23).

During the study period, two different approaches were used to treat a symptomatic PDA that failed to close after one or two courses of indomethacin. During Period 1 (January 1999 through December 2004), an early surgical approach was used to treat a PDA that failed to close after indomethacin: enteral feedings were stopped and all PDAs were surgically ligated, as soon as possible. The decision to ligate was not dependent on the need for respiratory support or the degree of left-to-right shunt. Even infants who required only nasal cannula oxygen underwent ligation if the ductus was patent on the echocardiogram. The rationale behind this early surgical approach was based on a review of prior RCTs that examined the morbidities of *prolonged* exposure to a symptomatic PDA (8,9).

In January 2005 we changed our treatment approach. During Period 2 (January 2005 through July 2009), a more conservative approach was used to treat a symptomatic PDA that failed to close after indomethacin treatment. Enteral feedings were continued (in spite of the presence of a persistent PDA) and PDAs were ligated *only if* symptoms of cardiopulmonary compromise developed. Cardiopulmonary compromise, related to the PDA, was defined as the presence of one or more of the following symptoms: a) increasing ventilatory needs over several days, b) persistent hypotension requiring inotropic support, c) persistent oliguria/renal failure, or d) feeding intolerance/failure to gain weight. These symptoms were attributed to the PDA only when no other explanation could be found to explain the infant's deteriorating condition. There were no changes in our protocols for prophylactic indomethacin, feeding advances or ventilator management between the two Periods.

Risk Factors and Outcome Variables

A single neonatologist (RIC) prospectively evaluated and recorded all of the perinatal/neonatal risk factors and outcome measures during the hospitalization (Table I). Gestational age was determined by the date of last menstrual period and early ultrasounds (before 24 weeks gestation). If there were discrepancies, the early ultrasound dating was used. Necrotizing enterocolitis (NEC) was defined as Bell's classification II or greater (this included NEC that was treated medically or surgically, and "spontaneous perforations" that occur before 7 days) (24). Bronchopulmonary dysplasia (BPD) was defined as a supplemental oxygen requirement at 36 weeks' gestational age to maintain oxygen saturation >90%. Retinopathy of prematurity (ROP) was defined as stage 2 (with plus disease) or $\geq$ stage 3 (25). Intracranial hemorrhage (ICH) was classified using the four-level grading system (26). Periventricular leukomalacia (PVL) was defined as echodensities on ultrasound that progressed to cystic degeneration. All infants were examined with serial bedside cranial ultrasounds initiated within the first week of life. These were repeated weekly or biweekly for the first 4 weeks. After 1 month, imaging was repeated prior to discharge or, more frequently, if there were any abnormal findings.

The echocardiographic studies included two dimensional imaging, M-mode, color flow mapping and Doppler interrogation (27). A single cardiologist (AMG), blinded to clinical data, interpreted all echocardiograms. The ductus arteriosus was scored as either closed or open; if open, the left-to-right shunt was scored as small, moderate or large. The magnitude of the left to right shunt was based on the presence of a combination of echocardiographic measures previously described as reflective of the degree of PDA shunt (28-31): ductus diameter ≥ 1.5 mm, left atrium-to-aortic root (LA/Ao) ratio ≥ 1.6 , and presence of holodiastolic reversal of flow in the descending aorta (at the level of the diaphragm) (Table II; available at www.jpeds.com).

Statistical Models

Qualitative factors were compared with a chi-square test. The Student *t* test, or Mann-Whitney test, was used to compare means and median values. We used an adjusted logistic

regression model to determine if the change in PDA treatment approach (among infants that failed to close their PDA after one or two courses of indomethacin) had an effect on neonatal morbidity. Odds ratios and 95% CIs were calculated to estimate the differences in prognostic risk between infants treated with the two approaches. For each morbidity studied, we used a multivariate model that included the following variables: 1) *Treatment approach* (early surgery or conservative), plus 2) *gestation*, plus 3) *Period of admission* (Period 1 or 2), plus 4) each of the following perinatal/neonatal risk factors: antenatal betamethasone, preeclampsia, chorioamnionitis, male sex, and Respiratory Severity Score (Mean Airway Pressure $\times$ FiO₂ at 24 hours after birth). A P-value <0.05 was considered to be significant.

Results

Infants were excluded from the analysis if they died (≤ 4 d) before the first echocardiographic evaluation (Figure). There were no differences between Period 1 and Period 2 in the percent of infants that were excluded from the study (11% due to early death), that failed to permanently close their ductus after prophylactic indomethacin, that were retreated with indomethacin, that failed indomethacin re-treatment, or that were considered to have failed indomethacin treatment (24%) (Figure). Nor were there differences between the two Periods in the incidence of perinatal or neonatal risk factors (except chorioamnionitis), or in the incidence of neonatal morbidities (Table I). The same findings were observed when we examined the subpopulation of infants that permanently closed their ductus after indomethacin treatment (Table I).

Infants that failed indomethacin treatment

Among infants that failed indomethacin treatment, there were no differences between those that were treated with early surgery (Period 1) and those treated with a more conservative approach (Period 2) in the incidence of perinatal and neonatal risk factors (except male sex) (Table III).

During Period 2 (when a more conservative approach was used), the PDAs that failed indomethacin treatment did so at an earlier age than they did during Period 1 (Table III). This was due to differences in the initial patterns of response to indomethacin prophylaxis. During Period 1, 46% of the infants that ultimately failed indomethacin treatment failed to close their PDA with the initial indomethacin prophylaxis (the other 54% initially closed their ductus with indomethacin prophylaxis but then reopened it at a later date). In contrast, during Period 2, 86% of the infants that ultimately failed indomethacin treatment failed to close their PDA with the initial indomethacin prophylaxis (14% failed after reopening a PDA that had closed with indomethacin prophylaxis).

During Period 1 (the early surgery period), 100% of the 52 infants that failed indomethacin treatment were ligated (Table III). The interval between the echocardiogram (that documented the presence of a persistent PDA) and the ligation (2.3 ± 2.3 days) varied according to the surgeon's availability and/or the need to clear an ongoing bacteremia (Table III).

During Period 2 (the conservative approach period), infants that failed indomethacin treatment underwent ligation *only if* they developed specific symptoms. 72% (31/43) of the more conservatively treated infants developed criteria for ligation and were ligated before hospital discharge (Table III). The primary reasons for ligation were increasing ventilatory needs (87%) and/or persistent hypotension requiring inotropic support (39%) that could not be explained by other causes. Ten percent of the infants undergoing ligation also had persistent oliguria/renal failure that could not be explained by other causes. None of the infants had feeding intolerance or failure to gain weight as a reason for ligation. Infants born

at 24-25 weeks gestation were more likely to develop criteria for ligation (81%) compared with those born at 26-27 weeks (56%).

During Period 2, 28% (12/43) of the conservatively treated infants never developed criteria for ligation during the neonatal period: 8/12 closed their PDA spontaneously by 6 months corrected age (4 prior to and 4 following hospital discharge); and, 4/12 PDAs were closed via transcatheter coil embolization or were still open and being followed at 12-18 months corrected age.

Although the size of the PDA shunt at the time the infants failed indomethacin treatment was similar in both groups, infants that were treated with the conservative approach were ultimately exposed to significantly larger PDA shunts for significantly longer durations (Table III).

We used multivariable models that included gestation, period of admission and one or more of the perinatal/neonatal risk factors to determine if the change from an early surgical approach to a more conservative approach was associated with an increase or decrease in neonatal morbidities (Table IV). The rates of BPD, Sepsis, ROP, Neurological Injury, Death, and Death or BPD were not significantly different between the two treatment approaches (however, with our sample size, we only had sufficient power to detect a difference of >20% between the two treatment approaches) (Table IV). In the multivariate model, the rate of NEC among conservatively treated infants was significantly less than among infants treated with early surgery. The incidence of NEC that occurred *after* infants were assigned to the different treatment approaches tended to be less among the conservatively treated infants ($p=0.053$) (Table IV).

Discussion

In this study, spanning two consecutive time periods, we found no significant differences in the rates of BPD, sepsis, ROP, neurologic injury or mortality between infants treated with early PDA surgery compared with those treated more conservatively (with surgical ligation only if the PDA became hemodynamically significant following indomethacin treatment failure). We observed a decrease in risk for NEC in the conservatively treated infants. Although a more conservative approach still resulted in eventual surgical ligation in the majority of infants, a significant number of infants did not receive surgery prior to hospital discharge, and several had spontaneous closure of their PDA despite initial indomethacin failure.

Our study was not a randomized controlled trial because we were unable to find any neonatal units where the medical and nursing staffs felt that they could successfully randomize and implement the two different surgical approaches concurrently without introducing significant bias into their treatment decisions. Therefore, we evaluated the effects of a change in practice between two consecutive time periods. Even though our study cannot provide definitive evidence for the benefits of one treatment over the other, there are several features of our study that enable us to have some confidence in the associations that we observed: (a) during the years bracketed by our study there appeared to be no significant changes in our study population in the incidence of perinatal and neonatal risk factors (except for clinical chorioamnionitis) or in the incidence of neonatal morbidities (compare Periods 1 and 2 - Table I); nor were there changes in our protocols for prophylactic indomethacin, feeding advances or ventilator management during these Periods; (b) a treatment approach was uniformly applied to all infants during a study Period (i.e., none of the infants during Period 2 were treated with an Aggressive treatment approach, and vice versa during Period 1); and (c) multivariate statistical models were used to adjust for

potential differences between the two treatment approaches that might be due to differences in the period of birth or in other perinatal or neonatal risk factors.

For our study, we chose a “conservative” treatment approach that contained an option for ligation if symptoms of cardiopulmonary compromise developed. Although some authors have argued that any benefits derived from PDA ligation are outweighed by the risks of ligation (10), we did not feel that there was enough evidence to completely abandon the use of ligation: Numerous studies have demonstrated that infants with clinical and radiographic signs of pulmonary edema have improvement in their lung compliance following surgical ligation (32-35). In addition, the only RCTs that have examined the issue of PDA ligation versus *no intervention at all* to close a persistent PDA, found that significant pulmonary morbidity occurred in the group that was not allowed to have their PDA ligated when signs of congestive failure developed (8,9).

Currently, there are no RCTs that address the pros or cons of continuing enteral feeding in the presence of a PDA. Hemodynamic studies have shown that a PDA decreases mesenteric blood flow during both fasting and fed states (36-38) and population-based, retrospective, observational studies have found an association between the presence of a PDA and NEC (11-13). Currently, 70% of neonatologists in the United States believe that enteral feedings need to be stopped in the presence of a symptomatic PDA (22,39). In our study, infants treated with the “conservative” approach received enteral feedings despite the presence of a PDA. It is interesting to note that the rate of NEC among infants treated with the “conservative” approach was decreased compared with the infants treated with early surgery. This finding appears to support the feeding approach used by neonatologists outside of the United States (70% of whom believe that enteral feedings should continue in the presence of a symptomatic PDA) (22).

Despite our desire to avoid ligation in infants treated with the “conservative” approach, 72% of the infants ultimately met ligation criteria and were ligated during the neonatal period. The likelihood that infants would meet ligation criteria during the neonatal period was inversely related to their gestational age. Infants born at 24-25 weeks gestation were much more likely to meet ligation criteria (81%) than those born at 26-27 weeks (56%). The ligation rate continued to drop among more mature infants: only 14% of infants born at 28-29 weeks gestation, who were managed with the same conservative treatment approach (after failing to close their PDA with indomethacin), ultimately met ligation criteria (data not shown).

Although most of the conservatively treated immature infants ultimately met ligation criteria, there was a significantly longer delay (13 ± 8 days) before the ligation was performed (compared with infants ligated during the early surgery period (2.4 ± 2.3 days)). The delay in ligation may be beneficial because accumulating evidence suggests that several of the morbidities associated with ligation (hypotension and need for inotropic support (17,40), vocal cord paralysis (15), and bronchopulmonary dysplasia (18,41)) are significantly reduced when ligation is delayed.

In conclusion, we examined the effects of a conservative approach to PDAs that fail to close after indomethacin treatment. We found that a conservative approach (that tolerates the presence of a PDA as long as signs of cardiopulmonary compromise do not develop) is associated with a 28% decrease in the rate of ductus ligation and lower rates of NEC. These findings support the need for new controlled, randomized trials to reexamine the benefits and risks of different approaches to PDA treatment in the modern era.

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Abbreviations

PDA	Patent ductus arteriosus
NEC	necrotizing enterocolitis
BPD	bronchopulmonary dysplasia
ICH	intracranial hemorrhage
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity
MAP	mean airway pressure
FiO ₂	fraction of inspired oxygen
OR	odds ratio
CI	95% confidence interval

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Figure.
Response of the ductus to indomethacin treatment during Periods 1 and 2.

Table 1

Demographics of Total Population and of infants that closed their PDA after indomethacin treatment

	A) Total Population		B) Infants that closed their PDA with indomethacin	
	Period 1 (n=216)	Period 2 (n=180)	Period 1 (n=164)	Period 2 (n=137)
Gestation (wk)	25.8±1.1	25.9±1.1	26.0±1	26.1±1
Birth weight (gm)	830±197	827±185	842±201	840±192
Male Gender (%)	56	50	53	54
Antenatal Betamethasone (%)	75	72	79	77
Antenatal Betamethasone >24 h (%)	64	63	70	69
Preeclampsia (%)	14	21	17	22
Chorioamnionitis (%)	17	27*	17	27*
Surfactant (%)	93	93	91	93
Respiratory Severity Score @ 24h (units) ¹	2.1±1.9	1.9±1.1	1.8±1.5	1.8±0.9
PDAs that failed indo treatment (%) ²	24	24	NA	NA
1 st enteral feed (day)	9±5	9±8	7±4	8±7
Enteral feedings=80 ml/k/d (day)	22±12	25±12	19±10	23±12
Sepsis (%) ³	41	46	39	46
Intracranial hemorrhage ≥ Grade 3	9	12	7	13
Neuro injury (%) ⁴	13	17	10	18
NEC (%)	16	17	13	18
BPD (%)	32	28	23	24
ROP ≥2+ (%)	14	18	10	14
Death (%)	12	11	10	10
Death or BPD (%)	38	34	30	31

Values are mean±SD

ICH=intracranial hemorrhage, PVL=periventricular leukomalacia, NEC=necrotizing enterocolitis, BPD=bronchopulmonary dysplasia, ROP=retinopathy of prematurity, Indo=Indomethacin, NA=not applicable

*
p<0.05

¹ Respiratory Score (MAP × FiO₂) at 24 hours after birth

² Combined clinical symptoms and echocardiography evidence of left-to-right shunt after indomethacin treatment (see Patient Flow diagram (Figure 1))

³ Sepsis: symptoms and positive blood, urine or CSF culture

⁴ Neuro injury: ICH ≥ Grade 3 or PVL or ventricular-peritoneal shunt.

Table II
Echocardiographic grading scheme for magnitude of Patent Ductus Arteriosus Shunt

PDA grade	Minimum Ductus diameter (mm)	LA or LV enlargement	LA:Ao ratio	Diastolic retrograde Doppler flow in DAo	Ductus mean Doppler gradient (mmHg)
Closed	N/A	N/A	N/A	N/A	N/A
Small	<1.5	absent	≤ 1.5	absent	>8
Moderate	>1.5 [†]	present	≥ 1.6	present	>8
Large	≥ 1.5, 2.0 *	present	≥1.6	present	< 8

DAo, descending aorta at the level of the diaphragm; LA:Ao ratio, left atrium to aorta diameter ratio by M-mode; PDA, patent ductus arteriosus

[†] A ductal diameter of <1.5 mm was accepted if all other criteria for “moderate” were met

* Ductal diameter ≥ 1.5mm plus all other, or >2.0mm plus one other criterion for “large” resulted in a categorization of “large”

Table III

Demographics of infants that failed to close their PDA after indomethacin treatment

	Early Surgical Approach (n=52)	Conservative Approach (n=43)
Gestation (wk)	25.1±1.2	25.5±1.1
Birth weight (gm)	792±184	785±158
Male Sex (%)	63	37*
Antenatal Betamethasone (%)	63	56
Antenatal Betamethasone >24 h (%)	40	42
Preeclampsia (%)	8	16
Chorioamnionitis (%)	15	26
Surfactant (%)	100	93
Respiratory Severity Score @ 24h (units)	2.9±2.6	2.2±1.7
Age when PDA failed final indo treatment (d)	13±9	7±4*
PDA shunt size when failed final indo treatment:		
(% moderate or large)	35	33
Largest PDA shunt after failing final indo treatment:		
(% moderate or large)	55	81*
(% large)	13	47*
Duration of exposure to PDA shunt (d) ¹	median=2	median=17*
Age when PDA finally closed (d) ²	median=14	median=23*
PDA's ligated prior to discharge (%)	100	72*
PDA shunt size at time of ligation:		
(% moderate or large)	50	93*
1 st enteral feed (day)	13±7	13±8
Enteral feedings=80 ml/kg/d (day)	33±15	32±13
Intracranial hemorrhage ≥3 (%)	15	9
Neuro injury (%)	20	15
NEC (%)	27	12
NEC that occurred after failing indo treatment (%)	22	10
Sepsis that occurred after failing indo treatment (%)	47	44
BPD (%)	60	40
ROP ≥2+ (%)	27	28
Death (%)	17	9
Death or BPD (%)	65	44

Values are mean±SD

see Legend to Table 1 for definitions

*
p<0.05

¹ interval between the echocardiogram (that documented the presence of a persistent PDA) and the time of final closure: values are expressed as median values since 19% of the infants in the conservative treatment approach still had a PDA at the time of discharge; the mean duration of PDA exposure for the infants in the Early Surgical treatment approach was 2.3±2.3 days.

² values are expressed as median values since 19% of the infants in the conservative treatment approach still had a PDA at the time of discharge.

Table IV

Comparison between an early surgical approach and a more conservative approach for infants that failed indomethacin treatment: effects on neonatal morbidity (adjusted for gestation, year of admission and perinatal/neonatal variables)

Morbidity	Conservative Approach versus Early Surgery Odds Ratio (CI)
NEC	0.26 (0.07 – 0.95) *
NEC that occurred after failing indo treatment	0.25 (0.06 – 1.01) #
Sepsis that occurred after failing indo treatment	0.86 (0.32 – 2.31)
Intracranial hemorrhage $\geq$ Grade 3	0.33 (0.07 – 1.48)
Neuro Insult	0.40 (0.11 – 1.48)
BPD	0.53 (0.18 – 1.50)
ROP	1.04 (0.30 – 3.72)
Death	0.55 (0.12 – 2.50)
Death or BPD	0.49 (0.18 – 1.30)

see Legend to Table I for definitions

The logistic regression neonatal morbidity models were constructed as described in *Methods (Statistical Models)*. The Odds Ratios are for the morbidity models that included Treatment approach (Early Surgery or Conservative), Gestation, Year of admission (Period 1 or 2), and sex. The Odds Ratios included each of the other perinatal or neonatal variables (*Respiratory Severity Score (MAP $\times$ FiO₂ at 24 hours after birth)*, *preeclampsia*, *chorioamnionitis*, and *antenatal betamethasone exposure*) were similar.

*
p<0.05

p=0.53