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The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial

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Abstract

Objective—To reexamine data from a randomized controlled trial of prophylactic ductus ligation to determine if ligation contributes directly to the development of BPD in ELBW infants.

Methods—We The control group was ligated only if they developed a symptomatic PDA. We hypothesized that the incidence of BPD would be higher in the prophylactic ligation group because more ligations were performed than in the control group.

Results—Prophylactic ligation significantly increased the incidence of BPD (defined as a supplemental oxygen requirement at 36 weeks postmenstrual age) and the incidence of mechanical ventilation at 36 weeks. The groups were statistically similar in gestation, sex, race, fluid administration, IVH, pulmonary air leaks, and survival to 36 weeks. The lower incidence of BPD in the control group occurred despite the fact that the incidence of necrotizing enterocolitis (a known risk factor for BPD) was significantly elevated in the control group. Only infants that had previously undergone a PDA ligation developed BPD in the control group.

Conclusion—Prophylactic ligation, while eliminating the PDA, increases the risk for BPD.

Keywords

patent ductus arteriosus; indomethacin; ductus ligation; bronchopulmonary dysplasia; necrotizing enterocolitis; surgery

A persistent patent ductus arteriosus (PDA) has been shown to impair pulmonary mechanics (1–5), prolong the need for mechanical ventilation (6), increase the risk of pulmonary hemorrhage (7–10), and alter alveolar surface area (11) in premature infants and in non-human primates. Pharmacologic closure of the PDA prevents the deterioration of pulmonary function and alveolar development (3,4,7–9,11).

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Although ductus ligation eliminates the PDA, it does not appear to have the same beneficial effects on lung development (9,11–14). Whereas pharmacologic closure of the PDA minimizes the arrest of alveolar development that occurs with preterm birth (11), surgical ligation has no such beneficial effect (15). There has been concern that PDA ligation may actually contribute to the pulmonary morbidity it is trying to prevent (9,13,14). Population-based, observational studies, have found that surgical ligation is an independent risk factor for the development of BPD (13,14). The non-randomized, observational design of these studies makes it difficult, however, to determine whether the increased incidence of BPD is due to the ligation, itself, or to other factors (like prolonged exposure to a PDA) that might coexist in infants that require ligation.

Only two randomized controlled trials have examined the effects of ductus ligation on the preterm newborn. In the first trial, surgical ligation of the PDA was compared with pharmacologic closure (16): infants treated with surgery required longer durations of CPAP than infants treated with indomethacin ($p=0.06$). Although the difference between the groups could have been due to a morbid effect of surgery, it could also have been due to a beneficial effect of indomethacin (11). The other randomized controlled trial compared the effects of prophylactic surgical ligation (in infants that weighed ≤ 1000 grams and that required supplemental oxygen during the first 24 hours after birth) with a control group, where surgery was performed only if a hemodynamically “important” PDA developed (12). In that trial, prophylactic ligation decreased the incidence of necrotizing enterocolitis but had no statistically apparent effect on the incidence of BPD (12).

We were particularly interested in the prophylactic ligation trial by Cassady et al (12) because it is the only randomized trial to date, where the ligated infants were not previously exposed to a symptomatic PDA and where the comparison group was not treated with a different form of therapy (indomethacin). In the trial, BPD was defined according to the criteria of Bancalari et al (12,17): “1) required intermittent positive pressure ventilation during the first week of life, 2) developed clinical signs of chronic respiratory disease ... persisting for longer than 28 days, 3) required supplemental oxygen for more than 28 days to maintain a PaO₂ over 50 mm Hg, and 4) chest radiograph showed persistent strands of densities in both lungs, alternating with areas of normal or increased lucency.” In addition, a combination of histologic findings and radiographic criteria (for stage III or IV BPD (18)) were used in infants who died (12, 17).

In recent years, the definition of BPD has been expanded to better reflect the degree of respiratory burden. A persistent supplemental oxygen requirement at 36 weeks’ postmenstrual age has been used to differentiate infants with no or mild BPD from those with moderate or severe BPD (19,20). We hypothesized that if surgical ligation really contributes to the development of BPD, then the increased frequency of surgical ligation in the prophylactic ligation group should have increased the incidence of moderate/severe BPD in that group. We also hypothesized that the definition of BPD that was used in the trial by Cassady et al (12) may have underestimated the true burden of BPD in their study population. Therefore, we re-examined the summary data sheets from the original trial by Cassady et al (12) to determine if prophylactic surgical ligation increased the incidence of moderate/severe BPD.

Methods

The review of the summary data sheets from the original study was performed after obtaining Institutional Review Board approval. A complete description of the details of the population and study design have been published previously (12). Briefly, infants that were ≤ 1000 grams and required supplemental oxygen to maintain a PaO₂ ≥ 50 torr were eligible for the study. Eligible infants were at highest risk for neonatal problems. Twenty percent of infants with birth

weights ≤ 1000 grams required no supplemental oxygen during the first 24 hours after birth and were excluded from the study (12). Eighty-four babies were randomized after parental consent was obtained. Infants in the control group ($n=44$) received standard care. Standard care included nasal CPAP as the initial treatment for hypoxemia due to respiratory distress. Endotracheal intubation and mechanical ventilation were begun only after respiratory failure ($\text{PaCO}_2 \geq 70$ torr) or refractory apnea. None of the infants received exogenous surfactant. Ligation was the only treatment given for a hemodynamically significant PDA. Indomethacin was not used in any study baby. Indications for ligation included a pulmonary-to-systemic flow ratio above 3.0 (21) or ventilator-dependence with a left-to-right PDA shunt confirmed by echocardiography and Doppler examination. Ventilator adjustments, enteral feedings, and fluid therapy were adjusted according to protocol (12).

Forty infants were randomly assigned to receive prophylactic ductus ligation within 24 hours of birth. The ligation occurred regardless of the presence or absence of signs or symptoms of a PDA. The ligation was intended to be truly prophylactic for infants in the prophylactic treatment group; this is in contrast to its therapeutic use in the control group. All other care was the same for both groups.

Several of the demographic and clinical variables (birthweight, gestation, small for gestational age, race, sex, intraventricular hemorrhage, ductus ligation, necrotizing enterocolitis, and survival) were previously reported (12). They have been included in Table I to clarify the comparisons between the two treatment groups. Necrotizing enterocolitis was defined as Bell's stage III or IV (22). Intraventricular hemorrhage was defined as grade III or IV according to the criteria of Papile et al (23). Survival was defined as survival to one year after birth. We added survival to 36 weeks postmenstrual age for the present re-analysis. The need for mechanical ventilation or supplemental oxygen at either 28 days postnatal age or at 36 weeks postmenstrual age was determined from the summary patient data sheets. Individual patient records were not available. Although the data sheets contained information about the duration of supplemental oxygen and duration of mechanical ventilation that the infants required, there was no information about the FiO_2 or the ventilator settings.

Data are presented as percentages or mean + standard deviation. Where appropriate, we used Student's t-test or Chi-square test to compare the variables and outcomes. Because we anticipated that the incidence of BPD would be higher in the prophylactic ligation group based on the prior epidemiologic, observational, and animal studies (9,11,13–15), we used a one sided alpha of 0.05. The sample size of the study ($n=84$) enabled us to detect a 25% difference in BPD rates between the groups with a power of 80%.

Results

There were no statistically significant differences between the two treatment groups in birthweight, gestation, small for gestational age, race, sex, intraventricular hemorrhage, pulmonary air leak syndromes (pulmonary interstitial emphysema and/or pneumothorax), survival to 36 weeks, or survival to 1 year (Table I). Ninety-five percent of the infants in the prophylactic ligation group were ligated (two infants in the prophylactic ligation group had active bleeding and cardiovascular instability and were not ligated before their deaths at 4 days). Despite randomization to the control group, fifty-two percent of the control infants were ligated after developing a hemodynamically significant PDA. Necrotizing enterocolitis was four-times more common in the control group than in the prophylactic surgery group, as was previously reported.

The number of infants that required supplemental oxygen at 28 days was similar in both treatment groups. On the other hand, the number of infants that still required supplemental

oxygen at 36 weeks postmenstrual age was significantly higher in the prophylactic ligation group (Table I). Similarly, the number of infants that still required mechanical ventilation at 36 weeks postmenstrual age was significantly higher in the prophylactic ligation group (Table I). The increased need for oxygen supplementation and mechanical ventilation in the prophylactic ligation group was present even when the subpopulation of infants that survived to 36 weeks was examined by itself (Table II). There were no differences between the groups in daily fluid administration or incidence of air leak syndromes (pulmonary interstitial emphysema and/or pneumothorax) (Table II).

Discussion

Surgical ligation of the ductus arteriosus has been identified as an independent risk factor for the development of BPD in earlier observational studies (13,14), even when other risk factors for BPD (like immature gestation, male sex, and necrotizing enterocolitis) have been included in the statistical model (14). Because infants in these studies were usually ligated after exposure to a PDA, and after failing indomethacin treatment, it is difficult to know if the increased incidence of BPD is due to the ligation itself, or to other factors that may coexist in infants that require ductus ligation.

We examined the data from the controlled trial by Cassady et al because the ligated infants in the study treatment group were randomized to ligation and were not exposed to indomethacin or to a persistent PDA (12). We hypothesized that infants in the prophylactic ligation group would have a higher incidence of BPD because they had more surgical ligations than infants in the control group. The original report of this trial concluded that prophylactic ductus ligation reduced the incidence of necrotizing enterocolitis, but had no effect on the incidence of BPD (12). We re-examined the original data set, using as our definition of BPD a supplemental oxygen requirement at 36 weeks postmenstrual age (which includes both moderate and severe forms of BPD) (13,14). We found that BPD was more common among infants in the prophylactic ligation group. We also found that the most severe form of BPD (infants that still required mechanical ventilation at 36 weeks postmenstrual age) was significantly higher in the prophylactic ligation group. These findings are even more striking when one considers that the incidence of necrotizing enterocolitis (a known risk factor for BPD) was significantly higher in the control group, and that more than half of the infants in the control group also underwent PDA ligation (although, at a later time than in the prophylactic ligation group (Table II). Infants who were eligible for this study were the sickest of the ELBW infants (12). Fifty percent did not survive to 36 weeks postmenstrual age. There was no difference between the groups in the rate of survival to 36 weeks, although mortality was high in both study groups. The incidence of BPD was higher in the prophylactic ligation group even when we examined the subpopulations that survived to 36 weeks postmenstrual age.

The present study may be criticized for comparing prophylactic surgery with later surgery. If so, we may be understating the potential deleterious effects of surgical ligation on the lungs. It is also possible that later surgery may not have the same deleterious effects as early surgery. It should be noted, however, that all four of the infants in the Control group that required supplemental oxygen at 36 weeks postmenstrual age had undergone ductus ligation. Therefore, although PDA ligation decreased the incidence of necrotizing enterocolitis in this trial, it also significantly increased the risk of moderate/severe BPD.

An important caveat needs to be mentioned if one tries to extrapolate our results to present day clinical care. The study patients in the original trial differed in many ways from today's neonatal population. They were not exposed to prenatal steroids and did not receive surfactant or indomethacin. A large proportion were also small-for-gestational age. In addition, changes in

perinatal management, fluid management, ventilation strategies, and advances in early nutrition, etc, may limit the applicability of our findings to the present day.

On the other hand, ductus ligation is associated with several known morbidities: thoracotomy, post-operative myocardial dysfunction (24), hypotension (25), pneumothorax (16), chylothorax, and infection. In addition, the incidence of unilateral vocal cord paralysis (which increases the requirements for tube feedings, respiratory support and hospital stay) has been recognized recently in a significant proportion of infants following PDA ligation (26). Neonatal transport to another facility may also be necessary if skilled surgeons are not readily available. Ductus ligation, while eliminating one potential cause for neonatal morbidity, may thus introduce another set of problems.

Our results should not be used as justification for abandoning surgical ligation as a treatment for PDA. Ligation can improve pulmonary function and lessen the burden of BPD when the alternative is prolonged exposure to a moderate/large PDA shunt (1,2,5,6). Our findings suggest that although prophylactic ductus ligation eliminates the PDA, it may contribute to the very problem it is trying to prevent - BPD.

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Abbreviations

PDA	Patent ductus arteriosus
BPD	bronchopulmonary dysplasia
IVH	Intraventricular hemorrhage
ELBW	extremely low birth weight
CPAP	continuous positive airway pressure
FiO₂	fraction of inspired oxygen

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Table 1
 Characteristics of Total Study Population (n=84)

	Control (n=44)	Prophylactic Ligation (n=40)
Birthweight (gm)	795±98	800±125
Gestation (wks)	27.6±1.5	27.4±1.8
Small for Gestational Age (%)	26 (59%)	19 (48%)
Non-Caucasian (%)	25 (57%)	26 (65%)
Female (%)	26 (59%)	20 (50%)
5 min Apgar <6 (%)	16/43 (36%)	9 (23%)
IVH (grade III/IV) (%)	23/41 (56%)	16/35 (46%)
Ductus Ligation (%)	23 (52%)	38 (95%)*
Interstitial Emphysema or Pneumothorax (%)	19/38 (50%)	17/33 (52%)
Necrotizing Enterocolitis (%)	13 (30%)	3 (8%)*
Oxygen requirement at 28 days (%)	16 (36%)	16 (40%)
Oxygen requirement at 36 wks postmenstrual age (%)	4 (9%)	11 (28%)*
Mechanical ventilation at 36 wks postmenstrual age (%)	0 (0%)	6 (15%)*
Survival beyond 35 wks postmenstrual age (%)	19 (43%)	23 (57%)
Survival (%) [†]	18 (41%)	15 (38%)

Values are mean±sd.

[†] survival through one year after birth.

* p<0.05.

Table 2

Characteristics of study infants that survived beyond 35 weeks postmenstrual age (n=42)

	Control (n=19)	Prophylactic Ligation (n=23)
Birthweight (gm)	854±82	827±107
Gestation (wks)	27.1±1.9	27.7±1.4
Small for Gestational Age (%)	6 (32%)	11 (48%)
Non-Caucasian (%)	11 (58%)	16 (69%)
Female (%)	12 (63%)	13 (57%)
5 min Apgar <6 (%)	7 (37%)	4 (17%)
IVH (grade III/IV) (%)	10 (53%)	7 (30%)
Ductus Ligation (%)	14 (73%)	23 (100%) [*]
Age at Ligation (days)	8.0±4.7	0.8±0.2 [*]
Interstitial Emphysema or Pneumothorax (%)	6/14 (43%)	8/19 (42%)
Necrotizing Enterocolitis (%)	7 (37%)	0 (0%) [*]
Oxygen requirement at 28 days (%)	13 (68%)	14 (61%)
Oxygen requirement at 36 wks postmenstrual age (%)	4 (21%)	11 (48%) [*]
Mechanical ventilation at 36 wks postmenstrual age (%)	0 (0%)	6 (26%) [*]
Daily Fluid Intake (ml/day)		
Day 1	119±20	126±23
Day 2	140±15	153±42
Day 3	173±40	184±63
Day 4	170±42	197±53
Day 5	185±46	203±46
Day 6	203±53	215±52
Day 7	204±49	220±41
Day 8	188±53	211±48
Day 9	191±51	209±43
Day 10	184±53	196±56

Values are mean±sd.

*
p<0.05