ORIGINAL ARTICLE

Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management

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Accepted August 2004
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Background: Surgical ligation of patent ductus arteriosus (PDA) is widely practised in preterm infants despite no clear evidence that this improves outcomes. Geographical isolation meant that ductal ligation was not an option in King Edward Memorial Hospital until recently.
Objective: A retrospective data analysis to test the hypothesis that outcomes of infants with persistent PDA were no worse than those of infants with no significant duct or a duct that closed after medical treatment.
Patients and Methods: A total of 252 infants (gestation ≤28 weeks) born between 1 January 2000 and 30 June 2002 were divided into three groups: group 1, no significant PDA (n = 154); group 2, significant PDA which closed after medical treatment (n = 65); group 3, significant PDA remaining patent after medical treatment (n = 33). A significant PDA was defined by a left atrium to aortic root ratio of >1.4 or a ductal diameter >1.5 mm with a left to right shunt.
Results: Twenty four (10%) infants died at median (interquartile range) 15.5 (9–35) days. After adjustment for gestational age, relative to group 1, the infants from group 3 were at a 4.02 times increased risk of death (95% confidence interval 1.12 to 14.51). There was no significant difference between groups in the incidence of chronic lung disease, chronic lung disease or death, necrotising enterocolitis, intraventricular haemorrhage, duration of oxygen, or hospital stay.
Conclusion: Mortality was higher in infants with a persistent PDA, but other morbidities were not significantly different. A randomised trial is needed to determine whether surgical ligation will reduce mortality in such infants.

Patent ductus arteriosus (PDA) with a significant left to right shunt is associated with chronic lung disease (CLD),[1] intraventricular haemorrhage (IVH),[2][3] and necrotising enterocolitis (NEC)[4][5] in preterm neonates. The medical management of a haemodynamically significant PDA includes fluid restriction, diuretics, and intravenous prostaglandin synthetase inhibitors, such as indometacin. Indometacin, either as treatment or prophylaxis, has been shown to reduce the incidence of symptomatic PDA, the need for duct ligation, and the incidence of severe IVH.[6][7] Surgical ligation is usually reserved for PDA refractory to medical management. Surgical ligation has been reported to have a low morbidity and has been proposed as a primary treatment of PDA and the treatment of PDA that responds poorly to indometacin.[8] A systematic review identified a single randomised controlled trial comparing surgical ligation and indometacin for closure of PDA in preterm infants with birth weight <1750 g. No significant differences in hospital stay, CLD, NEC, or IVH were noted.[9]

There are insufficient data and no clear evidence that surgical ligation of haemodynamically significant PDA is associated with improved outcomes. Historically, conservative management of PDA (waiting for spontaneous closure over several days or weeks while continuing ventilatory support) in preterm infants is reported to be associated with a high frequency of "bronchopulmonary dysplasia" in survivors.[10] Given the advances in neonatal intensive care in the surfactant era, including the increased use of antenatal steroids, this may no longer be the case. King Edward Memorial Hospital for Women is the tertiary perinatal referral centre for the state of Western Australia, which spans 2.5 million km^2 and serves a population of 1.8 million with 25 000 births per annum. Lack of on site facilities for

surgical ligation and geographical isolation from the nearest cardiac surgical centre (Melbourne, 3456 km and four hours flight time) meant that surgical ligation of PDA was not an option until recently. Our clinical experience suggested that the outcome of infants with persistent PDA was no worse than those of infants with no significant duct or a duct that closed after medical treatment. A retrospective data analysis was undertaken to test this hypothesis.

PATIENTS AND METHODS

All infants of ≤28 weeks gestation born between 1 January 2000 and 30 June 2002 were included in the study. Outborn infants and those with congenital heart disease were excluded. Infants who died within the first 72 hours of life were also excluded, as even if there was a significant PDA, it was too short a time for closure to be achieved by prophylactic indometacin or surgery. After collecting basic and clinical data, infants were divided into three groups for further analysis: group 1, no PDA or no significant PDA; group 2, significant PDA, which closed after medical treatment; group 3, significant PDA, which remained patent after medical treatment.

Echocardiograms were obtained by either a consultant paediatric cardiologist or an echocardiography technician with subsequent report from a consultant paediatric cardiologist. Significant PDA was defined as echocardiogram findings of a left atrium to aortic root ratio of >1.4[7] or a ductal diameter >1.5 mm,[11][12] associated with a left to right shunt into the main pulmonary artery from the PDA with low

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Abbreviations: CLD, chronic lung disease; CRIB, clinical risk index for babies; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus

Table 1 Basic characteristics of all infants of ⩽28 weeks gestation born between 1 January 2000 and 30 June 2002

	All infants (n = 252)	Group 1 (n = 154)	Group 2 (n = 65)	Group 3 (n = 33)	p Value
Gestation*	26 (22–28)	27 (23–28)	25 (22–27)	24 (22–28)	<0.001
Birth weight (g)*	893 (410–1475)	998 (470–1475)	775 (410–1330)	695 (410–1260)	<0.001
SGA	23 (9%)	12 (8%)	7 (11%)	4 (12%)	0.638
Male sex	127 (50%)	79 (51%)	25 (39%)	23 (70%)	0.013
Multiple birth	69 (27%)	36 (23%)	20 (31%)	13 (39%)	<0.001
Antenatal steroids					
⩾one dose	216 (87%)	135 (88%)	52 (80%)	29 (88%)	0.311
Complete†	101 (47%)	69 (51%)	23 (44%)	9 (31%)	0.133
Any ventilation	215 (85%)	118 (77%)	65 (100%)	32 (97%)	<0.001
CRIB score*	4 (1–8)	2 (1–5)	6 (3–9)	9 (5–10)	<0.001

*Values are median (range). The units for gestation are completed weeks.
†Defined as two doses 12 hours apart between 24 hours and 7 days before delivery.
Group 1, no significant PDA; group 2, significant PDA which closed after medical treatment; group 3, significant PDA remaining patent after medical treatment;
PDA, patent ductus arteriosus; SGA, small for gestational age, defined as weight <10th centile for gestational age; CRIB, clinical risk index for babies.

velocity (<1 m/s)[12][13] at end diastole. If an echocardiogram was unavailable, a PDA was labelled as ''significant'' on clinical grounds (systolic murmur, bounding pulses, hyperdynamic praecordium, wide pulse pressure, cardiomegaly, and pulmonary plethora on chest radiograph). A PDA was classified as closed on clinical and echocardiographic assessment over the first month of life.

Medical treatment of such significant PDA included fluid restriction, diuretics, and up to three courses of indometacin. Two different indometacin regimens were used during the study period; 100 μg/kg/day for five days or 200 μg/kg 12 hourly for three doses. The decision as to which regimen to use was at the discretion of the consultant on service. Prophylactic indometacin was not used.

Outcomes assessed included CLD (defined as need for oxygen or respiratory support at 36 weeks postconceptual age, aiming for oxygen saturations >96%), IVH (grade 3 or 4),[14] proven NEC,[15] duration of hospital stay, and ventilatory support and survival with or without CLD.

Statistical analysis
Categorical data were summarised using frequency distributions, and continuous data were summarised using medians and interquartile ranges. Univariate analyses included χ^2 and Fisher exact test, as appropriate, for categorical comparisons, and Mann-Whitney and Kruskal-Wallis tests for continuous outcomes. Univariate and multivariate logistic regression was performed to examine the risk factors for each of the clinical outcomes considered (such as CLD or death). Duration of ventilation, oxygen, and hospital stay were estimated using Kaplan-Meier probability estimates, and medians together with 25th and 75th centiles were determined for complement of survival times (transfers to another institution and deaths were censored for this analysis). Analysis of duration of

ventilation, oxygen requirement, and hospital stay was carried out using the Cox proportional hazards regression model. SPSS statistical software was used for data analysis. All hypothesis tests were two sided, and a p<0.05 was considered significant.

RESULTS
A total of 284 infants of ⩽28 weeks gestation were admitted to the neonatal unit between 1 January 2000 and 30 June 2002. The outcomes for 252 infants were analysed. Thirty two infants were excluded from the analysis (13 were outborn, one had complex congenital heart disease, and 18 died within the first 72 hours of life). Ninety eight cases (39%) of significant PDA were noted (96 were diagnosed by echocardiography and two were diagnosed on clinical grounds). Of the 98 infants who presented with a significant duct, PDA was successfully closed with medical treatment in 65 and remained open in 33 (34%). Table 1 shows descriptive statistics for the entire group and groups stratified by the PDA status. The infants with significant PDA that remained open after medical treatment were born at earlier gestations (p<0.001), had lower birth weight (p<0.001), and had higher clinical risk index for babies (CRIB) scores[16] (p<0.001).

Eighty nine infants (91%) with a significant PDA received indometacin: seventy eight (88%) of these infants were started on a five dose regimen, 11 infants (12%) received a three dose regimen, and treatment was stopped prematurely in 13 infants (15%) because of adverse effects of indometacin. The median age at start of treatment was 5 days (interquartile range 2–8, range 1–24). A maximum of three courses of indometacin were administered, with 10 infants (30%) in group 3 receiving multiple courses compared with 12 (18.5%) in group 2 (table 2). No significant effects of multiple courses of indometacin were evident for any of the outcomes considered.

Twenty four infants died (10%), with the age of death ranging between 4 and 306 days (median 15.5, interquartile range 9–35). Median gestational age for these infants was 25 weeks (range 23–28). Six of these infants (4%) were from group 1, seven from group 2 (11%), and 11 from group 3 (33%). Mortality was significantly different between groups in a univariate groups comparison, and remained significantly different when gestational age and CRIB score were controlled for (table 3). Relative to the infants in group 1, the infants in group 3 were at a higher risk of death (odds ratio (OR) = 4.02, p = 0.033). Mortality did not differ significantly between groups 2 and 1 (OR = 1.13, p = 0.849). The causes of death ranged from extreme prematurity and lung hypoplasia to grade 4 IVH and severe NEC (table 4).

Table 2 Indometacin use during study period

	Group 2 (n = 65)	Group 3 (n = 33)
Received indometacin	58 (89)	31 (94)
Indometacin regimen		
Five doses	50 (77)	28 (85)
Three doses	8 (12)	3 (9)
Treatment stopped because of adverse effects	9 (14)	4 (12)
Multiple number of courses	12 (18.5)	10 (30)

Values are number (%).
Group 2, significant patent ductus arteriosus (PDA) which closed after medical treatment; group 3, significant PDA remaining patent after medical treatment.

Table 3 Dichotomous clinical variables adjusted for gestational age and clinical risk index for babies (CRIB) score

| Outcome | No of diagnoses (%) | Adjusted OR | | |
		OR	95% CI	p Value
Death	24 (10)			
PDA insignificant	6 (4)	1.00		
PDA closed	7 (11)	1.13	0.31 to 4.15	0.849
PDA open	11 (33)	4.02	1.12 to 14.51	0.033
Death/CLD* at 36 weeks	143 (57)			
PDA insignificant	68 (44)	1.00		
PDA closed	47 (72)	1.22	0.55 to 2.66	0.627
PDA open	28 (85)	1.67	0.50 to 5.69	0.400
CLD* (n = 237)	121 (51)			
PDA insignificant	64 (43)	1.00		
PDA closed	40 (67)	1.13	0.53 to 2.35	0.778
PDA open	7 (63)	0.58	0.20 to 1.67	0.315
NEC	17 (7)			
PDA insignificant	8 (5)	1.00		
PDA closed	5 (8)	1.10	0.31 to 3.94	0.888
PDA open	4 (12)	1.57	0.36 to 6.83	0.546
IVH grade 3–4	18 (7)			
PDA insignificant	6 (4)	1.00		
PDA closed	8 (12)	1.53	0.44 to 5.28	0.503
PDA open	4 (12)	1.05	0.23 to 4.79	0.954

Data were evaluated using logistic regression analysis. Adjusted ORs were obtained in a multivariate logistic regression. No significant effects of sex and intrauterine growth retardation were found in addition to gestational age at delivery and CRIB score.
*CLD limited to the infants alive at 36 weeks postconceptional age.
CLD, Chronic lung disease; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; OR, odds ratio.

No clear association could be derived between cause of death and ductal patency.

CLD developed in 127 (51%) of the 237 infants who survived until 36 weeks postconceptional age. A higher proportion of infants from group 3 (PDA open) developed CLD than from group 1 (63% v 43%). This difference was not significant after gestational age at delivery had been controlled for (table 3). Similar findings were observed when a composite outcome of CLD at 36 weeks postconceptional age or death was examined (table 3).

Proven NEC was diagnosed in 17 infants (7%). The incidence was not different in the three groups after adjustment for gestational age. Similarly, the overall incidence for severe IVH (grade 3–4) was 7%, with no significant differences in the risk of developing IVH between groups (table 3). Five infants (2%) were diagnosed with

Table 4 Causes of death

Study group	Gestation	Birth weight (g)	Cause of death	Age at death (days)
Group 1 (n = 6)	24	645	Grade 4 IVH	9
	27	1225	Multiorgan failure, bilateral subdural haemorrhage	5
	25	785	Sepsis	306
	23	535	HMD, PIE, extreme prematurity	4
	26	735	Respiratory failure secondary to pulmonary hypoplasia	150
	28	1150	NEC and cerebral ischaemia	36
Group 2 (n = 7)	28	1190	Gram negative septicaemia	10
	23	650	Candida septicaemia with DIC	18
	25	835	Cardiac tamponade secondary to TPN effusion	55
	23	665	Pneumonia and CLD	14
	25	890	Perforated NEC	10
	23	670	Perforated NEC with peritonitis	13
	25	410	Perforated NEC with multiorgan failure	12
Group 3 (n = 11)	23	640	Grade 4 IVH	27
	23	490	Overwhelming sepsis and cardiac failure	17
	23	570	Systemic candidiasis	23
	23	700	Pneumonia, extreme prematurity	28
	25	550	PPHN and severe PIE	12
	23	505	Pulmonary haemorrhage	6
	23	645	NEC, prematurity	5
	25	620	Perforated NEC with multiorgan failure	33
	24	740	Perforated NEC	37
	27	410	Perforated NEC with multiorgan failure	41
	27	1095	HMD and pneumothoraces	9

Gestation is given as completed weeks.
Group 1, no significant PDA; group 2, significant PDA which closed after medical treatment; group 3, significant PDA remaining patent after medical treatment;
CLD, chronic lung disease; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; HMD, hyaline membrane disease;
PIE, pulmonary interstitial emphysema; DIC, disseminated intravascular coagulation; total parenteral; PPHN, persistent pulmonary hypertension of the newborn.

Table 5 Continuous clinical variables adjusted for gestational age and clinical risk index for babies (CRIB) score

Outcome	Median (Q1–Q3)*	Adjusted HR		
		HR	95% CI	p Value
Duration of ventilation	25 (7–53)			
PDA insignificant	14 (4–31)	1.00		
PDA closed	37 (20–62)	0.86	0.63 to 1.19	0.336
PDA open	60 (41–75)	0.70	0.44 to 1.11	0.130
Duration of oxygen	62 (20–103)			
PDA insignificant	48 (20–103)	1.00		
PDA closed	90 (76–103)	0.89	0.63 to 1.27	0.526
PDA open	85 (44–120)	1.20	0.73 to 1.98	0.476
Hospital stay	91 (71–119)			
PDA insignificant	80 (65–100)	1.00		
PDA closed	111 (8–127)	0.75	0.53 to 1.07	0.177
PDA open	111 (94–159)	0.85	0.48 to 1.50	0.579

Analysis was performed using Cox proportional hazards regression. Adjusted HRs were obtained in a multivariate regression model. In all regression models, data for infants who died (n = 24, table 3) or were transferred (group 1, 2, 3: n = 3, 1, 3 respectively) were censored. No significant effects of sex and intrauterine were found in addition to gestational age at delivery and CRIB score.
*Q1 and Q3 list the number of days that 25th and 75th centiles of infants remained on ventilation, oxygen, or stayed in the hospital.
PDA, Patent ductus arteriosus; HR, hazard ratio.

periventricular leucomalacia, and associations with the PDA status were not analysed because of the small sample size.

The duration of ventilation was longer (60 v 14 days) in infants with a persistent duct (group 3) than in infants from group 1. However, this difference was not significant after adjustment for gestational age and CRIB score (p = 0.13). The durations of oxygen supplementation and hospital stay were also not significantly different between groups (table 5).

All surviving infants were followed over the first 12 months of life by neonatologists. One infant (group 3) was referred to Princess Margaret Hospital for surgical ligation at 8 weeks of age and was subsequently discharged home.

DISCUSSION

Our results indicate that the risk of death may be significantly higher in infants with persistent patency of the duct. Early surgery may thus be of benefit in reducing mortality in this group of infants. We found no evidence that persistent patency of the duct was associated with CLD, IVH, or NEC. Mortality and morbidity in our unit is comparable to national data: CLD 52% v 45%, grade 3–4 IVH 7% v 12%, NEC 6.7% v 6.3%, and mortality 16% v 20% ⩽ 28 weeks gestation, Western Australia v Australian and New Zealand Neonatal Network.[15] The incidence of CLD appears somewhat higher because of Western Australia having a higher oxygen saturation target (>95% Spo₂) for infants with CLD than other centres.

Evidence on the effect of PDA and its closure on respiratory status in preterm neonates is not clear. Stefano et al,[17] Yeh et al,[18] Gerhardt and Bancalari,[19] and Szymankiewicz et al[20] have all reported improved lung function after closure of PDA after indometacin[17 18] or surgical ligation.[19 20] Farstad and Bratlid,[21] however, found no difference in compliance with ductal closure in infants with respiratory distress syndrome. Van Woerkom et al,[22] in their analysis of very low birthweight infants who underwent PDA ligation, reported no short term benefits in mean airway pressure, fractional inspired oxygen, oxygenation, or ventilation index. In fact, they noted a trend towards adverse outcome after controlling for the variables of sex, gestational age, birth weight, and age at ligation. Carboni and Ringel[23] in their retrospective analysis of echocardiograms in infants <35 weeks gestation found that the presence of PDA after two weeks did not relate to duration of ventilation, oxygen therapy, or hospital stay. Also, a late

closure of PDA in a subgroup of 11 infants did not appear to affect these variables. They hypothesised that closure of PDA beyond the second week may not improve the infants' respiratory status. The lack of difference in durations of ventilation, oxygen therapy, and hospital stay between infants in group 3 compared with infants in group 2 in our study may also be related to a late postnatal age at the time of ductal closure.

Larger PDA diameters have been shown to be associated with all grades of IVH.[2] Prophylactic indometacin is known to decrease the incidence of symptomatic PDA and grade 3–4 IVH.[24–26] However, whether the effect of prophylactic indometacin on IVH is secondary to PDA closure per se is not clear. PDA is also a significant risk factor for the development of NEC.[4 25 27] Cassady et al[28] in a randomised controlled trial showed a significant reduction in the incidence of NEC in very low birthweight infants when a PDA was ligated within 5 days of birth compared with infants where the duct was either ligated late or not at all. The lack of difference in the incidence of IVH or NEC between the three groups in our study may be related to inadequate power to test these variables.

In summary, our results indicate that mortality is significantly higher in infants with persistent PDA but that respiratory morbidity, IVH, and NEC are unaffected by patency of the duct. Thus routine surgical ligation of a duct refractory to medical treatment may not decrease CLD or affect morbidities such as IVH and NEC in preterm infants. The clinical significance of higher mortality in infants with a persistent PDA is uncertain given the wide confidence intervals and the lack of a clear relation between PDA and causes of death. A randomised controlled trial of surgical ligation of ductus patent after medical treatment is needed to confirm our findings. The design of any such trial needs to carefully consider the difference in baseline risk between the reference population and those infants randomised to surgical ligation or no ligation.

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Competing interests: none declared

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