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*Original Article*

# Outcome of patent ductus arteriosus ligation in premature infants in the East of England: a prospective cohort study

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**Abstract** *Background:* Surgical ligation of patent ductus arteriosus is considered when medical treatment fails or is contraindicated. This study aims to determine the mortality and morbidity of preterm neonates referred for patent ductus arteriosus ligation. *Methods:* A prospective study was conducted in the East of England to follow the outcome of premature infants under 37 weeks' gestation undergoing patent ductus arteriosus ligation. A standardised proforma was used to collect information before and after the procedure. *Results:* A total of 102 premature infants were recruited, and patent ductus arteriosus ligation was performed in 92. Surgical complications occurred in 8.7% (8/92), which included pneumothorax (5/8), recurrent laryngeal nerve palsy (2/8), and chylothorax (1/8). Morbidity outcome data were not available for all infants. The incidence of chronic lung disease was 88% (88/99); intraventricular haemorrhage was 49% (49/100); necrotising enterocolitis 39% (39/99), and retinopathy of prematurity 42% (41/97). The overall mortality rate in our study was 7.8% (8/102). Mortality rate in infants who had patent ductus arteriosus ligation was 4.3% (4/92). The 30-day survival rate after ligation was 99% (91/92). Beyond 30 days post-ligation, three infants died from other causes that were not directly related to surgery. *Conclusion:* Patent ductus arteriosus ligation in premature infants is associated with low mortality and complication rates; however, there is a high incidence of neonatal morbidity. Surgical capacity for patent ductus arteriosus ligation needs to be carefully planned nationally as the duration of "waiting time" and transport to another surgical centre could adversely affect outcomes in this high-risk population.

Keywords: Patent ductus arteriosus; ligation; neonate; mortality; morbidity

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Persistent patent ductus arteriosus is common in premature infants in the first weeks of life and can lead to increased morbidity and mortality. Left-to-right shunting through the patent ductus arteriosus increases pulmonary blood flow and diverts blood away from the systemic circulation to the lungs, resulting in systemic hypoperfusion.[1–3] These haemodynamic changes may be responsible for the morbidities associated with patent ductus arteriosus, such as chronic lung disease,[4,5] acute pulmonary haemorrhage,[6] necrotising enterocolitis,[7,8] intraventricular haemorrhage,[9,10] and retinopathy of prematurity. Failure of patent ductus arteriosus closure has been shown to be a risk factor for the increased mortality rate of 70% compared with 11% in infants who had successful closure in a single-centre retrospective study.[11]

The optimal management of patent ductus arteriosus in the preterm infant remains a subject

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of controversy. The rationale for closing the patent ductus arteriosus has also been challenged because of a lack of evidence of risks and benefits of treatments from randomised controlled trials comparing different treatment strategies, particularly when up to 50% of patent ductus arteriosus may close spontaneously with no treatment.[12,13] In the United Kingdom, initial strategies to manage a patent ductus arteriosus in a symptomatic preterm infant frequently include careful fluid administration, diuretics, and prostaglandin synthetase inhibitors such as indometacin or ibuprofen. Prostaglandin synthetase inhibitors have been used successfully in premature infants, but can be associated with significant side effects such as thrombocytopaenia, bleeding, gastrointestinal perforation, and renal dysfunction.[14,15] Persistent symptomatic patent ductus arteriosus, on the other hand, can cause significant pulmonary morbidity requiring prolonged ventilatory support.[16,17]

Surgical ligation may be considered when the patent ductus arteriosus fails to close after medical treatment or when prostaglandin synthetase inhibitor therapy is contraindicated. The timing of surgical ligation is widely debated. Several studies have suggested that early surgical ligation may have detrimental effects on lung function and growth and may even contribute to the development of bronchopulmonary dysplasia.[18,19] Surgical ligation of patent ductus arteriosus produces definitive closure, with low morbidity and mortality rates in experienced centres. Reported complications associated with patent ductus arteriosus ligation include tension pneumothorax, intra-operative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy, and thoracic scoliosis.[20] In addition, several studies have suggested that surgical closure of patent ductus arteriosus causes an increased risk of long-term morbidity and adverse neurodevelopmental outcomes.[19,21,22]

The primary aims of this study were to determine the number of preterm neonates referred for patent ductus arteriosus ligation from the East of England and the outcome of the procedure. The population in the East of England is 5 million, with 60,000 births per annum in 18 delivery units. There are currently three level 3 neonatal units (Cambridge, Norwich, and Luton), 12 level 2 units, and three level 1 units. There is no paediatric cardiac surgical centre in the region, and neonates requiring patent ductus arteriosus ligation are transferred to cardiothoracic centres where capacity exists. The secondary aims were to identify complications of the procedure, the relationship between prostaglandin synthetase inhibitor administration and timing of ligation, and finally to determine the incidence of chronic lung disease, pulmonary haemorrhage, necrotising enterocolitis, intraventricular haemorrhage, and retinopathy of prematurity in this group of premature infants.

## Methods

This prospective study with the support of the East of England Perinatal Network was conducted between 1 December, 2004 and 1 April, 2009. In all cases, the patent ductus arteriosus was diagnosed by echocardiography usually performed by a neonatal paediatrician. Haemodynamically significant patent ductus arteriosus were those that resulted in an increased left atrial aortic ratio, with a dilated left heart and a patent ductus arteriosus diameter of $>2$ mm. These findings were confirmed by cardiologists in outreach clinics or when the baby was transferred to the surgical centre. All premature infants referred for patent ductus arteriosus ligation were notified by local paediatricians and identified from the regional Acute Neonatal Transport Service. Referred infants who died or who had their procedure cancelled before patent ductus arteriosus ligation were also included as intention to treat. Infants with other significant congenital heart disease and infants who had patent ductus arteriosus ligation after discharge from hospital were excluded from this study.

When an infant was referred for patent ductus arteriosus ligation, the lead clinician of the local neonatal unit completed a two-part proforma. The first part of the proforma was collected at the time of referral/transfer and included pre-operative details such as gestational age, birth weight, use of prostaglandin synthetase inhibitor, date of decision made for ligation, and date of transfer for ligation. The referring paediatrician was contacted after the infant was transferred back after surgery to provide follow-up information before hospital discharge. The second part of the proforma included information on whether patent ductus arteriosus ligation was performed, as well as operative details including weight and age at ligation, post-operative outcome, surgical complications, age, and cause of death. The presence of comorbidities at discharge, such as chronic lung disease – defined as oxygen dependency at 36 weeks corrected gestational age – intraventricular haemorrhage, necrotising enterocolitis, and retinopathy of prematurity, was also recorded. We did not conduct a case–control study comparing this surgical sub-group with those managed medically. Formal ethics review was not required as this study was deemed an evaluation of service provision.

## Results

### *General demographic data*

Over the 4-year study period, 102 premature infants were referred for patent ductus arteriosus ligation

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Table 1. Comparison of outcome of patent ductus arteriosus ligation with and without prostaglandin synthetase inhibitor treatment.

| | No PSI treatment (n = 19) | PSI treatment (n = 73) | p-value |
|---|---|---|---|
| Age at ligation, median (95% CI) | 26.5 (12–94) days | 34.5 (10–91) days | 0.29** |
| Incidence of CLD | 16 (84%) | 63 (86%) | 0.72* |
| Death | 0 | 4 (5%) | 0.57* |

CLD = chronic lung disease; PSI = prostaglandin synthetase inhibitor
*Fisher's exact test
**Mann–Whitney U test

(26 from level 2 unit and 76 from level 3 unit), and the procedure was performed in 92. Most of the babies transferred from the level 2 units had been previously managed on the level 3 units where the patent ductus arteriosus had been diagnosed. The level 3 referrals were generally more immature, smaller infants who were ventilator dependent. There were 10 infants who did not undergo patent ductus arteriosus ligation: four died before surgery, and in six infants the patent ductus arteriosus was thought to be haemodynamically insignificant when reviewed in the surgical centre.

The 102 infants included in this study were born at a median of 25 (range 23–36) weeks' gestation, weighing a median of 721 g (range 462–2420). In all, 65 infants were male and 37 were female. In this cohort, 85 (83%) were born at <28 weeks' gestation. In the 92 infants who underwent surgical ligation of patent ductus arteriosus, the procedure was performed at a median postnatal age of 34 (range 10–94) days and a median weight of 1005 g (range 627–3080).

### *Use of prostaglandin synthetase inhibitor and effects on ligation and outcome*

Of the 102 infants, 81 (79%) were treated with prostaglandin synthetase inhibitor: 34 infants received a single course, 33 infants received two courses, and eight infants received three courses. There were six infants who received prostaglandin synthetase inhibitor, but the exact treatment details were unclear. In all, 21 infants (21%) were not treated with prostaglandin synthetase inhibitor before referral for ductus arteriosus ligation. Contraindications were: suspected or proven necrotising enterocolitis (n = 8), renal dysfunction (n = 4), thrombocytopaenia (n = 4), severe intrauterine growth restriction (n = 3), pulmonary haemorrhage (n = 1), and parental refusal (n = 1). In all, 70 infants received Indometacin, 62 exclusively. The majority of infants who received Indometacin were given 0.1 mg/kg/dose at 24-hour intervals for 6 days as a complete course. Infants who received more than one course of Indometacin received either the same dosing schedule or three doses of 0.2 mg/kg at 12- to 24-hour intervals. There were 19 infants who were treated with Ibuprofen, 11 exclusively. The Ibuprofen dose given was 10 mg/kg followed by two further 5 mg/kg doses at 24-hour intervals. There were eight infants who were treated with both Indometacin and Ibuprofen.

A comparison of the outcomes between infants who did not receive any prostaglandin synthetase inhibitor with those who were treated medically before ligation showed no significant differences in chronic lung disease or mortality rates (Table 1).

### *Surgical ligation procedure*

Following a decision to proceed with ligation, the "waiting" time from referral to surgery and transport to a paediatric cardiothoracic unit was 7 (range 3–39) days. Infants from this region were referred to five different cardiothoracic centres in London and the Midlands. The 92 procedures were performed in: Great Ormond Street Hospital, London (n = 49); Evelina Children's Hospital, London (n = 23); Royal Brompton Hospital, London (n = 6); Glenfield Hospital, Leicester (n = 13); and Birmingham Children's Hospital, Birmingham (n = 1). The median travelling distance between the referring hospital and cardiac centre was 47 miles (range 34–140 miles). One ligation was performed as a day case procedure.

### *Surgical complications and neonatal morbidity*

Surgical complications contributing to immediate morbidity occurred in 8 of 92 ligated infants (8.7%), which included pneumothorax (n = 5), recurrent laryngeal nerve palsy (n = 2), and chylothorax (n = 1). All these complications resolved over time with appropriate management. Other longer-term morbidity outcome data were not available for all infants. The incidence of chronic lung disease as defined by oxygen requirement at 36 weeks corrected gestational age was 88% (88/99); intraventricular haemorrhage of any grade was 49%

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(49/100); necrotising enterocolitis 39% (39/99), and retinopathy of prematurity 42%(41/97).

*Mortality after patent ductus arteriosus ligation*

The overall mortality rate in our study was 7.8% (8 of 102 died). The mortality rate in the group that had patent ductus arteriosus ligation was 4.3% (4/92). The 30-day survival rate after ligation was 99% (91/92). The child who died within the 30-day operative period developed an acidosis, hypotension secondary to poor cardiac function associated with myocardial hypertrophy. Post-mortem studies confirmed a mitochondrial cytopathy. The other infants who died more than 30 days after ligation had complications relating to their prematurity: necrotising enterocolitis in two infants and sepsis in one infant.

## Discussion

This prospective study showed an excellent short-term outcome following surgical ligation of patent ductus arteriosus, with a high survival rate of 99% at 7 and 30 days post-operatively. There was also a low surgical complication rate of 8.7% in our study. These rates are similar to other studies that have shown that this procedure is safe and effective in preterm low birth weight infants.[23] There was a further 3% mortality between 30 days and hospital discharge, which was not related to surgery but rather represented the high risk of mortality and morbidity in this population, resulting from complications of the premature birth. One-year survival figures were not collected. The number of pre- and post-operative deaths were identical. In all, four infants died before surgery while awaiting admission to a cardiothoracic centre. These results show improved survival to hospital discharge when compared with the previous retrospective UK studies.[24,25] More importantly, they are in line with the current UK Congenital Cardiac Audit Database survival figures for surgical patent ductus arteriosus ligation performed in 2009 and 2010 where 30-day mortality was 2.8% and 1-year mortality 12.1%.[26]

Arranging patent ductus arteriosus ligation can be difficult with significant delays following referral due to lack of capacity in the surgical units. The mean waiting time of 7 days might be reduced if more procedures were performed as day cases.[27] However, these extremely small ventilated infants often do not tolerate long transfers well. The referral process could be improved by providing adequate capacity in the surgical centres for this patient population. Over the 4.3 years of this study, 24 babies were referred annually for ligation from a single neonatal network. Demographic details from the Standardised Electronic Neonatal Database show that within the East of England neonatal network an average of 164 neonates per year are admitted at <26 weeks' gestation. This study suggests that 14% of these neonates will be referred for patent ductus arteriosus ligation each year. Using the Epicure 2 data set, this would equate to 133 extremely preterm infants requiring patent ductus arteriosus ligation nationally every year.[28]

Previous studies have shown that patent ductus arteriosus ligation can be safely performed outside cardiac centres. The pressure on the cardiothoracic centres could be reduced if specialist teams travelled to the baby to perform the procedure. Such an outreach service has many potential advantages including reducing the delays in scheduling surgery, avoiding transport of critically ill neonates, achieving optimal continuity of care, and minimising upheaval to families. North American studies have demonstrated that an experienced surgical team can safely perform patent ductus arteriosus ligation in neonatal intensive care units of hospitals without on-site paediatric cardiac surgical facilities with no difference in peri-operative complications or procedure-related mortality.[29] Such an approach has not been tried or costed in the United Kingdom.

Another option would be to consider transcatheter interventional occlusion of the patent ductus arteriosus; however, published experience with preterm babies is limited. Francis et al[30] reported complete coil closure in seven of eight preterm infants, ranging from 27 to 32 weeks of age, with median weight at the time of procedure of 1100 g (range 930–1800 g). More recently, echocardiographically guided transcatheter closure of arterial ducts with placement of coils or Amplatzer duct devices in small premature infants in the Neonatal Intensive Care Unit have been reported. This is a significant advance in neonatal care, which will enable selected infants to avoid surgery and also the risks associated with transporting a sick preterm infant between units.[31]

This prospective study provides useful data on outcomes of patent ductus arteriosus ligation in preterm infants not only in terms of mortality but also morbidity. The incidence of chronic lung disease in this cohort was significantly higher compared with published figures of 20% to 26% in infants <1500 g.[32,33] Similarly, the incidence of necrotising enterocolitis in this cohort is higher than rates of 6–9% in those of gestational age 29 weeks or less.[34] It was difficult to compare incidences of intraventricular haemorrhage and retinopathy of prematurity owing to differences in classification. The significance of these mortality and morbidity figures are likely to result from the

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high-risk population rather than the procedure itself. Unfortunately, we did not conduct a case–control study, which would have allowed a direct comparison with infants managed medically.

Management of the patent ductus arteriosus in UK neonatal practice remains varied both in terms of medical and surgical treatments. Studies have suggested that the patent ductus arteriosus is less likely to close with Indometacin in premature infants <800 g if patent ductus arteriosus is associated with a large left atrial aortic ratio on echocardiography.[35] Medical treatment, although safe, is not without adverse side effects and often has to be discontinued before achieving the desired result. Surgical ligation ensures definitive closure of patent ductus arteriosus with reported success rates from 98% to 100%.[36,37] Studies comparing early surgical ligation versus Indometacin in extremely low birth weight infants have found no statistically significant difference in death and other morbidities, but a significant decrease in necrotising enterocolitis.[38,39]

This study shows a wide variation of clinical practice in the management of the patent ductus arteriosus including different regimens of Indometacin or Ibuprofen and the timing of ligation across a single perinatal network. Infants who were treated with prostaglandin synthetase inhibitor treatment had surgery later. The prevalence of chronic lung disease appears to be similar in both groups.

We conclude that patent ductus arteriosus ligation is a safe procedure with excellent post-operative survival. The ligation procedure is associated with a low incidence of surgical complications. However, this population has a significant risk of associated morbidities including chronic lung disease and necrotising enterocolitis. Larger prospective studies to compare the risks and benefits of surgical versus medical therapy in preterm infants are still required.

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