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[Intervention Review]

Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants

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ABSTRACT

Background

A patent ductus arteriosus (PDA) with significant left to right shunt increases morbidity and mortality in preterm infants. Early closure of the ductus arteriosus may be achieved pharmacologically or by surgery. The preferred initial treatment of a symptomatic PDA, surgical ligation or treatment with indomethacin, is not clear.

Objectives

To compare the effect of surgical ligation of PDA versus medical treatment with cyclooxygenase inhibitors (indomethacin, ibuprofen or mefenamic acid), each used as the initial treatment, on neonatal mortality in preterm infants with a symptomatic PDA.

Search methods

For this update we searched *The Cochrane Library* 2012, Issue 2, MEDLINE, EMBASE, CINAHL, Clinicaltrials.gov, Controlled-trials.com, Proceedings of the Annual Meetings of the Pediatric Academic Societies (2000 to 2011) (Abstracts2View™) and Web of Science on 8 February 2012.

Selection criteria

Randomised or quasi-randomised trials in preterm or low birth weight neonates with symptomatic PDA and comparing surgical ligation with medical treatment with cyclooxygenase inhibitors, each used as the initial treatment for closure of PDA.

Data collection and analysis

The authors independently assessed methodological quality and extracted data for the included trial. We used RevMan 5.1 for analyses of the data.

Main results

One study reporting on 154 neonates was found eligible. No significant difference between surgical closure and indomethacin treatment was found for in-hospital mortality, chronic lung disease, necrotising enterocolitis, sepsis, creatinine level or intraventricular haemorrhage. There was a significant increase in the surgical group in the incidence of pneumothorax (risk ratio (RR) 2.68; 95% confidence interval (CI) 1.45 to 4.93; risk difference (RD) 0.25; 95% CI 0.11 to 0.38; number needed to treat to harm (NNTH) 4 (95% CI 3 to 9)) and retinopathy of prematurity stage III and IV (RR 3.80; 95% CI 1.12 to 12.93; RD 0.11; 95% CI 0.02 to 0.20; NNTH 9 (95% CI 5 to 50)) compared to the

Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants (Review)**1**

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indomethacin group. There was a statistically significant decrease in failure of ductal closure rate in the surgical group as compared to the indomethacin group (RR 0.04; 95% CI 0.01 to 0.27; RD -0.32; 95% CI -0.43 to -0.21, number needed to treat to benefit (NNTB) 3 (95% CI 2 to 4)). No new trials were identified for inclusion in the 2012 update.

Authors' conclusions

There are insufficient data to conclude whether surgical ligation or medical treatment with indomethacin is preferred as the initial treatment for symptomatic PDA in preterm infants.

PLAIN LANGUAGE SUMMARY

Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants

The way an infant's blood is circulated changes soon after birth. Initially, premature infants have an opening (a patent ductus arteriosus, PDA) between the large blood vessel to the lungs and the large blood vessel that carries oxygenated blood to the rest of the body. Early symptomatic treatment of PDA, when clinical signs first appear, helps reduce the amount of time an infant needs assisted breathing (mechanical ventilation) and the likelihood of chronic lung disease and damaging inflammation of the gut (necrotising enterocolitis). Standard therapy includes restricting fluids, diuretics and cyclooxygenase inhibitors like indomethacin or ibuprofen. The PDA is closed surgically if these medical treatments do not work. Only one randomised controlled study could be included in this review (including 154 preterm infants that needed breathing support). Indomethacin and surgery gave similar benefits. There were no differences in deaths during the hospital stay, chronic lung disease, necrotising enterocolitis, cerebral or other bleeding. Surgery was more effective in closing the PDA (three needed to treat for one to benefit) but it was associated with complications (pneumothorax and retinopathy of prematurity). The one study found was carried out over 30 years ago. Clinical practice has changed a great deal and surgical closure of a PDA is safer. Therefore, whether the results of the study are applicable today is debatable. Updates of this review in July 2007 and February 2012 did not identify any additional randomised controlled studies for inclusion, but three observational studies indicated an increased risk for one or more of the following outcomes associated with PDA ligation: chronic lung disease, retinopathy of prematurity and neurosensory impairment.

BACKGROUND

There are numerous reports suggesting that prophylactic closure of the ductus arteriosus reduces the incidence of grade 3 or 4 intraventricular haemorrhage (IVH) and need for surgical ligation (Yeh 1981; Fowlie 1996; Fowlie 2002). Also, early symptomatic treatment of PDA (i.e. when clinical signs first appear) has been shown to decrease the incidence of chronic lung disease, duration of mechanical ventilation and necrotising enterocolitis when compared with late symptomatic treatment (i.e. after signs of congestive cardiac failure) (Clyman 1996). Standard therapy for a PDA includes fluid restriction, diuretics and cyclooxygenase inhibitors like indomethacin or ibuprofen, with surgical ligation reserved for medical failures. In 1976, it was first demonstrated that closure of the ductus arteriosus could be achieved pharmacologically using the cyclooxygenase inhibitor indomethacin (Friedman 1976; Heymann 1976). About the same time, Cotton et al (Cotton 1978b) showed the beneficial effect of surgical intervention to close the ductus arteriosus in preterm infants with a significant left to right shunt.

Efficacy and toxicity of indomethacin and other cyclooxygenase inhibitor drugs have been explored extensively and many variations in dosage regimens have been reported in the literature (Ng 1997; Yanowitz 1998; Patel 2000; Van Overmeire 2000). Rennie and Cooke (Rennie 1991) found higher ductal closure rates and fewer renal side effects with low-dose prolonged indomethacin therapy (0.1 mg per kilogram given daily for six days) compared with the conventional three-dose regimen (0.2 mg per kilogram given at 12-hour intervals). A study comparing the efficacy and toxicity of ibuprofen versus indomethacin found similar ductal closure rates in both treatment groups, except that indomethacin was more likely to be associated with oliguria (Van Overmeire 2000). There is a risk of failure to close the PDA with cyclooxygenase inhibitors. Failure of ductal closure with indomethacin is reported in between 30% to 40% of treated infants (Gersony 1983; Palder 1987). This may be more likely in the very immature infant (Palder 1987; Trus 1993; Weiss 1995; Perez 1998). Narayanan et al (Narayanan 2000) reported that 41% of infants treated with indomethacin for symptomatic PDA and 21% of infants given prophylactic indomethacin required eventual ductal ligation. Indomethacin treatment has been associated with several adverse effects such as transient or permanent alterations in renal function (Betkerur 1981; Gersony 1983; Van Bel 1991), necrotising enterocolitis, gastrointestinal perforation (Grosfeld 1996) and impairment of cerebral blood flow velocity (Edwards 1990; Ohlsson 1993). Indomethacin prophylaxis has been shown to reduce the incidence of PDA; however, it does not significantly affect the rate of survival without neurosensory impairment at 18 months (Schmidt 2001).

Description of the condition

For more than 30 years it has been recognised that a significant left to right shunt through a patent ductus arteriosus (PDA) in preterm infants increases morbidity and mortality (Thibeault 1975; Cotton 1978b; Jacob 1980). The reported incidence of PDA ranges from less than 10% to 60% depending on gestational age, day of life and diagnostic criteria used (Ellison 1983; Duddell 1984). A symptomatic PDA may occur in up to 50% of infants with birth weight less than 1500 grams (Mouzinho 1991). Infants with respiratory distress syndrome (RDS) (Thibeault 1975), perinatal asphyxia (Cotton 1981) and those who have received excessive fluids during the first days of life (Bell 1980) are more susceptible to

the development of a clinically symptomatic PDA. A symptomatic PDA increases the ventilation and oxygen requirements, and increases the risk of intraventricular haemorrhage (Duddell 1984) and chronic lung disease (Brown 1979) in very low birth weight (VLBW) infants. The phenomenon of diastolic steal associated with a PDA may cause renal impairment, intestinal ischemias, necrotising enterocolitis (NEC) and reduced middle cerebral artery blood flow velocity (Nestrud 1980; Martin 1982; Shimada 1994; Weir 1999).

The clinical criteria used for the diagnosis of a symptomatic PDA are the presence of a heart murmur, bounding pulses, tachycardia, hyperdynamic precordial impulse, widened pulse pressure or worsening respiratory status (tachypnoea and increasing fraction of inspired oxygen, ventilatory requirements, or both) (Davis 1995). Echocardiographic and Doppler criteria for the confirmation of a symptomatic PDA include the following (Dani 2000; De Carolis 2000; Lago 2002):

1. demonstration of left to right shunt;
2. left atrial:aortic root ratio > 1.3;
3. ductal size greater than 1.5 mm;
4. disturbed diastolic flow in the main pulmonary artery with a diastolic backflow in the aorta immediately below the ductus arteriosus and a forward flow above the ductal insertion.

Description of the intervention

Surgical ligation in preterm neonates with a symptomatic PDA has been shown to be successful, with minimal complications (Palder 1987; Satur 1991; Pokharel 1998; Chen 1999). There are reports suggesting that surgical ligation may be the preferred first line of treatment compared to indomethacin in preterm infants less than 800 grams (Palder 1987; Trus 1993). One study has shown that a PDA is less likely to close with indomethacin if it is associated with a large LA/AO (left atrial-aortic) ratio on echocardiography and that surgical ligation may be the better option (Trus 1993). Ibuprofen is as effective as indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency. Given the reduction in NEC noted in the latest Cochrane update, ibuprofen currently appears to be the drug of choice (Ohlsson 2010). Studies are needed to evaluate the effect of ibuprofen compared to indomethacin treatment on longer-term outcomes in infants with PDA (Ohlsson 2010). The use of ibuprofen versus surgical ligation has not been tested in a randomised controlled trial.

How the intervention might work

The reported success rates for surgical closure of PDA are 98% to 100% (Palder 1987; Koehne 2001). However, occasional failure of surgery to close a symptomatic PDA can occur; for example, if the ductal clip is malpositioned or dislodged (Koehne 2001). Some investigators have reported significant complications associated with surgical ligation including tension pneumothorax, hypothermia, intraoperative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy and thoracic scoliosis (Mikhail 1982; Zbar 1996; Seghaye 1997; Koehne 2001). In a retrospective study comparing indomethacin with surgical ligation, the overall fatality rates were found to be 16 of 101 (16%) for indomethacin and 14 of 55 (25%) for surgery (Koehne 2001). Although open surgical division is a safe and reliable procedure, concerns about chest wall deformity (Westfelt 1991) and postoperative pain syndromes associated with standard posterolateral thoracotomy have motivated a search for

a less traumatic approach. Video-assisted thoracoscopic surgery (VATS), a recent advancement in surgical management of PDA, uses endoscopic instruments through 3 mm incisions in the chest wall to approach the PDA (Burke 1999).

Why it is important to do this review

Although both surgical and pharmacological interventions for ductal closure are widely used, morbidity and mortality associated with these therapies have not been systematically reviewed. Even though there may be a general consensus to use indomethacin as the initial therapy for a symptomatic PDA, and to reserve surgical ligation for indomethacin failures, this therapeutic approach may not represent the optimal management for PDA in the extremely preterm neonate.

This review compares the effectiveness and safety of surgical versus medical treatment with cyclooxygenase inhibitor drugs as initial treatment in preterm infants with a symptomatic PDA.

OBJECTIVES

Primary objective

To compare the effect of surgical ligation of PDA versus medical treatment with cyclooxygenase inhibitors (indomethacin, ibuprofen or mefenamic acid), each used as the initial treatment, on neonatal mortality in preterm infants with a symptomatic PDA.

Secondary objectives

To determine in subgroup analyses the effectiveness and safety of surgical ligation versus medical treatment with cyclooxygenase inhibitors to close the symptomatic PDA in relation to the following criteria:

- gestational age (< 28 weeks, 28 to 32 weeks, 33 to 37 weeks);
- birth weight (< 1000 grams, 1000 to 1500 grams, > 1500 to < 2500 grams);
- different dosage regimens (0.2 mg/kg/dose q 12-hourly x 3 doses, 0.1 mg/kg/dose q 24-hourly x 5 to 7 doses) of indomethacin;
- different types of cyclooxygenase inhibitors (indomethacin, ibuprofen or mefenamic acid);
- number of courses of cyclooxygenase inhibitors for treatment of PDA;
- methods used to diagnose a PDA.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Preterm infants < 37 weeks gestational age or low birth weight infants (< 2500 grams) with symptomatic PDA diagnosed either clinically or by ECHO criteria in the neonatal period (< 28 days).

Types of interventions

Surgical ligation for closure of PDA versus medical treatment with cyclooxygenase inhibitors, each used as the initial

treatment. Surgical ligation after failure of medical treatment with cyclooxygenase inhibitors was incorporated in the medical arm. The cyclooxygenase inhibitors may have been used in any dose and any number of repeated courses.

Types of outcome measures

Studies that reported one or more of the following outcomes.

Primary outcomes

- All causes of mortality during the initial hospital stay.

Secondary outcomes

- Neonatal mortality (death during the first 28 days of life).
- Infant mortality (death during the first year of life).
- Failed ductal closure (presence of symptomatic PDA by clinical and echocardiographic criteria).
- Chronic lung disease (CLD) (defined as supplemental oxygen need at 28 days postnatal age or at 36 weeks postmenstrual age (PMA) in addition to compatible clinical and roentgenographic findings).
- Need for surgical closure of PDA after failure of primary intervention.
- Duration of ventilator support (days).
- Duration of supplemental oxygen requirement (days to last discontinuation of any supplemental oxygen).
- Intraventricular haemorrhage (IVH) all grades, as per Papile et al (Papile 1978).
- Periventricular leukomalacia (PVL), defined as cystic changes in the periventricular areas.
- Necrotising enterocolitis (NEC) (Bell 1978).
- Gastrointestinal haemorrhage.
- Low platelet count (< 50,000/microlitre).
- Gastrointestinal perforation (defined by presence of free air in the peritoneal cavity on an abdominal x-ray).
- Renal function.
- Time to full enteral feeds (postnatal age at time of achieving full enteral feeds).
- Retinopathy of prematurity (ROP) based on international classification of ROP, stage I to II and stage III to IV (ICROP 1984).
- Pneumothorax (presence of air in the pleural space diagnosed either on clinical examination, transillumination or chest radiograph).
- Definite sepsis (clinical symptoms and signs of sepsis and a positive bacterial culture in a specimen obtained from normally sterile fluids or tissue obtained at autopsy).
- Probable sepsis (clinical symptoms and signs of sepsis and abnormal findings on a laboratory screening test for infection).
- Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardised and validated assessment tool, a child developmental specialist or both) at any age (outcome data will be grouped at 6, 9, 12, 18, 24 months if available).
- Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death).

Search methods for identification of studies

See: Cochrane Neonatal Review Group search strategy (cochrane.neonatal.org).

Electronic searches

For this update we searched *The Cochrane Library* 2012, Issue 2, MEDLINE, EMBASE, CINAHL, Clinicaltrials.gov, Controlled-trials.com, Proceedings (2000 to 2011) of the Annual Meetings of the Pediatric Academic Societies (Abstracts2View) and Web of Science on 8 February 2012.

For the previous update of this review ([Malviya 2008](#)) we searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2007, Issue 2) and MEDLINE (1966 to July 2007) using MeSH terms: newborn, infant, premature (or preterm) or low birth weight infant, patent ductus arteriosus or PDA, ligation and cyclooxygenase inhibitors; indomethacin, ibuprofen, mefenamic acid.

Other databases that we searched included: EMBASE (1980 to July 2007), CINAHL (1982 to July 2007) and the reference lists of identified trials and abstracts of Pediatric Academic Societies annual meetings published in *Pediatric Research* (1990 to July 2002) or electronically (May 2002 to July 2007). We reviewed reference lists of published narrative and systematic reviews. We did not seek unpublished data. We did not apply language restrictions. Three review authors (MM, AO, SS) screened the search results to identify articles eligible for inclusion in the review. For the update of this review, AO undertook the literature search.

Searching other resources

We screened the reference list of the identified trial for additional trials for inclusion.

Data collection and analysis

Selection of studies

The three review authors assessed all abstracts and published full reports identified as potentially relevant by the literature search for inclusion in the review. We used the standardised review methods of the Cochrane Neonatal Review Group (CNRG) to assess the methodological quality of studies. The three authors conducted independent quality assessments and were not blinded to authors, institution or journal of publication. We used the following criteria:

- Blinding of randomisation?
- Blinding of outcome measure assessment?
- Completeness of follow-up?

There are three potential answers to these questions: yes, can't tell, no.

Data extraction and management

Each author extracted data separately using pre-designed data abstraction forms, then compared and resolved differences. One review author (MM) entered data into RevMan ([RevMan 2011](#)) and the others cross-checked the printout against their own data. We resolved disagreements by consensus.

Assessment of risk of bias in included studies

We evaluated the following headings and associated questions (based on the domains in the 'Risk of bias' tool) and entered them into the 'Risk of bias' table.

Selection bias (random sequence generation and allocation concealment)

Adequate sequence generation?

For each included study, we categorised the risk of selection bias as:

- low risk - adequate (any truly random process e.g. random number table; computer random number generator);
- high risk - inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk - no or unclear information provided.

Allocation concealment?

For each included study, we categorised the risk of bias regarding allocation concealment as:

- low risk - adequate (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk - inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk - no or unclear information provided.

Performance bias

For each included study, we categorised the methods used to blind study personnel from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention):

- low risk - adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group);
- high risk - inadequate - personnel aware of group assignment;
- unclear risk - no or unclear information provided.

Detection bias

For each included study, we categorised the methods used to blind outcome assessors from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention). We assessed blinding separately for different outcomes or classes of outcomes. We categorised the methods used with regards to detection bias as:

- low risk - adequate; follow-up was performed with assessors blinded to group;
- high risk - inadequate; assessors at follow-up were aware of group assignment;
- unclear risk - no or unclear information provided.

Attrition bias

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we would

have re-included missing data in the analyses. We categorised the methods with respect to the risk attrition bias as:

- low risk - adequate (< 10% missing data);
- high risk - inadequate (> 10% missing data);
- unclear risk - no or unclear information provided.

Reporting bias

For each included study, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk - adequate (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);
- high risk - inadequate (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk - no or unclear information provided (the study protocol was not available).

Other bias

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk - no concerns of other bias raised;
- high risk - concerns raised about multiple looks at the data with the results made known to the investigators, difference in number of patients enrolled in abstract and final publications of the paper;
- unclear - concerns raised about potential sources of bias that could not be verified by contacting the authors.

Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

The statistical analyses followed the recommendations of the Cochrane Neonatal Review Group. We did not perform subgroup analyses as we could not identify subgroups according to the criteria listed under objectives. We did not perform sensitivity analyses.

We analysed the treatment effects in the individual trial using RevMan 5.1 (RevMan 2011).

Dichotomous data

We reported dichotomous data using risk ratio (RR) and risk difference (RD) with respective 95% confidence intervals (CI). We calculated the number needed to treat to benefit (NNTB) or number needed to treat to harm (NNTH) and respective 95% CIs for those outcomes with a statistically significant RD for the pooled estimate from the meta-analysis.

Continuous data

We reported continuous data using mean difference (MD) with 95% CI. We would have used the standardised mean difference (SMD) to combine trials that measured the same outcome but used different scales.

Unit of analysis issues

The unit of randomisation was the unit of analysis (individual infant). We did not include cross-over or cluster-randomised trials. An infant was considered only once even if the infant may have been randomised twice by the investigators.

Dealing with missing data

Additional data would have been requested from authors of each trial if data on important outcomes were missing or needed clarification. The analysis was by intention-to-treat. Where data had still been missing then we would have examined the reported infants and the effect of losses in sensitivity analysis using a best-worst scenario.

Assessment of heterogeneity

Only one trial was identified and thus tests for heterogeneity were not applicable. If more than one trial had been identified we would have used RevMan 5.1 software to assess heterogeneity of treatment effects between trials (RevMan 2011). We would have used the following two formal statistics described below.

1. The Chi² test, to assess whether observed variability in effect sizes between studies was greater than would be expected by chance. Since this test has low power when the number of studies included in the meta-analysis is small, we planned to set the probability at the 10% level of significance.
2. The I² statistic to ensure that pooling of data was valid. We planned to grade the percentages for heterogeneity as follows: < 25% no heterogeneity, 25% to 49% low, 50% to 74% moderate and 75% or more as a high percentage of heterogeneity (Higgins 2003). Where there was evidence of apparent or statistical heterogeneity, we planned to assess the source of the heterogeneity using sensitivity and subgroup analysis, looking for evidence of bias or methodological differences between trials.

Assessment of reporting biases

We planned to assess reporting and publication bias by examining the degree of asymmetry of a funnel plot in RevMan 5.1, provided that a sufficient number of studies (n = 10) were available (RevMan 2011). As only one trial was identified the use of a funnel plot graph was not applicable.

Data synthesis

We performed statistical analyses according to the recommendations of CNRG (<http://neonatal.cochrane.org/en/index.html>). We analysed all infants randomised on an intention-to-treat basis. We analysed the treatment effects in the one individual trial that we identified. We used a fixed-effect model for meta-analysis in the first instance to combine the data. For estimates of typical RR and RD, we used the Mantel-Haenszel method. We used the inverse variance method for measured quantities.

Subgroup analysis and investigation of heterogeneity

As we only identified one trial there could be no between-study heterogeneity. If we had identified substantial heterogeneity, we would have examined the potential cause of heterogeneity in subgroup and sensitivity analysis. If we had judged meta-analysis to be inappropriate, we planned to analyse and interpret individual trials separately. We performed no subgroup analyses as we could not identify subgroups according to the criteria listed under objectives.

Sensitivity analysis

We performed no sensitivity analyses. We planned to perform a sensitivity analysis if more than one trial was included. We would assess whether our findings were affected by including only studies of adequate methodology, defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and < 10% losses to follow-up.

RESULTS

Description of studies

Three studies assessing the effect of surgical ligation versus medical treatment as a primary treatment for closure of symptomatic PDA in preterm infants were identified (Levitsky 1976; Cotton 1978b; Gersony 1983). All these studies were published as full-text articles. However, the studies by Levitsky et al and Cotton et al were excluded because cyclooxygenase inhibitors were not a part of the medical treatment protocol, which consisted only of fluid restriction and digoxin. The study performed by Gersony 1983 includes a report of two trials, trial A and trial B; trial B was eligible for inclusion in this review. The updated literature searches in July 2007 and February 2012 did not identify any additional studies for inclusion.

In Gersony 1983, 421 preterm infants weighing < 1750 grams with symptomatic PDA were entered to evaluate the role of indomethacin. Randomisation was done at two stages. In stage one (trial A), infants with symptomatic PDA were randomised to either indomethacin or placebo. In addition, both the groups received usual medical management (fluid restriction, diuretics and/or digoxin). In stage two (trial B) infants in the placebo arm of trial A whose PDA remained symptomatic (increased pulse pressure and positive findings on echocardiogram or chest radiograph) and who required significant respiratory support (assisted ventilation for seven or more consecutive days, deteriorating respiratory status or inability to decrease level of respiratory support over a 72-hour period despite maximum medical therapy) were randomised to either surgical closure of PDA or indomethacin treatment. Clinical and echocardiographic criteria were used to diagnose PDA for study entry and to assess the response of treatment

groups. Outcome variables measured included ductal closure rate, mortality before hospital discharge, incidences of adverse conditions during hospitalisation, length of hospital stay and duration of respiratory support. Outcomes for all 421 infants were reported. Trial B included 154 infants (79 randomised to the surgical group and 75 to the indomethacin group). Trial B of this larger study is relevant to this review and hence the outcomes of trial B are reviewed.

Risk of bias in included studies

Gersony 1983 was a multicentre, randomised trial performed at 13 clinical centres in the USA. The assignments in trial A were done by random number generation, within blocks of nine (three indomethacin, six placebo). In trial B assignments were done by random number generation at the co-ordinating centre using sealed envelopes. Physicians were not blinded to the intervention, as surgery was one of the treatments. Follow-up was complete. Intention-to-treat analysis was performed. Blinding of outcome measurements in trial B is not mentioned in the report.

Effects of interventions

Surgical ligation versus medical treatment with indomethacin (comparison 1)

The results of this review are based on trial B by Gersony 1983. All comparisons are between surgery and medical (indomethacin) treatments. No trials comparing surgery to other cyclooxygenase inhibitors (ibuprofen or mefenamic acid) were found. The trial included 154 infants which are included in all the outcomes reported below.

Mortality during hospital stay

There was no statistically significant difference between the two groups (risk ratio (RR) 0.67; 95% confidence interval (CI) 0.34 to 1.31; risk difference (RD) -0.07; 95% CI -0.20 to 0.05) (Analysis 1.1).

Failure of ductal closure

One infant in the surgical group died before surgery. No operated infant in the surgical group had failed ductal closure. In 33% of the infants in the indomethacin group the ductus failed to close and these infants required back-up surgery. There was a statistically significant decrease in failure of ductal closure rate in the surgical group as compared to the indomethacin group (RR 0.04; 95% CI 0.01 to 0.27; RD -0.32; 95% CI -0.43 to -0.21); number needed to treat to benefit (NNT) 3 (95% CI 2 to 4) (Analysis 1.2).

Chronic lung disease (CLD)

There was no statistically significant difference between the two groups (RR 1.28; 95% CI 0.83 to 1.98; RD 0.09; 95% CI -0.06 to 0.24) (Analysis 1.3).

Intraventricular haemorrhage

There was no statistically significant difference between the two groups (RR 0.83; 95% CI 0.32 to 2.18; RD -0.02; 95% CI -0.11 to 0.08) (Analysis 1.4).

Necrotising enterocolitis (NEC)

There was no statistically significant difference between the two groups (RR 0.95; 95% CI 0.29 to 3.15; RD 0.00; 95% CI -0.08 to 0.07) (Analysis 1.5).

Creatinine level > 1.8 mg/dl

There was no statistically significant difference between the two groups (RR 0.57; 95% CI 0.14 to 2.30; RD -0.03; 95% CI -0.10 to 0.04) (Analysis 1.6).

Retinopathy of prematurity (ROP) stage III and IV

There was a statistically significant increase in the surgical group compared to the indomethacin group (RR 3.80; 95% CI 1.12 to 12.93; RD 0.11; 95% CI 0.02 to 0.20); number needed to treat to harm (NNH) 9 (95% CI 5 to 50) (Analysis 1.7).

Pneumothorax

There was a statistically significant increase in the incidence of pneumothorax in the surgical group (RR 2.68; 95% CI 1.45 to 4.93; RD 0.25; 95% CI 0.11 to 0.38); NNH 4 (95% CI 3 to 9) (Analysis 1.8).

Sepsis

There was no statistically significant difference between the two groups (RR 1.14; 95% CI 0.62 to 2.09; RD 0.03; 95% CI -0.10 to 0.16) (Analysis 1.9).

Other bleeding (pulmonary, gastrointestinal tract and disseminated intravascular coagulation)

There was no statistically significant difference between the two groups (RR 1.54; 95% CI 0.68 to 3.51; RD 0.06; 95% CI -0.05 to 0.17) (Analysis 1.10).

Trial B of Gersony 1983 found no significant difference for duration of mechanical ventilation (more than 14 days) or duration of hospital stay (mean days of hospital stay in the surgical group was 94 days and in the indomethacin group was 83 days).

Trial B of Gersony 1983 did not make any comments on the following outcome variables: periventricular leukomalacia (PVL), thrombocytopenia, gastrointestinal perforation, time to reach full enteral feeds and long-term neurodevelopmental outcome.

The preplanned subgroup analyses could not be performed because we were unable to obtain the necessary data from the report.

DISCUSSION

Summary of main results

Only one study, trial B in Gersony 1983, was eligible for inclusion in this review. Updated searches of the literature in July 2007 and February 2012 did not identify any additional studies. The trial of Gersony 1983 compared the effect of surgical ligation of patent ductus arteriosus (PDA) versus medical treatment with indomethacin, each used as the initial treatment after failure of placebo and usual medical management in preterm infants with a symptomatic PDA. This trial found no statistically significant difference in mortality at discharge between the two groups.

Trial B of Gersony 1983 found a statistically significant decrease in the failure of ductal closure rate in the surgical group as compared to the indomethacin group (1% versus 30%). However, it is important to note here that PDAs that closed spontaneously in Trial A (35% in the placebo group) would have been attributed to indomethacin if indomethacin had been the primary treatment.

Thus, the difference in closure rates between the surgery and indomethacin groups observed in Trial B likely underestimates the difference that would have been observed if trial entry had occurred earlier.

Trial B of Gersony 1983 found significantly higher incidences of pneumothorax and retinopathy of prematurity (ROP) of stage III and IV in the surgical ligation group compared to the indomethacin group. The incidence of pneumothorax reported in the study by Gersony et al is higher in both groups as compared to incidences reported in other retrospective and prospective studies. The incidence of pneumothorax reported with surgical closure in other studies varies between 6% to 10% (Cotton 1978b; Palder 1987; Satur 1991; Koehne 2001). The higher incidences of pneumothorax found in the study by Gersony et al may be due to delayed intervention or due to the surgery itself. The surgical technique of PDA ligation is at the discretion of the surgeon and some surgeons perform extrapleural dissection in an effort to avoid the need for an intercostal drain postoperatively (Palder 1987). Others use a transpleural approach, with care to avoid disrupting the visceral pleura and thus avoid the need for an intercostal drain (Miles 1995). Some surgeons use an intrapleural approach to the PDA and routinely insert a chest drain postoperatively (Niinikoski 2001). Gersony et al (Gersony 1983) did not describe the surgical technique in the report, making it difficult to comment on the aetiology of pneumothorax.

Trial B of Gersony 1983 found a significantly higher incidence of ROP of stage III and IV in the surgical ligation group compared to the indomethacin group. The incidence of ROP reported with surgical closure varies between 1% to 10% in other studies (Cotton 1978b; Satur 1991; Koehne 2001). This particular finding had not been noted by other clinicians using indomethacin or surgical closure. No biologically plausible explanation for this association in the study by Gersony et al is apparent.

Trial B of Gersony 1983 found no statistically significant difference in other morbidity variables (chronic lung disease (CLD), necrotising enterocolitis (NEC), other bleeding, sepsis, creatinine clearance, duration of hospital stay, intraventricular haemorrhage (IVH) or duration of mechanical ventilation). The duration of mechanical ventilation and hospital stay were measured from admission to the neonatal intensive care unit (NICU) and not from the day of randomisation in Trial B. The two could be quite different if randomisation in trial B was rather late.

Overall completeness and applicability of evidence

We were surprised at the paucity of trials comparing surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic PDA in preterm infants. There are several possible reasons for this.

- Logistic difficulties associated with randomisation to surgical ligation (parental consent for surgery, possible need for transfer to NICU with surgical care).
- The ease with which the treatment with cyclooxygenase inhibitors can be instituted.
- The most important reason might be that the high success rate of indomethacin therapy prompts treating physicians to use indomethacin as initial treatment for a symptomatic PDA. Gersony 1983 found that even delayed use of indomethacin avoided surgery in 70% of the infants.

Quality of the evidence

Trial B of [Gersony 1983](#) has the following limitations as far as the objectives of this review are concerned.

- The report makes no comments on the postnatal age at which infants were randomised to the indomethacin group or the surgical ligation group. In Trial A one-third of the infants were randomised after 10 days, so the postnatal age at entry to trial B would be greater, perhaps by two to seven or more days. Therefore, interventions in both groups were delayed after the initial diagnosis of symptomatic PDA, as both groups received initial treatment with placebo. This raises the question as to how much the delay in intervention influenced effects on morbidity and mortality.
- The demographic characteristics (birth weight, gestational age and sex) for the infants in the two arms of trial B included in this review were not separately identified.
- The study by [Gersony 1983](#) was performed 30 years ago and the practice of neonatology has changed considerably since then. The surgical techniques have also changed. With better intraoperative thermal protection and safer anaesthetic agents, the mortality associated with surgical ligation of PDA has decreased in the last decade. Therefore, it is debatable whether the results of the study are applicable today.

Potential biases in the review process

We are not aware of any potential biases in our review process.

Agreements and disagreements with other studies or reviews

Three studies addressed the possible association between surgical closure of a PDA and neurosensory impairments, CLD or both ([Chorne 2007](#); [Kabra 2007](#); [Raval 2007](#)). [Kabra et al \(Kabra 2007\)](#) studied 426 infants with a symptomatic PDA, 110 of whom underwent PDA ligation and 316 of whom received medical therapy only. All infants were enrolled in the multicentre Trial of Indomethacin Prophylaxis in Preterms (TIPP) and were observed to a corrected age of 18 months. The adjusted odds ratio (OR) comparing those who survived after PDA ligation ($n = 95$) compared to those who survived after receiving medical therapy only ($n = 245$) for neurosensory impairment was 1.98 (95% confidence interval (CI) 1.18 to 3.30), for CLD was 1.81 (95% CI 1.19 to 3.03) and for severe ROP was 2.20 (95% CI 1.19 to 4.07). [Raval et al \(Raval 2007\)](#) conducted a retrospective review of 197 infants less than 38 weeks of postmenstrual age, undergoing PDA ligation via thoracotomy between 1 January 1992 and 1 January 2004. Only 44 (22%) survived to discharge without CLD (defined as the need for supplemental oxygen at 36 weeks postmenstrual age). In a retrospective cohort study [Chorne et al \(Chorne 2007\)](#) included all infants (< 28 weeks gestation) admitted to the William H. Tooley Nursery at University of California, San Francisco and who were treated according to a PDA care-oriented protocol, which included prophylactic indomethacin. Logistic regression analysis was used to examine the effects of several PDA-related variables (presence of symptomatic PDA, the number of indomethacin doses used, the ductus response to indomethacin, and the use of surgical ligation) on the incidence of ROP, NEC, CLD, death and neurodevelopmental impairment. Most of the predictive effects that the presence of a PDA and its treatment had on neonatal morbidity could be accounted for by the infants' immature gestation. Use of surgical

ligation was significantly associated with the development of CLD (adjusted OR 1.91; 95% CI 1.02 to 3.57) and was independent of immature gestation, other PDA-related variables or other perinatal and neonatal risk factors known to be associated with CLD. The corresponding adjusted OR for ROP was 1.00 (95% CI 0.45 to 2.21), for neurodevelopmental impairment or death was 1.18 (95% CI 0.56 to 2.49) and for NEC was 1.19 (95% CI 0.61 to 2.33). Although the study design was not a randomised controlled trial comparing surgical to medical closure of a PDA, the findings in these three studies suggest an increased risk of one or more of the following outcomes associated with PDA ligation: chronic lung disease, retinopathy of prematurity and neurosensory impairment. It is possible that the duration of the 'waiting time' and transport to another facility with surgical capacity to have the PDA ligated could adversely affect outcomes, as could perioperative care.

[Jhaveri et al \(Jhaveri 2010\)](#) reported that in January 2005 at the Department of Pediatrics, University of California, San Francisco, they changed their approach to infants born at age ≤ 27 weeks gestation who failed indomethacin treatment. They changed from an early surgical approach, in which feedings were stopped and all PDAs were ligated (period 1: January 1999 to December 2004; $n = 216$) to a more conservative approach in which feedings continued and PDAs were ligated only if cardiopulmonary compromise developed (period 2: January 2005 to August 2009; $n = 180$). All infants in both periods received prophylactic indomethacin therapy. The two periods had similar rates of perinatal/neonatal risk factors and indomethacin failure (24%), as well as ventilator management and feeding advance protocols. The conservative approach (period 2) was associated with decreased rates of duct ligation (72% versus 100%; $P < 0.05$). Even though infants subjected to this approach were exposed to larger PDA shunts for longer durations, the rates of CLD, sepsis, ROP, neurologic injury and death were similar to those in period 1. The overall rate of NEC was significantly lower in period 2 compared with period 1. Their findings support the need for randomised controlled trials to re-examine the benefits and risks of different approaches to PDA treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review, which includes data from only one clinical trial, do not allow development of clear guidelines for the initial treatment of symptomatic patent ductus arteriosus (PDA) in preterm infants. The data are insufficient regarding net benefit/harm to make a conclusion as to whether surgical ligation or medical treatment with cyclooxygenase inhibitors is preferable as initial treatment for symptomatic PDA in preterm infants. There are concerns about an increased risk of retinopathy of prematurity (ROP) and chronic lung disease (CLD) following PDA ligation based on the study included in this review. It should be noted that three out of four observational studies indicated an increased risk for one or more of the following outcomes associated with PDA ligation: CLD, ROP and neurosensory impairment. It is possible that the duration of the 'waiting time' and transport to another facility with surgical capacity to have the PDA ligated could adversely affect outcomes, as could the perioperative care.

Implications for research

Future research should be directed toward addressing the question of whether surgical ligation is preferred to indomethacin for closure of a symptomatic PDA in preterm infants. The rationale for the study question includes:

1. lack of randomised controlled trials in this field;
2. some retrospective studies suggesting better outcomes in extremely low birth weight infants with surgical ligation compared to indomethacin therapy (however, three out of four observational studies indicated an increased risk for one or more of the following outcomes associated with PDA ligation: CLD, ROP and neurosensory impairment);

3. morbidity (necrotising enterocolitis, gastrointestinal perforation and renal side effects) and failure of the ductus to close are still concerns associated with indomethacin treatment;
4. closure of PDA remains unpredictable after indomethacin treatment as compared to the definitive effect of surgical ligation.

The important subgroups will be extremely low birth weight infants and infants with a large PDA with a left atrial to aortic ratio of more than 1.5 on echocardiography, because of high failure rate of ductal closure associated with indomethacin treatment in these infants. The study should evaluate short-term outcomes such as death and pulmonary morbidity, as well as clinically significant long-term outcomes such as neurodevelopmental status and CLD.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gersony 1983

Methods	13 centres, randomised controlled trial I. Blinding of randomisation - yes II. Blinding of intervention, trial B - no III. Blinding of outcome measurement(s) trial B - not mentioned in the report IV. Complete follow-up - yes
Participants	Inclusion criteria: 1. Infants with birth weight $\leq$ 1750 grams with haemodynamically significant PDA Exclusion criteria 1. Birth weight $\leq$ 500 grams 2. Congenital anomalies 3. Chromosomal abnormalities 4. Death within the first 24 hours 5. Age more than 14 days on admission to study centre 6. Lack of parental consent for monitoring 7. BUN more than 30 mg/dl 8. Serum creatinine more than 1.8 mg/dl 9. Total urine output less than 0.6 ml/kg/hr 10. Platelet count $<$ 60,000/mm 11. Stool Hematest $>$ or $=$ to 3+ (or moderate to large) 12. Evidence of bleeding diathesis 13. Clinical or noninvasive evidence of intracranial haemorrhage within preceding 7 days Demographic data: values presented as number or percentage Total number of infants entered in trial B = 154 Surgery = 79 Indomethacin = 75 Recruitment period: April 1979 to April 1981
Interventions	79 infants underwent surgical closure for PDA 75 infants received intravenous indomethacin at 12-hour intervals for a total of 3 doses, unless contraindications developed or there was evidence of complete ductal closure. Infants received 0.2 mg/kg of body weight as initial dose and then a second and third dose depending upon infant age at time of entry, 0.1 mg/kg or 0.2 mg/kg or 0.25 mg/kg if less than 2 days or 2 to 7 days or more than 8 days respectively
Outcomes	Ductal closure rates, hospital mortality, duration of respiratory support, length of hospital stay. Incidence of adverse events (CLD, pneumothorax, IVH, NEC, sepsis, other bleeding, creatinine clearance $>$ or $=$ to 1.8, ROP of grade III and IV)

Gersony 1983 (Continued)

A diagnosis of significant PDA was made by clinical criteria (heart rate > 170 bpm, increased pulse pressure, hyperactive precordium, hepatomegaly > 3 cm) and echocardiographic demonstration of left atrial to aortic root ratio of = or > 1.15

Notes

National collaborative study involving 13 centres in USA
Study period: April 1979 to April 1981

Details about surgical procedure were not mentioned.

Postnatal age at which babies were randomised to surgical ligation or indomethacin was not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation at the co-ordinating centre
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing each assignment
Blinding (performance bias and detection bias) All outcomes	High risk	The intervention (surgery) could not be blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	As the participants were neonates, they would be blinded but personnel could not be blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Could not be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	The study was not registered in a trials registry and we cannot ascertain whether there were deviations between the study protocol and the study report
Other bias	Low risk	The study appears free of other bias

bpm = beats per minute
BUN = blood urea nitrogen
CLD = chronic lung disease
IVH = intraventricular haemorrhage
NEC = necrotising enterocolitis
PDA = patent ductus arteriosus
ROP = retinopathy of prematurity

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cotton 1978a	The study compared medical management versus surgical closure as primary treatment for symptomatic PDA in preterm infants, however the study did not use cyclooxygenase inhibitors in the medical management protocol
Levitsky 1976	The study compared medical management versus surgical closure as primary treatment for symptomatic PDA in preterm infants, however the study did not use cyclooxygenase inhibitors in the medical management protocol

PDA = patent ductus arteriosus

DATA AND ANALYSES

Comparison 1. Surgical versus medical treatment with indomethacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death before discharge	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.31]
2 Failure of ductal closure	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.27]
3 Chronic lung disease	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.83, 1.98]
4 Intraventricular haemorrhage	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.32, 2.18]
5 NEC	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.29, 3.15]
6 Creatinine level > 1.8 mg/dl	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.14, 2.30]
7 ROP grade III and IV	1	154	Risk Ratio (M-H, Fixed, 95% CI)	3.80 [1.12, 12.93]
8 Pneumothorax	1	154	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.45, 4.93]
9 Sepsis	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.62, 2.09]
10 Other bleeding	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.68, 3.51]

Analysis 1.1. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 1 Death before discharge.

Analysis 1.2. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 2 Failure of ductal closure.

Analysis 1.3. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 3 Chronic lung disease.

Analysis 1.4. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 4 Intraventricular haemorrhage.

Analysis 1.5. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 5 NEC.

Analysis 1.6. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 6 Creatinine level > 1.8 mg/dl.

Analysis 1.7. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 7 ROP grade III and IV.

Analysis 1.8. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 8 Pneumothorax.

Analysis 1.9. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 9 Sepsis.

Analysis 1.10. Comparison 1 Surgical versus medical treatment with indomethacin, Outcome 10 Other bleeding.

WHAT'S NEW

Date	Event	Description
27 January 2020	Amended	Arne Ohlsson deceased.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 3, 2003

Date	Event	Description
19 July 2012	New search has been performed	<p>This updates the review 'Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants' (Malviya 2008).</p> <p>This review was updated in March 2012. New searches of the literature in February 2012 did not identify any new trials.</p>
8 February 2012	New citation required but conclusions have not changed	Conclusions were not changed. One additional observational study found a decreased risk of necrotising enterocolitis following a conservative approach to surgical ligation.

Date	Event	Description
11 June 2008	Amended	Converted to new review format.
27 October 2007	New search has been performed	<p>This updates the previously published review 'Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants' published in <i>The Cochrane Library</i> 2003, Issue 3 (Malviya 2003).</p> <p>A repeat search of the literature in July 2007 did not identify any new trials for inclusion.</p> <p>The conclusions remain the same. However, it should be noted that three recent observational studies indicated an increased risk for one or more of the following outcomes associated with PDA ligation: chronic lung disease, retinopathy of prematurity and neurosensory impairment. It is possible that the duration of the 'waiting time' and transport to another facility with the surgical capacity to have the PDA ligated could adversely affect outcomes, as could the perioperative care.</p>
27 October 2007	New citation required but conclusions have not changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

MM, AO and SS contributed to all stages of the review.
The update of this review in 2008 was undertaken by AO.

The current update in 2012 was conducted by the three authors. All three authors screened all the literature searches for eligible trials and AO updated the text of the review.

DECLARATIONS OF INTEREST

None.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Cyclooxygenase Inhibitors [*therapeutic use]; Ductus Arteriosus, Patent [*drug therapy] [*surgery]; Indomethacin [therapeutic use]; Infant, Premature; Infant, Very Low Birth Weight; Ligation; Pneumothorax [etiology]; Postoperative Complications; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn