

Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants (Review)

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ABSTRACT

Background

Patent ductus arteriosus (PDA) is associated with increased mortality and morbidity in preterm infants. Prophylactic indomethacin results in favorable intermediate outcomes such as reduction of significant PDA, need for surgical ligation, severe intraventricular hemorrhage and serious pulmonary hemorrhage without modifying long-term neurosensory outcomes. Little is known about the effectiveness and safety of prophylactic surgical closure of the PDA in extremely low birth weight (ELBW) infants.

Objectives

To identify and summarize evidence from randomized controlled trials investigating the effectiveness and safety of prophylactic surgical ligation of the PDA on mortality and morbidities of preterm infants less than 1000 g at birth as compared to no prophylaxis or prophylactic cyclooxygenase inhibitors.

Search strategy

The standard search strategy for the Cochrane Neonatal Review Group was performed by two review authors. Searches were made of MEDLINE (1966 to December 2006), EMBASE (1980 to December 2006), the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2006), and abstracts of annual meetings of the Society for Pediatric Research (1995 - 2006). Contacts were made with the authors of published articles.

Selection criteria

Randomized or quasi-randomized controlled trials that enrolled infants less than 28 weeks gestation or less than 1000 g at birth who are on assisted ventilation and/or supplemental oxygen without clinical signs of hemodynamic significance of the ductus arteriosus were considered. Trials addressing prophylactic surgical ligation of the patent ductus arteriosus (i.e. procedure done during the first 72 hours of life) versus no intervention or cyclooxygenase inhibitor prophylaxis were included. The primary outcome was bronchopulmonary dysplasia (BPD). Other important short and long-term neonatal outcomes were also considered.

Data collection and analysis

Standard methods of the Cochrane Collaboration and its Neonatal Review Group were used to assess the methodologic quality of the trials. Retrieved articles were assessed for eligibility and data was abstracted independently by two reviewer authors. Where data were incomplete, the primary investigators were contacted for further information and clarifications. For dichotomous outcomes, relative risk (RR) and its associated confidence interval were calculated. For continuous outcomes, treatment effect was expressed as mean difference and its calculated standard deviation. When appropriate, meta-analysis of pooled data was performed assuming a fixed effect model.

Main results

Only one eligible study that enrolled 84 ELBW infants was identified. The prophylactic group had ductal ligation performed within 24 hours of life following a pre-specified protocol, while the control group received standard care without indomethacin. Prophylactic

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surgical ligation of the PDA resulted in a statistically significant reduction of severe stage II or III necrotizing enterocolitis (NEC), [RR 0.25, 95% CI (0.08,0.83), p value 0.02, NNT 5]. The study found no statistically significant difference in mortality, severe grade III and IV intraventricular hemorrhage (IVH), BPD, and retinopathy of prematurity (ROP). Of note, the study was unblinded and underpowered to detect clinically important differences in the above mentioned outcomes.

Authors' conclusions

Prophylactic surgical ligation of the PDA did not decrease mortality or BPD in ELBW infants. A significant reduction of stage II or III NEC was noted. Based on the current evidence, the high rate of spontaneous closure, availability of effective safe medical therapies, and the potential short and long-term complications of surgical ligation, the use such prophylactic surgical therapy is not indicated in the management of the preterm infants.

PLAIN LANGUAGE SUMMARY

Pending

BACKGROUND

Patent ductus arteriosus (PDA) is the most common cardiac condition among preterm infants. It affects approximately 40 - 55% of preterm infants born at less than 29 weeks gestation and/or weighing under 1500 g at birth (Reller 1993; Trus 1993; Mouzinho 1991). In spite of significant advances in neonatal care over the last two decades, the approach to PDA management remains one of the most controversial topics in neonatal medicine.

PDA remains hemodynamically significant in preterm infants for a variety of reasons including decreased ductal sensitivity to the partial pressure of oxygen, increased circulating prostaglandin E₂, and increased ductal tissue sensitivity to prostaglandin E₂ and nitric oxide (Clyman 2000; Clyman 1998; Clyman 1990; Brook 1995). A hemodynamically significant PDA is associated with left to right shunting of systemic blood with subsequent pulmonary overcirculation and a diastolic steal that results in hypoperfusion of vital organs. In very low birth weight (VLBW) infants, symptomatic PDA increases the risk of prolonged ventilation and oxygen requirements, pulmonary hemorrhage (Kluckow 2000), and bronchopulmonary dysplasia (BPD) (Rojas 1995; Brown 1979; Bancalari 2003). The diastolic steal is associated with renal hypoperfusion (Hammerman 1995), intestinal ischemia, necrotizing enterocolitis (NEC), reduced middle cerebral artery blood flow velocity (Martin 1982; Nestrud 1980; Shimada 1994; Weir 1999), and decreased superior vena cava (SVC) flow with concurrent increased risk of intraventricular hemorrhage (IVH) (Duddell 1984; Osborn 2003). If not managed appropriately, complications of symptomatic PDA may lead to death (Cotton 1979).

The increased number of surviving preterm infants has led to a higher number of infants requiring medical or surgical intervention for the PDA. Standard therapies include fluid restriction and use of cyclooxygenase inhibitors such as indomethacin or ibuprofen. Surgical ligation is used when medical treatment fails or is

contraindicated (Clyman 1996; Kitterman 1972; Wagner 1984). There is no consensus as to what is the best time of treatment and the optimal management strategy among this high-risk vulnerable population.

Prophylactic indomethacin has been shown to have favorable intermediate outcomes, such as reductions in the risk of significant PDA, the need for surgical ligation, severe intraventricular hemorrhage (Schmidt 2001; Fowle 2002), and pulmonary hemorrhage (AlFaleh 2004). Prophylactic indomethacin has not been shown to alter long-term outcomes including the rate of survival without neurosensory impairment at 18 months of corrected age (Schmidt 2001). Given the limitation of medical treatment, prophylactic surgical closure of the PDA may be a reasonable alternative in a high-risk population, since it results in ultimate ductal closure and, therefore, might prevent associated neonatal morbidities.

Routine surgical ligation of a PDA refractory to medical treatment is widely practiced (Palder 1987; Pokharel 1998; Satur 1991; Chen 1999). However, there is no clear evidence that surgical ligation of a hemodynamically significant PDA is associated with improved long-term outcomes in preterm infants. Furthermore, surgery may potentially result in significant morbidities such as pneumothorax, hypothermia, intra-operative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy and thoracic scoliosis. On the other hand, there are reports suggesting that surgical ligation may be the preferred first line of treatment when compared to indomethacin in preterm infants less than 800 g (Palder 1987; Trus 1993). Even though there may be a general consensus with respect to the use of indomethacin as the initial therapy for a symptomatic PDA while reserving surgical ligation for indomethacin failures, this therapeutic approach may not represent the optimal management of PDA in extremely low birth weight infants (ELBW), the population at greatest risk for PDA (Malviya 2003).

OBJECTIVES

The primary objective of this systematic review was to identify and summarize evidence from randomized controlled trials investigating the effectiveness and safety of prophylactic surgical ligation of the PDA on mortality and morbidities in preterm infants less than 1000 g at birth as compared to no prophylaxis or to the use of prophylactic cyclooxygenase inhibitors. The secondary objective was to investigate the role of prophylactic ligation in a subgroup of high-risk infants < 750 g at birth.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomized and quasi-randomized controlled trials were included.

Types of participants

Infants < 28 weeks gestation or less than 1000 g at birth who were on assisted ventilation and/or supplemental oxygen without clinical signs of a hemodynamically significant PDA.

Types of intervention

Prophylactic surgical ligation of the patent ductus arteriosus (i.e. procedure done during the first 72 hours of life in asymptomatic ELBW infants) versus no prophylactic intervention or medical prophylaxis (cyclooxygenase inhibitors) without dose specification.

Types of outcome measures

Primary outcomes:

- All cause neonatal mortality at 36 weeks postmenstrual age
- Bronchopulmonary dysplasia (BPD) defined as oxygen requirement at 36 weeks postmenstrual age

Secondary outcomes

1. a) any intraventricular hemorrhage (IVH); b) severe grade III, IV IVH as per Papile criteria (Papile 1978)
2. Severe NEC (stage II or more) as per Bell's criteria (Bell 1978)
3. Periventricular leukomalacia (PVL) defined as cystic changes in the periventricular area
4. a) Retinopathy of prematurity (ROP) (defined by ICORP classification: any ROP and severe ROP stage 3 or worse); b) any ROP
5. Nosocomial sepsis, defined as positive bacterial blood or cerebrospinal fluid cultures taken beyond five days of age
6. Time to establish full enteral feeds (days)
7. Duration of ventilation and supplemental oxygen (days)
8. Duration of hospital stay (days)
9. Neurodevelopmental impairment i.e. rates of cerebral palsy, cognitive delay defined as a Mental Development Index score of

- less than 70 (2 SD below the mean of 100) on the Bayley Scales of Infant Development II (Bayley 1993), deafness, blindness or their composite reported at 18 months corrected age or later
10. Pneumothorax
11. Vocal cord palsy

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Neonatal Group methods used in reviews.

The standard search strategy for the Cochrane Neonatal Review Group was used. Randomized and quasi-randomized controlled trials that evaluated prophylactic surgical ductal closure in the management of premature infants were identified from OVID MEDLINE-National Library of Medicine (1966 to December 2006) using the following subject headings (MeSH) and text word terms: "neonate(s), newborn(s), infant(s), patent ductus arteriosus or PDA, ligation, indomethacin, ibuprofen, cyclooxygenase inhibitors and publication type 'controlled trial'". No language restrictions were applied.

Other databases were searched including: EMBASE (1980 to December 2006), The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2006). Two review authors performed the electronic database search independently. A manual search of the abstract books published from the Society of Pediatric Research (SPR) and the European Society of Pediatric Research (ESPR) for the period of 1985 - 2006 was performed. Additional citations were sought using references in articles retrieved from searches. Subject experts were contacted to identify the unpublished and ongoing studies. Authors of the published trials were contacted to clarify or provide additional information. Two review authors independently screened candidate articles to check the eligibility for inclusion in the review.

METHODS OF THE REVIEW

Study Quality and Data extraction

Standard methods of the Cochrane Collaboration and its Neonatal Group were used to assess the methodological quality (validity criteria) of the trials. For each trial, information was sought regarding the method of randomization, blinding and reporting of all outcomes of all the infants enrolled in the trial. Each criteria was assessed as yes, no, can't tell. Retrieved articles were assessed for eligibility and data abstracted independently by two review authors. Discrepancies were resolved by discussion and consensus. Where data were incomplete, the primary investigator was contacted for further information and clarifications.

Data Analysis

For dichotomous outcomes, relative risk (RR) and its associated confidence interval were calculated. For continuous outcomes, treatment effect was expressed as mean difference and its calculated standard deviation. If appropriate, meta-analysis of pooled data was performed assuming a fixed effect model. Review Manager 4.2.8 software was used for statistical analysis.

The review includes two comparisons:

1. Prophylactic surgical ligation vs. no prophylactic treatment
2. Prophylactic surgical ligation vs. prophylactic cyclooxygenase inhibitors.

If possible, a sensitivity analysis was planned to assess the effect of trials methodological quality on results of the meta-analysis.

In addition, subgroup analyses were planned to investigate the effect of prophylactic surgical ligation of the ductus in high risk infants < 750 grams, to investigate the effect of timing of surgical prophylaxis (i.e. < 24 hr vs. > 24 hr after birth).

Heterogeneity was examined using the I-squared test. Potential sources of heterogeneity might include differences in the timing of surgical ligation or use of cyclooxygenase inhibitors in the second arm of the study, the population under study, and study quality.

DESCRIPTION OF STUDIES

Initial electronic search using OVID MEDLINE and EMBASE yielded 106 MEDLINE and 86 EMBASE potentially relevant citations. After reading abstracts, two articles were identified as potentially relevant. Review of full text articles identified one study (Cassady 1989) investigating the use of prophylactic PDA surgical ligation in preterm infants. Only one study (Cotton 1978) was excluded for reasons outlined in the Table of Excluded Studies. There was total agreement among both review authors with regard to the search process. Details of the included study is shown in the table "Characteristics of Included Studies".

Cassady 1989 was a single center randomized controlled trial. Eighty-four preterm infants less than 1000 g were enrolled in both study arms. The surgical intervention group (n = 40) had a PDA ligation within 24 hours of life following a pre-specified protocol while the control group (n = 44) received standard care defined as: 1) nasal CPAP initially for hypoxemia due to RDS or pulmonary edema 2) endotracheal intubation and ventilation for respiratory failure (PCo₂ > 70) or refractory apnea 3) bedside Echo and radionuclide studies routinely performed to detect "silent" ducts

Ligation was performed for hemodynamically significant ducts based on predefined criteria. Neither group received any cyclooxygenase inhibitor during or before the study period. Infants with echo defined criteria or hemodynamically significant PDA underwent subsequent surgical ligation. The main outcome mea-

asures were survival to one year after birth, NEC (Bell's stage III, IV), IVH defined by cranial ultrasound, BPD and ROP. Long-term neurosensory outcomes were not assessed. The study was suspended after 14 months since only few physicians were available to conduct the study properly.

METHODOLOGICAL QUALITY

Details of the included study are presented in the "Characteristics of Included Studies" table. The methodologic details of the study were extracted from the published data.

Cassady et al (Cassady 1989) was a single center study. Two groups of 84 infants were randomized to receive either early prophylactic surgical PDA ligation (within 24 hours of birth) or control (no intervention). Randomization was possibly adequate and allocation was adequately concealed. The intervention was not blinded. Measurement of outcomes was blinded for NEC and BPD. Blinding of other outcomes was not clear. All randomized infants were accounted for in the analysis. Of note, the sample size of this study was calculated to detect a large difference of 50%, which rendered the study underpowered to detect smaller meaningful clinical differences among the study groups.

RESULTS

PROPHYLACTIC SURGICAL DUCTAL LIGATION VS. CONTROL (Comparison 01):

Results of outcomes presented in Cassady 1989 study are summarized in the analysis part of this review.

Death

The prespecified outcome of all cause neonatal mortality at 36 weeks postmenstrual age was not presented in the study. The author presented data with regard to death within 28 days of birth and within one year of life. These results are described below.

Death within 28 days of birth (Outcome 01.01):

16/40 infants died within 28 days of life in the treatment group as compared 20/44 in the control group [RR 0.88, 95% CI (0.53, 1.45), p value 0.62].

Death to one year of age (Outcome 01.02):

A total of 25/40 infants died within one year of age in the treatment group as compared to 26/44 in the control group [RR 1.06, 95% CI 0.75, 1.49), p value 0.75].

Severe grade III, IV Intraventricular Hemorrhage (Outcome 01.03):

16/35 infants in the prophylactic ductal ligation group developed grade III or IVH as compared to 23/41 in the control group [RR 0.81, 95% CI (0.52, 1.28), p value 0.37]. Data with regard to all grades of IVH were not presented in the published manuscript.

Severe NEC (Outcome 01.04):

The assessment of this outcome was blinded. Only 3/40 infants in the prophylactic ductal ligation group developed severe stage III or IV NEC as compared to 13/44 in the control group [RR 0.25, 95% CI (0.08,0.83), p value 0.02, NNT 5].

Bronchopulmonary Dysplasia (Outcome 01.05):

The definition used for BPD was different from the pre-specified definition (i.e. oxygen requirement at 36 weeks postmenstrual age). In Cassady 1989, BPD was defined using the criteria of Bancalari et al (histologic finding or radiographic criteria). 15/24 infants in the prophylactic ligation group developed BPD as compared to 14/24 in the control group [RR 1.07, 95% CI (0.68, 1.69), p value 0.77].

Retinopathy of Prematurity (Outcome 01.06):

The criteria and method of measurement of this outcome was not specified in the manuscript. 7/22 infants in the prophylactic group developed ROP as compared to 10/21 in the control group [RR 0.67, 95% CI (0.31, 1.43), p value 0.30]. Out of these, only one infant had severe stage III or IV ROP in the prophylactic ligation group as compared to 3 in the control group [RR 0.32, 95% CI (0.04, 2.8), p value 0.30].

Subgroup analysis:

The secondary objective of this review was to investigate the role of prophylactic surgical ligation in a subgroup of high risk infants <750 g at birth. No data was found in the included trial that relates specifically to this high-risk group.

Data with regard to nosocomial sepsis, hospital stay, pneumothorax, vocal cord palsy, periventricular leucomalacia, and long term neurosensory impairment were not presented in this study.

DISCUSSION

Only one study (Cassady 1989) that compared the effect of early prophylactic PDA ligation in extreme low birth weight infants versus later or no intervention was eligible for inclusion in this review. Prophylactic surgical ligation of the duct resulted in no significant differences in mortality, IVH, BPD and ROP between the two study groups. Interestingly, the study was able to show a significant reduction of severe NEC in the prophylactic surgical group as compared to infants who received selective treatment for hemodynamically significant PDA (20% vs. 79%). While it is possible this is a result of a true effect, it is important to note that feeds were introduced earlier in the control group. Strong conclusions can not be made since the study is underpowered to detect minimally important clinical differences in outcomes other than NEC.

Ligation of the ductus arteriosus is not without risks and it is often associated with significant hypotension and postoperative cardiorespiratory instability secondary to cardiovascular physiologic

adaptation. There is limited information on the ability of preterm infants to compensate for the dramatic changes in left ventricular afterload following ligation (Teixeira 2006). Surgical ligation also poses risks of potential morbidity from infection, pneumothorax, chylothorax and vocal cord paralysis. Surgical ligation may not be easily accessible to all centers. In addition, evidence is accumulating regarding PDA ligation and its association with a higher incidence of BPD, ROP and unfavorable neurodevelopmental outcomes (Kabra 2007).

Since the publication of the included trial, the practice of neonatal medicine has advanced significantly. Over the last 16 years, many trials were published addressing the efficacy of prophylactic cyclooxygenase inhibitors (i.e. indomethacin and ibuprofen) in reducing the incidence of PDA and other short and long-term morbidities in ELBW infants. The use of prophylactic indomethacin reduces the incidence of PDA by more than 50%, surgical ligation of the duct by 50% and severe grade III and IV IVH by 35% with no apparent adverse effect in long-term neurosensory outcomes (Fowlie 2002). With the high rate of spontaneous closure, availability of effective safe medical therapies, potential short and long-term complications of prophylactic surgical ligation (Kabra 2007), and the recent doubts raised concerning the need to close all significant PDA's in preterm infants (Laughon 2004, Laughon 2007), there is no obvious role for prophylactic surgical ligation in the management of preterm infants.

Current evidence demonstrates that prophylactic indomethacin given to preterm infants reduces the incidence of symptomatic PDA, severe IVH, and serious pulmonary hemorrhage (Schmidt 2001; Fowlie 2002; AlFaleh 2004). Despite the reduction of the aforementioned morbidities (all of which are associated with poor long-term outcome), no improvements in long-term neurosensory outcome was noted. Giving indomethacin to unselected group of infants, irrespective of the ductal size, is a possible explanation (Osborn DA 2003). It has been suggested that future studies aimed at preventing IVH and improving neurodevelopmental outcome using medical agents to close the PDA should be directed at infants with large, hemodynamically significant PDA in the first hours of life (Osborn DA 2003).

The conclusions of our review are weakened by the inclusion of only one, small trial that addressed the intervention under study.

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic surgical ligation of the PDA did not decrease mortality or the incidence of BPD in ELBW infants. A significant reduction in the incidence of stage II or III NEC was noted. Based on the current evidence, the high rate of spontaneous closure, availability of effective and safe medical therapies, and the potential short and

long-term complications of surgical ligation, the use such prophylactic surgical therapy is not indicated in the management of the preterm infants.

Implications for research

A well-powered large randomized controlled trial to investigate early targeted prophylactic use of cyclooxygenase inhibitors (within first 24 hours of life and based on echocardiographic criteria) in reducing neonatal morbidities and long-term neurosensory outcomes in ELBW infants is indicated.

POTENTIAL CONFLICT OF INTEREST

None

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TABLES

Characteristics of included studies

Study	Cassady 1989
Methods	Randomized controlled un-blinded study Method of generating randomization sequence: Modified, balanced randomization technique Allocation concealment: Adequate Blinding of Intervention: No Blinding of outcome measurement: Yes for NEC and BPD Complete Follow-up: Yes
Participants	84 infants, weighed 1000 g or less at birth Exclusion criteria: Lethal anomalies, failure to be randomized within 24 hours of birth and judged to be moribund by medical staff. Demographic data: Intervention group : n=40, gestational age (weeks) 27(1.8), birth weight (g) 800 (126.3) Control group n=44, gestational age (weeks) 28(1.5), birth weight (g) 795 (97.7)
Interventions	Surgical group (n=40) had ligation within 24 hours of birth following designed protocol Control group (n=44) received standard care defined as 1) Initial NCPAP for hypoxemia due to RDS or pulmonary edema 2) Endotracheal intubation and ventilation for respiratory failure or refractory apnea 3) Echo and radionuclide studies routinely performed to detect silent ducts. Ligation was performed hemodynamically significant ducts based on a predefined criteria; Both groups received no indomethacin during or before the study period. Infants with echo defined criteria or hemodynamically significant PDA underwent subsequent surgical ligation.

Outcomes	Survival to one year after birth NEC, stage III, IV IVH defined by HUS BPD ROP
Notes	USA Period of study: Oct 1980- Oct 1981 suspended for 14 months Jan 1983- May 1986 (four years and four months) Published: 1989 Source of Funding: not specified in paper
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Cotton 1978	Surgery was done after 1 week of birth for infants needing ventilation or Oxygen supplementation. Therefore, the intervention was not prophylactic.

ANALYSES

Comparison 01. Prophylactic ductal ligation vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death within 28 days of birth	1	84	Relative Risk (Fixed) 95% CI	0.88 [0.53, 1.45]
02 Death till one year of age	1	84	Relative Risk (Fixed) 95% CI	1.06 [0.75, 1.49]
03 Severe grade III and IV IVH	1	76	Relative Risk (Fixed) 95% CI	0.81 [0.52, 1.28]
04 Severe NEC	1	84	Relative Risk (Fixed) 95% CI	0.25 [0.08, 0.83]
05 Bronchopulmonary dysplasia	1	48	Relative Risk (Fixed) 95% CI	1.07 [0.68, 1.69]
06 Retinopathy of prematurity			Relative Risk (Fixed) 95% CI	Subtotals only

COVER SHEET

Title	Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants
Authors	Mosalli R, AlFaleh K
Contribution of author(s)	In joint meetings, both review authors searched the literature, stated the objectives of the review and wrote the text of the protocol and review.
Issue protocol first published	2006/4
Review first published	2008/1
Date of most recent amendment	14 November 2007
Date of most recent SUBSTANTIVE amendment	31 August 2007

What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Rafat Mosalli Neonatal Fellow Pediatrics, Division of Neonatology McMaster University Medical Centre 1200 Main Street West Hamilton Ontario L8N 3Z5 CANADA E-mail: rafatmosali@hotmail.com Tel: 905 5222100 75612 Fax: 9053044521
DOI	10.1002/14651858.CD006181.pub2
Cochrane Library number	CD006181
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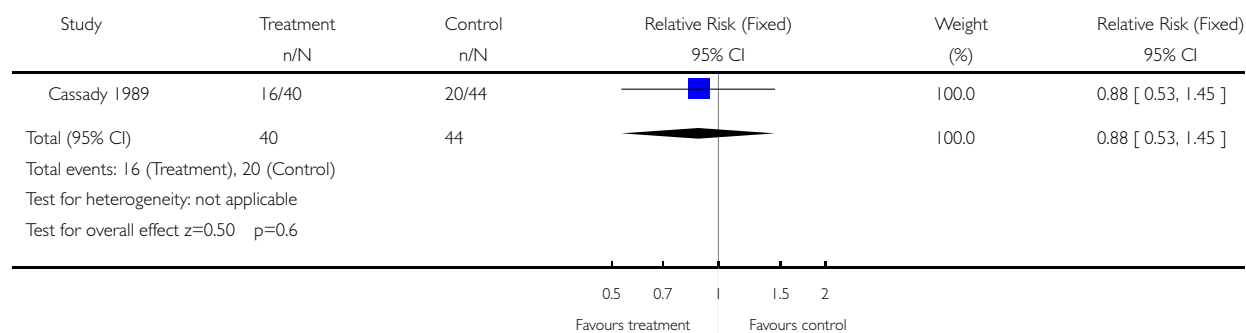
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Prophylactic ductal ligation vs. control, Outcome 01 Death within 28 days of birth

Review: Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants

Comparison: 01 Prophylactic ductal ligation vs. control

Outcome: 01 Death within 28 days of birth

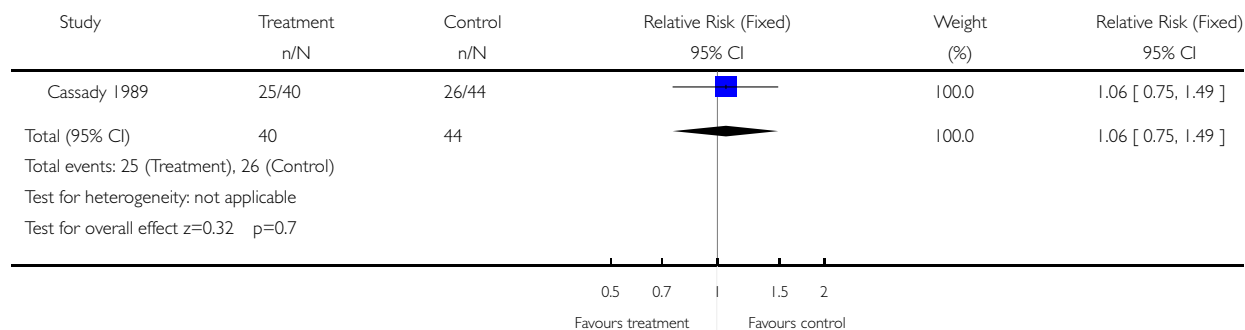


Analysis 01.02. Comparison 01 Prophylactic ductal ligation vs. control, Outcome 02 Death till one year of age

Review: Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants

Comparison: 01 Prophylactic ductal ligation vs. control

Outcome: 02 Death till one year of age

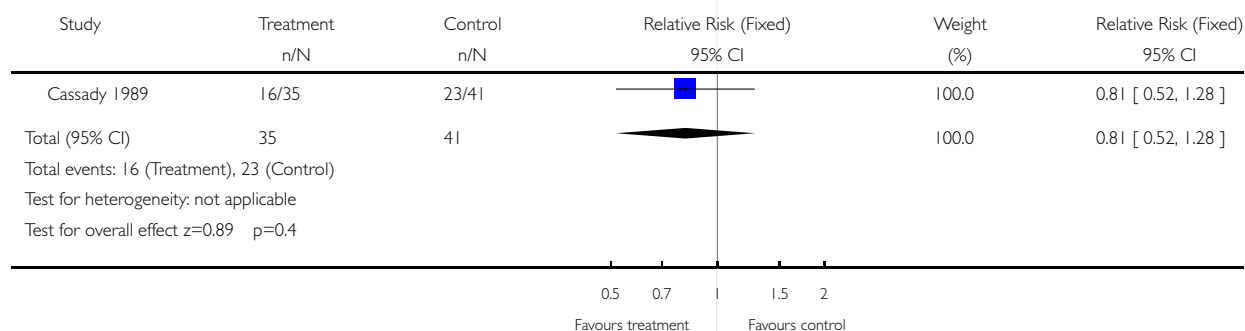


Analysis 01.03. Comparison 01 Prophylactic ductal ligation vs. control, Outcome 03 Severe grade III and IV IVH

Review: Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants

Comparison: 01 Prophylactic ductal ligation vs. control

Outcome: 03 Severe grade III and IV IVH

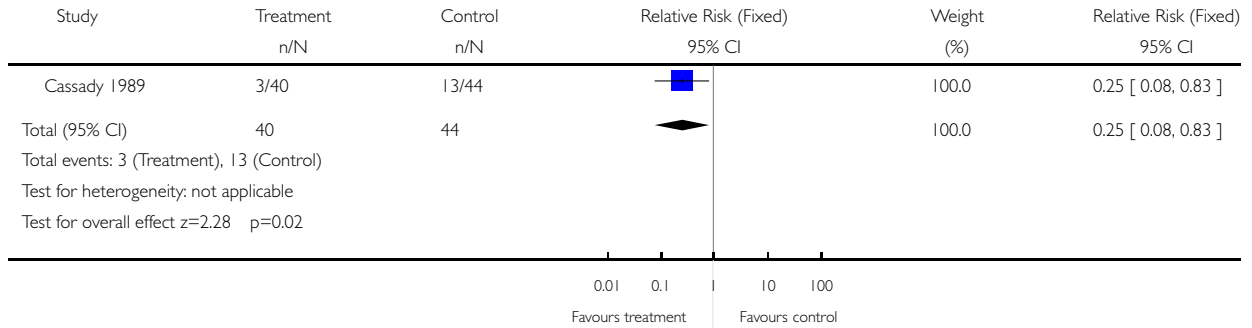


Analysis 01.04. Comparison 01 Prophylactic ductal ligation vs. control, Outcome 04 Severe NEC

Review: Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants

Comparison: 01 Prophylactic ductal ligation vs. control

Outcome: 04 Severe NEC

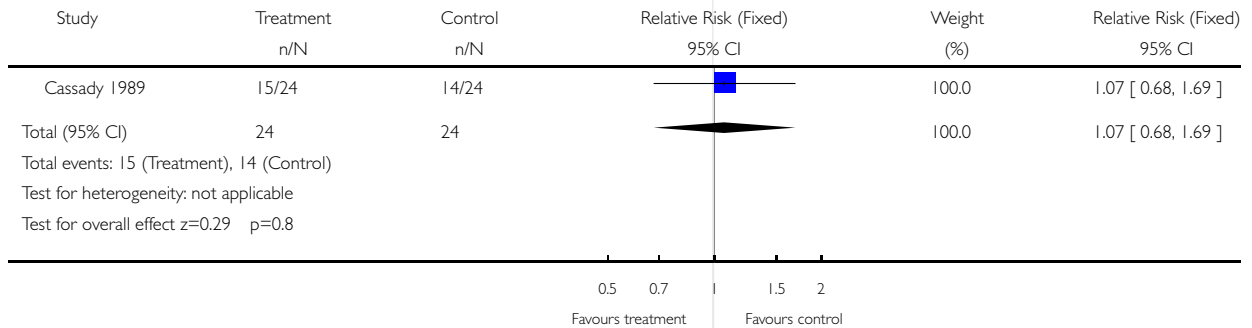


Analysis 01.05. Comparison 01 Prophylactic ductal ligation vs. control, Outcome 05 Bronchopulmonary dysplasia

Review: Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants

Comparison: 01 Prophylactic ductal ligation vs. control

Outcome: 05 Bronchopulmonary dysplasia



Analysis 01.06. Comparison 01 Prophylactic ductal ligation vs. control, Outcome 06 Retinopathy of prematurity

Review: Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants

Comparison: 01 Prophylactic ductal ligation vs. control

Outcome: 06 Retinopathy of prematurity

