BACKGROUND AND OBJECTIVE: Patent ductus arteriosus (PDA) ligation has been variably associated with neonatal morbidities and neurodevelopmental impairment (NDI). The objective was to systematically review and meta-analyze the impact of PDA ligation in preterm infants at <32 weeks' gestation on the risk of mortality, severe neonatal morbidities, and NDI in early childhood.

METHODS: Medline, Embase, Cochrane Central Register of Controlled Trials, Education Resources Information Centre (ERIC), Cumulative Index to Nursing and Allied Health (CINAHL), PsycINFO, and the Dissertation database were searched (1947 through August 2013). Risk of bias was assessed by using the Newcastle-Ottawa Scale and the Cochrane Risk of Bias tool. Meta-analyses were performed by using a random-effects model. Unadjusted and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were pooled when appropriate.

RESULTS: Thirty-nine cohort studies and 1 randomized controlled trial were included. Nearly all cohort studies had at least moderate risk of bias mainly due to failure to adjust for survival bias and important postnatal preligation confounders such as ventilator dependence, intraventricular hemorrhage, and sepsis. Compared with medical treatment, surgical ligation was associated with increases in NDI (aOR: 1.54; 95% CI: 1.01–2.33), chronic lung disease (aOR: 2.51; 95% CI: 1.98–3.18), and severe retinopathy of prematurity (aOR: 2.23; 95% CI: 1.62–3.08) but with a reduction in mortality (aOR: 0.54; 95% CI: 0.38–0.77). There was no difference in the composite outcome of death or NDI in early childhood (aOR: 0.95; 95% CI: 0.58–1.57).

CONCLUSIONS: Surgical ligation of PDA is associated with reduced mortality, but surviving infants are at increased risk of NDI. However, there is a lack of studies addressing survival bias and confounding by indication. Pediatrics 2014;133:e1024–e1046

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KEY WORDS: patent ductus arteriosus, neurodevelopmental impairment, death, chronic lung disease, retinopathy of prematurity, cerebral palsy, cognitive impairment, mortality

ABBREVIATIONS: aOR—adjusted odds ratio CI—confidence interval CLD—chronic lung disease GA—gestational age IVH—intraventricular hemorrhage NDI—neurodevelopmental impairment NEC—necrotizing enterocolitis NSAID—nonsteroidal antiinflammatory drug PDA—patent ductus arteriosus RCT—randomized controlled trial ROP—retinopathy of prematurity VCP—vocal cord paresis

Dr Weisz conceptualized and designed the study, acquired and interpreted the data, drafted the initial manuscript, and revised the manuscript; Dr More revised the protocol, acquired and interpreted the data, and revised the manuscript; Dr McNamara revised the protocol, interpreted the data, and revised the manuscript; Dr Shah conceptualized and designed the study, revised the protocol, interpreted the data, and revised the manuscript; and all authors approved the final manuscript.

This systematic review has been registered with PROSPERO (international database of prospectively registered systematic reviews) (identifier CRD42013005390).

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Patent ductus arteriosus (PDA) occurs in nearly 50% of preterm infants born at <32 weeks’ gestation. The PDA shunts blood away from the descending aorta into the pulmonary artery, resulting in systemic hypoperfusion and pulmonary overcirculation. It is considered a significant precursor to mortality and morbidity in extremely preterm neonates, including congestive heart failure, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), prolonged ventilator dependency, and chronic lung disease (CLD). Methods to close or minimize the effects of a clinically significant PDA include conservative management (eg, fluid restriction, diuretics, ventilation strategies), cyclooxygenase inhibitors (eg, indomethacin or ibuprofen), acetaminophen, or surgical ligation. Surgical ligation is usually only considered when medical treatment has either failed or was contraindicated. Several investigators have studied PDA ligation and its association with neonatal mortality, short-term morbidity, and neurodevelopmental impairment (NDI) in early childhood. Mirea et al found increased retinopathy of prematurity (ROP) and CLD in infants treated with ligation compared with non–surgically treated infants. Two large studies found that extremely preterm infants who were treated with surgical ligation had significantly higher odds of NDI at 2-year follow-up, although a third study showed no increased risk. In light of these concerns and somewhat conflicting results, the merits and safety of ligation have been questioned, with increasing uncertainty about appropriate patient selection and the optimal timing for surgery to minimize morbidity. This uncertainty has been associated with a secular trend toward a permissive approach to the PDA. However, few of the studies performed to date have controlled for confounding by indication, that infants referred for surgical ligation may represent a more “ill” cohort and may be at higher risk of NDI. As a result, there is a paucity of relevant, reliable studies to guide the PDA ligation decision. Our objective was to systematically review and meta-analyze the impact of PDA ligation in preterm infants at <32 weeks’ gestation on the risk of mortality, severe neonatal morbidities, and NDI.

METHODS
We conducted and reported this review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The protocol for this review was registered with PROSPERO, the international prospective register of systematic reviews (http://www.crd.york.ac.uk/NIHR_PROSPERO, identifier CRD42013005390).

Types of Studies
Randomized controlled trials (RCTs) and case-control or cohort studies with a comparator group were included if published in the form of an original research manuscript in a peer-reviewed journal, an abstract in conference proceedings, or a dissertation. Narrative reviews, letters, editorials, and commentaries were excluded but read to identify potential studies. Duplicated reports not providing additional information were excluded. Cross-sectional studies, case reports and series, qualitative studies, review articles, and studies that did not report methods were excluded but read to identify potential studies. Studies in infants with a PDA that did not report on outcomes in infants who underwent surgical ligation were excluded.

Types of Participants
Preterm infants born at a gestational age (GA) <32 weeks with a clinical and/or echocardiographic diagnosis of PDA were included. Studies in which some infants were born ≥32 weeks’ GA were included if >80% of infants in the study population had a GA <32 weeks. The diagnosis of PDA was made on the basis of clinical suspicion and/or echocardiography. Echocardiography diagnosis was preferable but not mandatory for inclusion in this review.

Exposure and Comparison
Studies must have included and compared, at a minimum, a surgically versus medically treated group or subgroup. Surgical subgroups included those infants treated with pharmacotherapy followed by surgical ligation ("pharmacotherapy and ligation" subgroup, indicating treatment with a nonsteroidal antiinflammatory drug [NSAID] or acetaminophen, followed by surgery) or those infants who underwent primary ligation ("primary ligation" subgroup, indicating surgical ligation without preceding pharmacotherapy). Medical subgroups included infants who received pharmacotherapy only ("pharmacotherapy only" subgroup, indicating treatment with NSAIDs or acetaminophen but not surgery) and those treated without surgery or pharmacotherapy ("conservative" subgroup). Conservative management referred only to watchful observation and the use of fluid restriction, diuretics, digoxin, and/or mechanical ventilation adjustment to manage the PDA shunt but excluded NSAID/acetaminophen and surgical treatments. Infants in the surgical or pharmacotherapy groups may have been treated with conservative measures initially before their respective definitive treatment. Surgical ligation must have been performed before 40 weeks’ corrected GA, either at the bedside or in the operating room, via a left lateral thoracotomy using a clip or ligature and not in conjunction with another surgery.
Outcomes

Studies were included if they reported at least 1 of the following outcomes for any treatment groups or subgroups:
1. death before discharge;
2. CLD, defined as the need for any form of respiratory support (oxygen or positive-pressure support) at 36 weeks’ corrected GA or at the time of transfer to a step-down unit21;
3. severe ROP, defined as stage ≥3 according to the international classification,22 or stage 2 with “plus” disease requiring treatment with laser therapy or vascular endothelial growth factor inhibitor;
4. NDI in early childhood (15–48 months’ corrected GA), defined as a composite of at least 1 of cognitive/language impairment, cerebral palsy, severe hearing impairment, or severe visual impairment (cognitive impairment was defined as a Bayley Scales of Infant Development II mental development index or Bayley Scales of Infant Development III cognitive or language score [or similar standardized examination] >2 SDs below the mean23,24; cerebral palsy was defined as a nonprogressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements [diagnosed on or before 24 months of age]25);
5. composite outcome of death or NDI in early childhood;
6. cognitive impairment as defined above; and
7. cerebral palsy as defined above.

Studies were included if neonatal or neurodevelopmental outcomes were complete for ≥90% and ≥75% of the cohort, respectively. A lower neurodevelopmental follow-up rate (≥70%) was accepted if infants lost to follow-up were described in detail and comparable to the cohort with known outcomes.

Review Methods

Search Strategy

The search strategy was designed with the assistance of an information scientist. We searched the following databases without language restriction: Medline (1948 through August 21, 2013), Embase Classic and Embase (1947 through August 21, 2013), Cochrane Central Register of Controlled Trials (through August 21, 2013), CINAHL (through August 21, 2013), ERIC (through August 21, 2013), PsycINFO (through August 21, 2013), Pediatric Academic Societies Conference E-abstracts (2002–2013), and Canadian Pediatric Society Conference E-abstracts (2010–2013). Detailed search terms are provided in Supplemental Information 1.

Data Extraction

Two authors (D.E.W. and K.M.) independently conducted the literature search. Information about study inclusion, study design, key characteristics, and outcomes was extracted independently by the 2 reviewers using a standardized data collection form. Discrepancies were resolved by consensus or by involving a third author (P.S.S.). Authors were contacted for clarifications and/or additional data.

Assessment of Risk of Bias

For randomized studies, we used the Cochrane Handbook Risk of Bias assessment tool.20 Studies were included if they had a low or moderate risk of bias. For observational studies, the risk of bias was assessed by using the information in the original publications, and included evaluation for selection (representative cohort or selected population), exposure assessment, outcome assessment, attrition, and confounding factor biases by using a modified Newcastle-Ottawa Scale,27 which was altered to reflect 2 different follow-up periods (neonatal and neurodevelopmental follow-up) and a focus on confounding by indication (Supplemental Information 2). Studies were included if they scored at least 6 (of 10 stars) on this modified Newcastle-Ottawa Scale.

We identified, a priori, that the use of surgical ligation as a “rescue” treatment after failure of medical therapy potentially imparts 2 important sources of bias. First, it may result in survival bias, because infants initially treated medically must have survived to be eligible for ligation. Second, it may result in confounding by indication, where ligated infants may be more likely to have increased pretreatment morbidity. Infants with higher illness severity after failed medical treatment, characterized by, for example, NEC, hypotension, or dependence on mechanical ventilation, may have been more likely to be referred for ligation. Included studies were therefore descriptively evaluated on how they adjusted for postnatal confounders at the time of the decision to treat the PDA.

The risk of bias assessment was performed independently by 2 authors (D.E.W. and K.M.). Differences of opinion were resolved by discussion and involvement of a third author (P.S.S.).

Data Synthesis and Statistical Analysis

Unadjusted and adjusted data were respectively combined in random-effects model meta-analyses (Review Manager 5.2; Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark).26 Meta-analyses were performed comparing all groups and subgroups based on the data presented in the included studies. The meta-analyses of adjusted data only included studies that had, at a minimum, controlled for GA. Similar to other meta-analyses, no adjustment for multiple analyses was made. Study weight in the meta-analyses was calculated by using the generic inverse
RESULTS

Description of Studies

The results of the search, the study selection log, and the number of studies are reported in Fig 1. One hundred twenty-three articles were reviewed in detail. Primary authors were contacted to obtain additional information, as needed. Six authors provided additional data or analyses not included in their original publication.28–32 Baseline characteristics of the 40 studies included (39 cohort studies and 1 RCT), encompassing 32,345 preterm infants, are reported in Table 1.

Eighty-three studies were excluded; 63 studies were excluded because they did not report sufficient data to compare outcomes of treatment assignment groups or subgroups.3,4,11,12,15–17,19,25–27 Five studies were excluded because they were a review or an editorial.128–130 Three studies were excluded because they represented cohorts already accounted for in another included study.213–135 Ten studies were excluded because >20% of infants in the cohort were ≥32 weeks’ gestational age (GA).136–140 Two studies were excluded because the cohort and analysis included all admitted infants rather than only infants with a patent ductus arteriosus (PDA).12,146 NSAIDs (ibuprofen or indomethacin) were the only pharmacologic therapies used.

Among the 9 cohort studies included in meta-analyses of multivariate results, 6 studies30,34,38–40 adjusted for perinatal covariates only. Three cohort studies30,38,61 adjusted for postnatal PDA-related morbidities. However, 2 of these studies30,61 adjusted for morbidities that were measured or occurred after the date of ligation (such as total duration of mechanical ventilation, CLD, and ROP), which may have introduced bias if these morbidities are on the causal pathway between ligation and the outcomes of death or NDI. Only 1
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type of Study</th>
<th>Population Definition and Diagnosis of PDA</th>
<th>Treatment*</th>
<th>Outcome‡</th>
<th>Covariates</th>
<th>Follow-up Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton, 1978</td>
<td>RCT</td>
<td>VLBW preterm infants, with HSPDA and dependent on invasive mechanical ventilation despite conservative management ((n = 25))</td>
<td>Randomly assigned to conservative management or immediate surgical closure.</td>
<td>Days to extubation, death, retrolental fibroplasia, CLD</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Merritt, 1978</td>
<td>Retrospective cohort</td>
<td>Preterm infants with an HSPDA (clinical and echo diagnosis) despite conservative management ((n = 59)). Comparison: Indo only ((n = 31)), Indo + Ligation ((n = 4)), Primary Ligation ((n = 24))</td>
<td>Common PDA treatment approach</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Merritt, 1979</td>
<td>Retrospective cohort</td>
<td>Preterm infants with an HSPDA (clinical ± echo diagnosis) despite conservative management ((n = 52)). Comparison: Indo only ((n = 26)), BW = 1433 ± 405 g, Primary Ligation ((n = 26)): BW = 1313 ± 330 g</td>
<td>Common PDA treatment approach</td>
<td>Death, cognitive delay (BSID MDI/PDI), neuromotor abnormality</td>
<td>None</td>
<td>Indo group: 95%, Ligation group: 80%–85%</td>
</tr>
<tr>
<td>Cats, 1980</td>
<td>Retrospective cohort</td>
<td>Preterm infants with BW &lt;2 kg with HSPDA (clinical diagnosis) ((n = 28)). Comparison: Indo only ((n = 9)): GA = 29 (26–33.5) wk; BW = 1260 (770–1900) g; Indo+Ligation ((n = 3)): GA = 30 (28–34) wk; BW = 1365 (1365–1900) g; Primary Ligation ((n = 15)): GA = 27.4 (25–30) wk; BW = 1090 (935–1500) g</td>
<td>Common PDA treatment approach in 1976–1977, using PO/PR indomethacin. In 1978–1979, moved to primary ligation if conservative treatment failed (no indo).</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Mikhail, 1982</td>
<td>Retrospective cohort</td>
<td>VLBW subset ((n = 413)) of preterm infants diagnosed with HSPDA. Comparison: Conservative ((n = 161)), Primary Ligation ((n = 252))</td>
<td>Treatment of HSPDA was initially conservative. Ligation performed after failure of conservative therapy.</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Zerella, 1983</td>
<td>Retrospective cohort</td>
<td>VLBW infants with severe RDS and PDA (clinical and echo diagnosis) ((n = 38)). Comparison: Indo only ((n = 9)), Indo+Ligation ((n = 11)), Primary Ligation ((n = 18))</td>
<td>Epoch A: PDA treatment initially with indo with ligation backup</td>
<td>Death</td>
<td>None</td>
<td>100% hospital discharge</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Type of Study</td>
<td>Population Definition and Diagnosis of PDA</td>
<td>Treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Outcome&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Covariates</td>
<td>Follow-up Complete</td>
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<tr>
<td>Wagner, 41 1984</td>
<td>Prospective cohort</td>
<td>April 1979–March 1981 Subset of preterm infants &lt;1750 g with HSPDA (clinical and echo diagnosis) enrolled in RCT (Gersony et al&lt;sup&gt;9&lt;/sup&gt;) treated with surgical ligation (n = 102). Comparison: Indo+Ligation (n = 28), Primary Ligation (n = 74)</td>
<td>Treatment allocation was randomized and decision to proceed with ligation standardized by study protocol.</td>
<td>Retrolental fibroplasia, death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Castanon, 42 1988</td>
<td>Retrospective cohort</td>
<td>1982–1986 Preterm infants with HSPDA (clinical and echo diagnosis) (n = 48). Comparison: Conservative (n = 21), Indo only (n = 9), Indo+Ligation (n = 3), Primary Ligation (n = 15)</td>
<td>Common PDA treatment approach</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Trus, 43 1993</td>
<td>Retrospective cohort</td>
<td>January 1988–December 1990 Preterm infants with BW &lt;3000 g with HSPDA (clinical ± echo diagnosis) and treated with NSAIDs ± Ligation (n = 49). Comparison: Indo only (n = 23): GA, 25.7 ± 2.0 wk; BW, 639 ± 97 g; Indo+Ligation (n = 17): GA, 24.6 ± 1.3 wk; BW, 662 ± 85 g</td>
<td>Common PDA treatment approach</td>
<td>BPD (not defined)</td>
<td>None</td>
<td>100% BPD outcomes</td>
</tr>
<tr>
<td>Perez, 44 1998</td>
<td>Retrospective cohort</td>
<td>1993–1997 VLBW infants with HSPDA (clinical ± echo diagnosis) (n = 76). Comparison: All Ligation (n = 40): GA, 26 wk; BW, 847 g; Medical Management only (n = 36): GA, 28 wk; BW, 997 g</td>
<td>Common PDA treatment approach</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Koehne, 45 2001</td>
<td>Retrospective cohort</td>
<td>January 1987–December 1998 VLBW infants treated for HSPDA (clinical and echo diagnosis) (n = 158). Comparison: Indo only (n = 67): GA, 26.4 wk; BW, 910 (525–1490) g; Indo+Ligation (n = 34): GA, 26.1 wk; BW, 885 (578–1450) g; Primary Ligation (n = 55): GA, 26.0 wk; BW, 760 (540–1250) g</td>
<td>Common PDA treatment approach, except indo course was initially 0.2 mg/kg q 12 h × 3 doses followed by 0.1 mg/kg q 24 h for up to 6 d.</td>
<td>Death, CLD</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Niinikoski, 46 2001</td>
<td>Retrospective cohort</td>
<td>1988–1998 VLBW infants with HSPDA (clinical and echo diagnosis) treated with surgical ligation (n = 101). Comparison: Indo+Ligation (n = 29), Primary Ligation (n = 76)</td>
<td>Infants &gt;1 kg treated with indo (0.2 mg/kg q 12 h × 3 doses); infants &lt;1000 g treated with primary ligation</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Little, 47 2003</td>
<td>Retrospective cohort</td>
<td>June 1998–March 2001 Neonates with HSPDA (clinical and echo diagnosis) (n = 212). Comparison: Indo alone (n = 125), Indo+Ligation (n = 42), Primary Ligation (n = 30)</td>
<td>Common PDA treatment approach</td>
<td>CLD (not defined)</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Type of Study</td>
<td>Population Definition and Diagnosis of PDA</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Covariates</td>
<td>Follow-up Complete</td>
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<tr>
<td>Hwang,49 2005</td>
<td>Retrospective cohort</td>
<td>January 1999–January 2002 ELBW infants with HSPDA (clinical and echo diagnosis) (n = 57). Comparison: Indo alone (n = 19): GA, 26.4 ± 1.6 wk; BW, 873 ± 70 g; Indo+Ligation (n = 8): GA, 25.0 ± 1.2 wk; BW, 749 ± 104 g; Primary Ligation (n = 14): GA, 26.5 ± 2.5 wk; BW, 784 ± 145 g.</td>
<td>Treatment allocation not described; indo treatment: 0.2 mg/kg q1 2h 3 doses</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Lee,50 2006</td>
<td>Retrospective cohort</td>
<td>1995–2000 Preterm VLBW infants treated with surgical ligation whose neonatal outcomes are known (n = 82). Comparison: Ligation only (n = 17), Indo+Ligation (n = 65)</td>
<td>Treatment allocation not described; user/homuse of NSAIDS known in 84%</td>
<td>Death, CLD</td>
<td>None</td>
<td>CLD: 86%; death: 89%; ROP: 81%</td>
</tr>
<tr>
<td>Pelausa,51 2006</td>
<td>Retrospective cohort</td>
<td>1994–2002 Infants with GA &lt;30 wk with HSPDA who failed medical treatment and underwent surgical ligation were matched (by GA, BW, gender) with infants who received only medical treatment (n = 88). Comparison: NSAID+Ligation (n = 44): GA, 25.6 ± 1.6 wk; BW, 778 ± 218 g; NSAID only (n = 44): GA, 25.7 ± 1.3 wk; BW, 796 ± 205 g</td>
<td>Treatment allocation not described</td>
<td>CLD, ROP (threshold)</td>
<td>Matched for GA, BW, gender</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Kabra,11 2007</td>
<td>Prospective cohort (subset of RCT)</td>
<td>January 1996–March 1998 Infants with BW 500–938 g with HSPDA (clinical and echo diagnosis) (n = 426). Comparison: Medical Management only (n = 318): GA, 25.6 ± 1.8 wk; BW, 771 ± 126 g; All Ligation (n = 110): GA, 25.1 ± 1.4 wk; BW, 742 ± 133 g</td>
<td>Subset of RCT where infants were randomly assigned to PI or placebo; treatment decision for ligation: assigned by attending physician</td>
<td>Severe ROP: laser or cryotherapy ≥1 eye or stage ≥4; CLD, death; CP; NDI: composite of hearing or vision loss, cognitive or CP</td>
<td>ACS, GA, gender, twins, maternal education, indo dose</td>
<td>100% neonatal outcomes; 83% 18- to 21-mo follow-up</td>
</tr>
<tr>
<td>Laughon,52 2007</td>
<td>Retrospective cohort</td>
<td>January 1997–December 2004 All 23- to 30-wk GA infants with a database diagnosis of PDA. Comparison: Conservative (n = 3886): GA, 27 wk (IQR: 26–29); BW, 970 g (IQR: 750–1220); Primary Ligation (n = 701): GA, 25 wk (IQR: 24–27); BW, 730 g (IQR: 624–898)</td>
<td>Treatment allocation not described</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
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<tr>
<td>First Author, Year</td>
<td>Type of Study</td>
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<tr>
<td>Qureshi,53 2008</td>
<td>Retrospective cohort</td>
<td>Infants with BW &lt; 1250 g with PDA (clinical and echo diagnosis) (n = 195). Comparison: Conservative (n = 34); Indo only (n = 90): GA, 27.4 wk; BW, 974 ± 19 g; Primary Ligation (n = 24): GA, 26.3 ± 0.2 wk; BW, 894 ± 30 g; Indo + Ligation (n = 47): GA, 26.3 ± 0.5 wk; BW, 845 ± 43 g</td>
<td>Treatment allocation not described</td>
<td>CLD</td>
<td>BW, GA, treatment type only univariate results available</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sato,54 2008</td>
<td>Retrospective cohort</td>
<td>ELBW infants who underwent PDA ligation over a 3-y period (n = 90). Comparison: Indo + Ligation (n = 37), Primary Ligation (n = 43)</td>
<td>Common PDA treatment approach</td>
<td>Death, ROP (stage 3/4/5), CLD (not defined)</td>
<td>None</td>
<td>Not specified</td>
</tr>
<tr>
<td>Tsuchuppert,55 2008</td>
<td>Retrospective cohort</td>
<td>January 1985–December 2005 Infants &lt; 35 wk GA treated for PDA (echo ± clinical diagnosis) (n = 210). Successful Medical Closure group (n = 154): BW, 1.1 ± 0.3 kg; versus failed Medical Closure group (n = 47): BW, 1.1 ± 0.3 kg. Comparisons: Primary Ligation (n = 9), Indo alone (n = 168), Indo + Ligation (n = 33)</td>
<td>Death, CLD</td>
<td>None</td>
<td>100% neonatal outcomes</td>
<td></td>
</tr>
<tr>
<td>Alexander,56 2009</td>
<td>Retrospective cohort</td>
<td>June 1996–April 2005 ELBW infants with HSPDA (clinical and echo diagnosis) (n = 258) Comparison: Conservative (n = 54), Indo only (n = 140), Indo + Ligation (n = 58), Primary Ligation (n = 46)</td>
<td>Common PDA treatment approach</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Ko,57 2009</td>
<td>Retrospective cohort</td>
<td>April 1992–March 2006 All VLBW infants who underwent PDA ligation. Comparison: Indo + Ligation (n = 37), Primary Ligation (n = 4)</td>
<td>Treatment allocation not described</td>
<td>Death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Madan,10 2009</td>
<td>Prospective cohort</td>
<td>January 2000–December 2004 Infants 23–28 wk and 401–1000 g who survived &gt; 72 h with HSPDA (clinical ± echo diagnosis) and had 18–21 mo follow-up assessment (n = 2838). Comparison: Conservative (n = 403): GA, 25.6 ± 1.5 wk; BW, 758 ± 148 g; Indo only (n = 1525): GA, 25.4 ± 1.3 wk; BW, 745 ± 139 g; Indo + Ligation (n = 775): GA, 24.8 ± 1.3 wk; BW, 719 ± 134 g; Primary Ligation (n = 150): GA, 25.1 ± 1.4 wk; BW, 726 ± 133 g</td>
<td>29% received PI. Treatment allocation assigned by attending physician.</td>
<td>Severe ROP: laser/cryotherapy ≥ 1 eye or stage ≥ 4, CLD, NDI (18–21 mo): composite of hearing aids, blindness ≥ 1 eye, severe cognitive delay, or moderate–severe CP</td>
<td>Center; GA, BW, gender, PI, labor, Apgar, RDS, IUGR, ACS, TORCH, sepsis, marital status, maternal age</td>
<td>100% (by inclusion criteria)</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Type of Study</td>
<td>Population Definition and Diagnosis of PDA</td>
<td>Treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Outcome&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Covariates</td>
<td>Follow-up Complete</td>
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</tr>
<tr>
<td>Qureshi, 58 2009</td>
<td>Retrospective cohort</td>
<td>Infants with BW &lt;1250 g with PDA (echo diagnosis) ( n = 178 ); Comparison: Medical Management only ( n = 110 ): GA, 27.4 wk; BW, 903 ± 36 g, including Conservative only ( n = 84 ), Indigo only ( n = 84 ), versus All Ligation ( n = 66 ), including Primary Ligation ( n = 19 ): GA, 25.3 ± 0.3 wk; BW, 808 ± 47 g; Indigo Ligation ( n = 47 ): GA, 28.3 ± 0.2 wk; BW, 894 ± 30 g</td>
<td>Treatment allocation not described</td>
<td>Death or NDI</td>
<td>GA, BW, PDA score, IVH, hypotension in first week</td>
<td>100% neonatal mortality; 85% neurodevelopmental follow-up</td>
</tr>
<tr>
<td>Vida, 59 2009</td>
<td>Retrospective cohort</td>
<td>Infants &lt;32 wk GA with HSPDA (clinical and echo diagnosis) treated with primary NSAID therapy ( n = 201 ); Comparison: Conservative ( n = 149 ): GA, 27 wk (IQR: 25–28); BW, 840 g (IQR: 670–1016); NSAID+Ligation ( n = 52 ): GA, 25 wk (IQR: 24–26.5); BW, 730 g (IQR: 595–915)</td>
<td>Iburopen was NSAID used; common PDA treatment approach</td>
<td>Death, CLD, ROP ((\geq 365))</td>
<td>None</td>
<td>100% neonatal outcomes</td>
</tr>
<tr>
<td>Chiruvolu, 60 2010</td>
<td>Retrospective cohort</td>
<td>January 2006–December 2008 ELBW infants with PDA (clinical and echo diagnosis) ( n = 190 ); Comparison: Conservative ( n = 16 ), NSAID only ( n = 53 ), Primary Ligation ( n = 61 ), NSAID+Ligation ( n = 58 )</td>
<td>Treatment allocation not described</td>
<td>Death; CLD; severe ROP: ((\geq 365))</td>
<td>None</td>
<td>100% neonatal outcomes</td>
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<tr>
<td>Lopes, 61 2010</td>
<td>Retrospective cohort</td>
<td>1999–2004 Cohort of 143 infants with BW ≤800 g ( n = 83 ); Comparison: Conservative ( n = 12 ), Indigo only ( n = 31 ), Indigo+Ligation ( n = 42 ), Primary Ligation ( n = 8 )</td>
<td>Treatment allocation not described</td>
<td>CP, cognitive delay ((\geq 365)), deafness, Psychomotor development</td>
<td>None</td>
<td>100% neonatal outcomes; 81% 18-mo follow-up (of cohort)</td>
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<tr>
<td>Natarajan, 62 2010</td>
<td>Retrospective cohort</td>
<td>January 2004–December 2006 Cohort of VLBW infants with an HSPDA (clinical and echo diagnosis) treated with surgical ligation ( n = 82 ); Comparison: Primary Ligation ( n = 28 ), NSAID+Ligation ( n = 54 )</td>
<td>Common PDA treatment approach; iiburopen and indo used</td>
<td>CLD, ROP (requiring treatment), death</td>
<td>None</td>
<td>100% neonatal outcomes</td>
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<tr>
<td>Rheinlaender, 63 2010</td>
<td>Retrospective cohort</td>
<td>January 1998–December 2003 VLBW infants with PDA (clinical and echo diagnosis) treated with NSAID+Ligation ( n = 182 ); Comparison: NSAID only ( n = 130 ), NSAID+Ligation ( n = 52 ); Infants with ductal patency after NSAID therapy ( 52 ) of 54 were then ligated had lower BW, GA, higher CRIB score, and more RDS, mechanical ventilation, ventilator days.</td>
<td>Common PDA treatment approach; indo 0.2 mg/kg q 12 h x 3 doses, then 0.1 mg/kg q 24 h up to 6 d; iiburopen 10/5.5 mg/kg q 24 h</td>
<td>Death, mortality at 2 y; CLD, ROP &gt; stage 2, hearing aids, blindness, CP, cognitive delay, composite poor outcome, death or poor outcome</td>
<td>Composite NDI: CRIB, BW, GA, BPD, gender, O&lt;sub&gt;2&lt;/sub&gt; days, intubation days, ROP, IVH, PVL, surfactant</td>
<td>89.6% 2y outcome (death or NDI known)</td>
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<td>Pelusa, 64 2011</td>
<td>Retrospective cohort</td>
<td>Infants &lt;28 wk GA with an HSPDA who survived &gt;7 d and treated with surgical ligation were matched for GA ((\geq 28)) wk with an infant with PDA who received only medical treatment ( n = 72 ); Comparison: All Ligation ( n = 38 ): GA, 25 ± 1.1 wk; BW, 709 ± 20 g, Medical Management only ( n = 36 ): GA, 24.9 ± 1.1 wk; BW, 726 ± 159 g</td>
<td>Treatment allocation not described</td>
<td>Death, developmental issues at 4 y of age (speech, developmental delays, CP, ADHD, autism, deafness, blindness)</td>
<td>Matched for GA ((\geq 28)) wk</td>
<td>Not specified</td>
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<tr>
<td>First Author, Year</td>
<td>Type of Study</td>
<td>Population Definition and Diagnosis of PDA</td>
<td>Treatment*</td>
<td>Outcome*</td>
<td>Covariates</td>
<td>Follow-up Complete</td>
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<td>Adrouche-Amrani, 65 2012</td>
<td>Retrospective cohort</td>
<td>August 2004–July 2009 ELBW infants with HSPDA (clinical and echo diagnosis) (n = 80). Comparison: NSAID only (n = 48): GA 25.4 ± 0.2 wk; BW 772 ± 16 g. NSAID + Ligation (n = 32): GA 24.9 ± 0.2 wk; BW 726 ± 24 g.</td>
<td>Common PDA treatment approach; sedibuprofen and indo</td>
<td>CLD, ROP (these data not included in analysis)</td>
<td>None</td>
<td>100% neonatal outcomes</td>
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<tr>
<td>Heuchan, 66 2012</td>
<td>Retrospective cohort</td>
<td>2001–2007 Preterm infants with HSPDA (clinical and echo diagnosis) with persistent need for respiratory support, treated with surgical ligation. Treatment groups (median [IQR]): NSAID + Ligation (n = 71): GA 26 (25–27) wk; BW 840 (735–1000) g; Primary Ligation (n = 54): GA 20 (25–27) wk; BW 830 (727–1080) g</td>
<td>Treatment allocation not described</td>
<td>Mortality at 1 y</td>
<td>None</td>
<td>100% 1-y mortality outcome</td>
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<td>Hsu, 34 2012</td>
<td>Retrospective cohort</td>
<td>1997–2007 VLBW infants with a PDA (echo diagnosis) (n = 10 780). Comparison: All Ligation (n = 2497), Medical Management only (n = 8283)</td>
<td>Treatment allocation not described</td>
<td>30-d postoperative mortality, hospital mortality</td>
<td>NICU level and unspecified comorbidities</td>
<td>100% neonatal outcomes</td>
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<td>Mirea, 8 2012</td>
<td>Retrospective cohort</td>
<td>2004–2008 Preterm infants with GA ≥ 32 wk, who survived ≥ 72 h, with a diagnosis of PDA (diagnosed clinically ± echo) (n = 556). Comparison: Conservative (n = 577): GA 28.3 ± 2.5 wk; Indo only (n = 2028): GA 27.0 ± 2.1 wk; Indo + Ligation (n = 628): GA 25.5 ± 1.7 wk; Primary Ligation (n = 327): GA 26.0 ± 2.3 wk</td>
<td>Common PDA treatment approach</td>
<td>Death, ROP ≥ stage 3, CLD; composite outcome not included in this review</td>
<td>GA, ACS, multiple births, gender, SGA, SNAP II score</td>
<td>Not specified</td>
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<tr>
<td>Moore, 33 2012</td>
<td>Retrospective cohort</td>
<td>January 1984–December 2005 Infants 23–26 wk GA with HSPDA (clinical and echo diagnosis) that did not close after 1 course of indo (n = 133). Ligated infants had lower BW and more inotrope use but similar GA to nonligated infants. Comparison: Indo only (n = 58), Indo + Ligation (n = 75)</td>
<td>Common PDA treatment approach</td>
<td>CLD, severe ROP: any need for laser therapy, death</td>
<td>Death: GA, ACS, SGA, gender</td>
<td>Not specified</td>
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<tr>
<td>Jawa, 30 2015</td>
<td>Retrospective cohort</td>
<td>2005–2010 VLBW infants with HSPDA (clinical and echo diagnosis) (n = 361). Comparison: Conservative (n = 85), Medical Management only (n = 178): GA, 27.1 ± 0.7 wk; All Ligation (n = 98): GA, 25.8 ± 0.8 wk</td>
<td>Treatment allocation not described</td>
<td>CLD, ROP &gt; stage 2, Death, CP at 2 y</td>
<td>CLD, ROP, death: GA, CP, CLD, IVH, ROP, sepsis</td>
<td>100% neonatal outcomes; 2-y follow-up not described</td>
</tr>
<tr>
<td>Tsui, 31 2013</td>
<td>Retrospective cohort</td>
<td>January 2006–December 2010 VLBW infants with PDA (n = 204). Comparison: Conservative only (n = 88), Indo only (n = 48), Indo + Ligation (n = 20), Primary Ligation (n = 47)</td>
<td>Treatment allocation not described</td>
<td>Severe ROP requiring laser treatment</td>
<td>None; univariate results used in this review</td>
<td>100% ROP outcomes</td>
</tr>
</tbody>
</table>
study adjusted for postnatal pre-ligation confounders, by controlling for IVH, hypotension, and a PDA-related illness severity score measured at the time of the decision to treat the PDA. The possibility of survival bias was not addressed by any cohort study.

Main Results

Meta-analyses of univariate and multivariate results for all treatment group and subgroup comparisons are presented in Table 2. The outcomes for ligated compared with medically treated infants are as follows:

1. Death before discharge from the NICU: a meta-analysis of studies that reported an adjusted risk of death revealed that infants who underwent surgical ligation had lower odds of death compared with those who were treated medically (5 studies, 7159 participants; pooled aOR: 0.54; 95% CI: 0.38 – 0.77; I² = 39%) (Fig 2A, Table 2). The association between ligation and decreased mortality was seen across all subgroup comparisons (Fig 2 B-D, Table 2).

2. CLD: meta-analysis revealed that surgical ligation was associated with higher odds of CLD compared with medical management alone (4 studies, 6703 participants; pooled aOR: 2.51; 95% CI: 1.98 – 3.18; I² = 44%) (Fig 3A, Table 2).

3. Severe ROP: meta-analysis revealed that surgical ligation was associated with higher odds of CLD compared with medical management alone (4 studies, 6703 participants; pooled aOR: 2.51; 95% CI: 1.98 – 3.18; I² = 44%) (Fig 3A, Table 2).

4. NDI in early childhood: meta-analysis revealed that NDI was higher among infants who underwent surgical ligation compared with those treated medically (3 studies, 3250 participants; pooled aOR: 2.23; 95% CI: 1.62 – 3.08; I² = 37%) (Fig 4A, Table 2).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>No. of Studies</th>
<th>Pooled OR (Univariate)</th>
<th>No. of Participants</th>
<th>$I^2$ (%)</th>
<th>No. of Studies</th>
<th>Pooled aOR (Multivariate)</th>
<th>No. of Participants</th>
<th>$I^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>All Ligation versus All Medical Management only</td>
<td>16</td>
<td>0.71 (0.54–0.94)</td>
<td>8667</td>
<td>56</td>
<td>5</td>
<td>0.54 (0.38–0.77)</td>
<td>7159</td>
<td>39</td>
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<td>NSAID and Ligation versus Primary Ligation</td>
<td>21</td>
<td>0.70 (0.51–0.95)</td>
<td>3170</td>
<td>25</td>
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<td>NSAID and Ligation versus NSAID only</td>
<td>18</td>
<td>0.77 (0.57–1.04)</td>
<td>6688</td>
<td>40</td>
<td>3</td>
<td>0.44 (0.37–0.53)</td>
<td>5111</td>
<td>0</td>
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<tr>
<td></td>
<td>NSAID and Ligation versus Conservative</td>
<td>7</td>
<td>0.35 (0.19–0.64)</td>
<td>2650</td>
<td>72</td>
<td>1</td>
<td>0.20 (0.13–0.31)</td>
<td>1201</td>
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<tr>
<td></td>
<td>Primary Ligation versus NSAID only</td>
<td>14</td>
<td>1.02 (0.71–1.46)</td>
<td>5123</td>
<td>37</td>
<td>2</td>
<td>0.85 (0.48–1.52)</td>
<td>4006</td>
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<tr>
<td></td>
<td>Primary Ligation versus Conservative</td>
<td>10</td>
<td>0.58 (0.41–0.83)</td>
<td>6722</td>
<td>57</td>
<td>2</td>
<td>0.29 (0.18–0.47)</td>
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<tr>
<td>CLD</td>
<td>All Ligation versus All Medical Management only</td>
<td>7</td>
<td>2.19 (1.43–3.34)</td>
<td>4603</td>
<td>82</td>
<td>4</td>
<td>2.51 (1.98–3.18)</td>
<td>6703</td>
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<td>NSAID and Ligation versus Primary Ligation</td>
<td>8</td>
<td>1.06 (0.75–1.50)</td>
<td>1489</td>
<td>30</td>
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<td>NSAID and Ligation versus NSAID only</td>
<td>12</td>
<td>2.49 (1.81–3.14)</td>
<td>3845</td>
<td>60</td>
<td>3</td>
<td>2.76 (2.10–3.62)</td>
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<td>NSAID and Ligation versus Conservative</td>
<td>3</td>
<td>4.98 (2.37–9.67)</td>
<td>1258</td>
<td>50</td>
<td>1</td>
<td>3.12 (2.32–4.20)</td>
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<td>Primary Ligation versus NSAID only</td>
<td>5</td>
<td>1.60 (0.95–2.77)</td>
<td>2642</td>
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<td>2.03 (1.57–2.61)</td>
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<td>Primary Ligation versus Conservative</td>
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<td>4.13 (2.56–6.88)</td>
<td>5279</td>
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<td>2.87 (1.88–3.77)</td>
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<td>Severe ROP</td>
<td>All Ligation versus All Medical Management only</td>
<td>5</td>
<td>3.97 (3.33–4.73)</td>
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<td>9.28 (4.85–17.70)</td>
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<td>Primary Ligation versus NSAID only</td>
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<td>3.51 (2.01–6.12)</td>
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<td>Death or NDI</td>
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<td>2.15 (1.34–3.44)</td>
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<td>Primary Ligation versus NSAID only</td>
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<td>3.33 (0.32–34.99)</td>
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<td>Cognitive impairment</td>
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AOR, adjusted odds ratio; OR, odds ratio; NSAID, non-steroidal anti-inflammatory drug; ROP, retinopathy of prematurity.
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<th>First Author, Year</th>
<th>Selection Representativeness of Exposed Cohort</th>
<th>Selection of Nonexposed Cohort</th>
<th>Ascertainment of Exposure</th>
<th>Demonstration That Outcome of Interest Not Present at Start</th>
<th>Comparability of Cohorts on Basis of Design/Analysis (Out of Possible 2)</th>
<th>Methodology Addresses Confounding by Indication</th>
<th>Assessment of Outcome</th>
<th>Follow-up Long Enough</th>
<th>Adequacy of Follow-up of Cohorts (to Discharge)</th>
<th>Adequacy of Follow-up of Cohorts (Long-term)</th>
<th>Overall</th>
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N/A, not applicable.

a Modified Newcastle-Ottawa scale (Supplemental Information 2).

b Maximum 9 (for studies reporting neonatal outcomes) or 10 (for studies reporting neurodevelopmental outcomes).
There was a trend toward higher NDI among infants treated with NSAIDs and ligation compared with infants treated with NSAIDs alone (2 studies, 2441 participants; aOR: 1.39; 95% CI: 0.97–1.98; $I^2 = 29\%$) (Fig 5B, Table 2). 

5. Death or NDI in early childhood: 4 studies reported the composite outcome comparing all surgically and medically treated infants. Madan et al.\textsuperscript{10} reported on the neurodevelopmental outcomes of 2838 infants with birth weights of 400 to 1000 g who survived >72 hours and had a symptomatic PDA and follow-up at 18 to 21 months’ corrected GA. Kabra et al.\textsuperscript{11} performed a secondary analysis of the Trial of Indomethacin Prophylaxis in Preterm Infants. Pelausa et al.\textsuperscript{64} performed a retrospective cohort study comparing a small group of ligated preterm infants with a group of medically treated infants matched for GA, body weight, and gender. Qureshi et al.\textsuperscript{58} reported a multivariate analysis of a retrospective cohort of preterm infants with PDA, adjusting for PDA-related illness severity at the time of the decision to treat the PDA. Meta-analysis of these studies revealed no difference in the composite outcome of death or NDI between surgically and medically treated infants (4 studies, 3512 participants; pooled aOR: 0.95; 95% CI: 0.58–1.57; $I^2 = 71\%$) (Fig 6, Table 2). Most of the statistical heterogeneity between these 4 studies is accounted for by 1 study,\textsuperscript{58} which was the only study to report a significant protective effect of surgical ligation. Importantly, this study was also the only one in this review to control for confounding by indication.

6. Cognitive impairment: only 1 study\textsuperscript{11} reported an adjusted estimate of cognitive impairment and found
increased odds associated with ligation compared with medical management alone \((331\) participants; \(aOR: 1.96; 95\% CI: 1.14–3.37\)) (Table 2).

7. Cerebral palsy: meta-analysis revealed that there was no difference in the odds of cerebral palsy\(^{11,63}\) between those who underwent surgical ligation and those treated medically \((2\) studies, \(616\) participants; pooled \(aOR: 1.51; 95\% CI: 0.86–2.63; \(I^2 = 0\%)\) (Fig 5C, Table 2).

**DISCUSSION**

In this systematic review and meta-analysis of the effects of PDA treatment assignment on neonatal and neurodevelopmental outcomes, we identified that surgical ligation is associated with...
decreased mortality but increased NDI in early childhood when compared with medical treatment alone. There are several possible explanations for the divergence of these competing outcomes: first, surgical ligation may improve the survival of infants but be simultaneously neurologically detrimental; second, surgical ligation may improve the survival of infants, but infants referred for ligation may be at higher preligation risk of NDI (confounding by indication); and finally, the decrease in mortality may be influenced by survival bias (where medically treated infants with a PDA die before being referred for ligation), with the increase in NDI explained by either confounding by indication or a true detrimental effect of ligation.

Several aspects of treatment with ligation have been proposed as contributing to an increased risk of NDI, such as surgical or anesthesia effects or postoperative hemodynamic compromise. Early surgical mortality associated with PDA ligation is reported to be low.49,56,66 Direct surgical morbidities include bleeding, pneumothorax, and left vocal cord paresis (VCP). The incidence of left VCP is variable but may complicate 5% to 50% of PDA ligations and is associated with an increased risk of death, extubation failure, CLD, need for gastrostomy tube, and gastroesophageal reflux disease.66,147–149 Recent studies have reported an association between the use of halothane gases for anesthesia in young children and NDI.150,151 Preterm infants are at risk of postligation hemodynamic instability, which may result in cerebral hypoperfusion, neuronal injury, and subsequent NDI.152–157 In our review, only 1 of the included studies30 reported on an association of VCP and NDI, and no study described an association between postligation hemodynamic...
instability and NDI. Infants with lower GA and weight <1 kg at the time of ligation are at highest risk of postligation hemodynamic instability, possibly due to decreased myocardial adaptability to altered loading conditions.\(^\text{158}\) This finding raises the possibility that age at ligation may contribute to the risk of NDI; however, a post hoc analysis of the Trial of Indomethacin Prophylaxis in Preterm Infants found no association between the timing of PDA ligation and the risk of NDI.\(^\text{11}\)

Despite the reported association between ligation and NDI, observational studies to date have not adequately differentiated the effect of bias versus a true detrimental effect of ligation. In general, observational studies are subject to bias when treatment assignment is not independent of baseline prognostic factors. Many of the included studies did not perform any adjustment for confounders. Infants who underwent surgical ligation of their PDA had significantly different baseline characteristics compared with their medically treated peers, with generally lower GA and birth weight (Table 1). The presence of these major confounders limits the validity of unadjusted comparisons. In addition, most of the multivariate analyses included in this review only adjusted for antenatal or perinatal covariates (Table 1). This set of covariates, if complete, would be sufficient to balance baseline prognostic factors for interventions that occur shortly after birth. However, PDA ligation often occurs several weeks after birth, and the interval accumulation of PDA-associated comorbidities influences both treatment assignment and outcomes.

The most important source of bias in the included multivariate studies is confounding by indication, in which infants with higher illness severity, who may be at higher risk of NDI,\(^\text{159,160}\) may be more likely to be assigned to ligation. Only 1 study\(^\text{56}\) adjusted for preligation postnatal confounders, such as IVH or the duration/intensity of mechanical ventilation at the time of the decision to treat the PDA. In the setting of surgical ligation, severe IVH is a potential confounder. It has been associated with PDA ligation\(^\text{45,52,62}\) and NDI\(^\text{161–165}\) and is not typically on the causal pathway between PDA ligation and NDI. Most IVH (90%) occurs in the first week of life,\(^\text{166}\) preceding the timing of surgical ligation reported in most studies.\(^\text{33,45,48,50,59}\) Other potential key confounders include prolonged duration of mechanical ventilation, severe hypotension, postnatal sepsis, and NEC, which increase illness severity but are also associated with PDA ligation, death, NDI, CLD, and ROP.\(^\text{167–175}\) These morbidities, however, can occur before, during, or after PDA treatments and thus may be considered confounders in some infants and outcomes in others. Therefore, data on the timing of these confounders relative to ligation should be incorporated into multivariable models examining the impact of surgical treatment.

The lower mortality in the ligated group may be attributable, in part, to survival bias. The PDA treatment algorithms in many of the included studies (Table 1) cited that infants were treated with ligation when indomethacin failed or was contraindicated. Ligation was often undertaken later in life relative to medical therapy, meaning that ligated infants were more likely to have already survived the period of high early neonatal mortality. This implies that some of the sickest infants, treated initially with conservative management and/or indomethacin, may have died before becoming “eligible” for ligation, resulting in selection bias in assembling the cohort of ligated infants. This issue was present in most of the cohort studies, and thus our findings of decreased mortality should be interpreted with caution. Future studies that compare surgical ligation with medical therapy should ensure careful matching of the control population with consideration of age at ligation.

The possibility of survival bias is supported by findings of the subgroup meta-analyses. Survival bias associated with ligation would be expected to manifest as an apparent survival advantage when ligation is performed later in life, but that ligation performed at a similar day of life as medical therapy would have similar mortality rates. We found that infants treated with NSAIDs and ligation had lower adjusted odds of death compared with infants who underwent treatment with primary ligation, NSAIDs alone, or conservative management (Table 3). In studies in which ligation was performed early in life (either as primary therapy or immediately after failure of indomethacin in the first week of life), there was no difference in mortality compared with medically treated infants.\(^\text{12,84}\)

If ligation truly improved survival (and survival bias was not a factor), then a reduction in rates of surgical treatment might be expected to increase mortality, assuming that the clinical characteristics of infants remained the same. Two studies\(^\text{14,17}\) reported no change in mortality across epochs after moving to a delayed selective ligation strategy from an early routine ligation strategy after indomethacin failure. However, other studies have reported an increase in mortality when surgical ligation was no longer available\(^\text{176}\) and when ligation was not performed in infants with a persistent PDA after failure of medical therapy.\(^\text{177}\) This finding suggests that both survival bias and a true survival benefit of surgical ligation may be present.

We found that infants exposed to PDA ligation also had increased CLD and severe ROP. This is biologically supported by the potential cardiorespiratory instability and inflammatory effects associated with surgical ligation\(^\text{178–180}\) and was shown in a secondary analysis.
of an RCT of early prophylactic ligation in extremely low birth weight infants.\textsuperscript{9,77}

Given its association with NDI, this risk of CLD may represent a plausible pathway for the increased NDI associated with ligation.\textsuperscript{161–163} Nonetheless, confounding by indication remains an important source of bias in these studies as well. Only 1 study controlled for postnatal sepsis,\textsuperscript{10} a known risk factor for CLD,\textsuperscript{184} and this study did not differentiate between sepsis that occurred before or after surgical ligation. In addition, ventilator dependence is commonly considered an indication for ligation in infants in whom medical therapy had failed or was contraindicated\textsuperscript{53,44,47,48,62} and yet it is also a risk factor for CLD.\textsuperscript{185} Given the association between CLD and ROP and death or NDI,\textsuperscript{181,182,185} it is important, when analyzing these outcomes, to adjust for preligation respiratory morbidity.

**Conclusions and Implications**

This systematic review and meta-analysis identified an association between PDA ligation and decreased odds of death, increased odds of CLD, ROP, and NDI in early childhood, and no difference in the composite outcome of death or NDI. However, this association comes predominantly from observational studies that inadequately addressed survival bias and confounding by indication. Many of these studies also lacked standardized echocardiographic and clinical criteria to define a hemodynamically significant PDA. Our review highlights the difficulty faced by clinicians considering surgical ligation. The clinician must navigate literature that reports an association with significant morbidity, albeit fraught with methodologic biases and clinical uncertainty regarding patient selection and the optimal timing for surgery.

This study provides direction to improve the available evidence to guide clinicians about the PDA ligation decision. Whereas an RCT examining 2 different PDA treatment protocols would be instructive, the variability in practice among centers may reduce the external validity of such a trial. Observational studies are therefore needed that adjust for preligation time-dependent covariates to fully elucidate the effects of PDA ligation.

**Strengths and Limitations**

This review encompasses a comprehensive search and explicit inclusion and exclusion criteria and poses clinically important questions. There was low to moderate clinical and statistical heterogeneity in most studies included in this review. This meta-analysis is limited by a paucity of studies that performed multivariate analyses and the insufficiency of these studies in addressing survival bias and confounding by indication for postnatal morbidities, such as ventilator dependence, IVH, sepsis, or NEC, that occurred before treatment with surgical ligation.

**ACKNOWLEDGMENTS**

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**REFERENCES**


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Mattia FR, deRegnier RA. Chronic physiologic instability is associated with neurodevelopmental morbidity at one and two years in extremely premature infants. *Pediatrics*. 1998;102(3). Available at: www.pediatrics.org/cgi/content/full/102/3/e35.


PDA Ligation and Health Outcomes: A Meta-analysis
Dany E. Weisz, Kiran More, Patrick J. McNamara and Prakesh S. Shah

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