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Overview of Reviews

The Cochrane Library and treatment of patent ductus arteriosus: an overview of reviews

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Background: Patent ductus arteriosus (PDA), the condition in which the ductus arteriosus (DA) does not close, is a common problem in preterm and low birth weight infants. It is associated with significant mortality and morbidity in these children.

Objectives: To critically evaluate the evidence available in *the Cochrane Library* regarding the treatment of PDA with ibuprofen (IBU) and indomethacin (INDO) in preterm and/or low birth weight infants.

Methods: The Cochrane Library was searched using the term 'patent ductus arteriosus.' Reviews discussing pharmacological interventions with IBU and INDO in premature infants were included. Data on clinically important outcomes were extracted by one author and independently evaluated. Primary outcomes pre-specified for inclusion in this overview were: failure to close a PDA, reopening of the ductus arteriosus after initial closure, need for retreatment/need for surgical closure and symptomatic PDA.

Main results: Four reviews, containing 31 trials and 1739 participants, were included in this overview. In these reviews five unique comparisons were indentified: IBU versus placebo or no treatment, IBU versus INDO, prolonged versus short course of INDO, INDO versus placebo for asymptomatic PDA, and continuous versus bolus INDO for symptomatic PDA. Of the primary outcomes, IBU decreased need for retreatment [risk ratio (RR) 0.38, 95% confidence interval (CI) 0.19 to 0.75; risk difference (RD) −0.22, 95% CI −0.36 to −0.08; number needed to treat (NNT) = 6] and INDO reduced the rate of subsequent symptomatic PDA (RR 0.36, 95% CI 0.19 to 0.60; RD −0.36, 95% CI −0.52 to −0.17; NNT = 5) when each was compared to placebo. Other primary outcomes (failure to close PDA, reopening of DA after closure and need for surgical ligation) were not statistically significant in any of the reviews in which they were reported. One review compared length of INDO treatment and showed that infants receiving shorter courses of drug had fewer episodes of necrotizing enterocolitis (NEC) (RR 1.87, 95% CI 1.07 to 3.27; RD 0.08, 95% CI 0.01 to 0.15; NNT = 15). Another review addressed efficacy of continuous versus bolus dose INDO in preterm infants with a symptomatic PDA. No statistically significant differences were found between these two regimens. In a separate review IBU was compared with placebo and with INDO for treatment of PDA. Twenty trials were included in the comparison of IBU versus INDO. The two drugs showed no difference in failure to close a PDA (RR 0.94, 95% CI 0.76 to 1.17); however, use of IBU was associated with a lower risk of NEC (RR 0.68, 95% CI 0.47 to 0.99; RD, −0.04, 95% CI −0.08 to 0.00; NNT = 27) as compared with INDO.

Authors' conclusions: Although both INDO and IBU successfully close the DA, our overview found no evidence of significant difference between these two drugs for the majority of outcomes reported. If medical treatment is undertaken for closure, there is no significant difference in rate of failure to close the PDA between INDO and IBU. There is an advantage to IBU as there is less association with NEC, although the magnitude of this benefit is small. If INDO is used it should be a short course, again to decrease the risk of NEC.

Keywords: Cochrane Library, meta-analysis, overview, patent ductus arteriosus, systematic review

Plain language summary

The ductus arteriosus (DA) is a blood vessel normally existing in all infants before birth; it allows blood to bypass the infant's lungs as they are not used for oxygen delivery at that time. Soon after an

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infant is born (1–5 days) the DA is expected to close spontaneously as the lungs are filled with air and blood must now flow to them. However, in some infants, especially in preterm newborns, the DA remains open (patent). Several conditions affecting the lungs, kidneys, digestive system, central nervous system and infant death have been associated with the presence of a patent ductus arteriosus (PDA). In this overview, we focus on pharmacological treatment with ibuprofen (IBU) and indomethacin (INDO) for closing the PDA. Both drugs are successful in closing PDA; our overview showed that there is no difference between them in achieving this target. There is, however, a slight advantage of IBU over INDO as there is a lower risk of a major bowel complication [necrotizing enterocolitis (NEC)] with IBU treatment. When INDO is chosen for treatment, a shorter course should be prescribed as there is no evidence that an extended course is more effective and there is a higher risk of NEC with a longer course.

Background

Description of the condition

The DA connects the pulmonary artery to the aorta and is an important structure in foetal life, shunting blood away from the lungs (1). The DA is expected to close as a part of normal transition from foetal to newborn circulation, equalizing the pulmonary and systemic circulations (2). Ductal closure is mediated by the rapid fall in pulmonary vascular resistance, increase in pulmonary blood flow and marked increase in the partial pressure of oxygen after birth (3, 4). In term newborns, closure generally occurs within 1–5 days of birth (5). In preterm newborns, PDA is a common clinical condition with incidence inversely related to both gestational age (GA) and birth weight (6, 7). In some studies, as many as 70% of infants born before 28 weeks gestation and under 1000 g birth weight have required treatment for PDA (8). The DA is generally considered to be persistently patent if it remains open beyond 72 hours of life (9). Studies of therapies aimed to close the PDA may overestimate the incidence of the condition by interrupting its natural history. In one study, spontaneous closure prior to discharge occurred in 47% of infants with birth weight under 1000 g at a median age of 56 days (10).

Patency of the DA is generally determined by echocardiography (11). Clinical signs may include murmur, presence of a third heart sound (S3), wide pulse pressure, full pulses, active precordium and congestive heart failure (2, 11). These clinical signs are inconsistent and unreliable for predicting the presence of a PDA (12, 13).

In numerous studies, PDA has been associated with prolonged ventilation (14), worsening pulmonary disease (15–17), pulmonary haemorrhage (18, 19), bronchopulmonary dysplasia (BPD) (20–23), NEC (24, 25), renal impairment (26), intraventricular haemorrhage (IVH) (27, 28), periventricular leukomalacia (PVL) (29), cerebral palsy (30) and death (6, 31, 32). There is significant uncertainty, however, concerning whether any of these associations are causal (33, 34). The PDA may be a sign of some significant underlying disease or physiological condition (34, 35). If the PDA were causal to any of these conditions, it would be expected that closure (medically or surgically) of the DA would result in a decrease in these outcomes. This has not been borne out in numerous studies and meta-analyses. The lack of decreased morbidity after DA closure and the presence of short- and long-term morbidities related to medical and surgical interventions to close the DA have led to yet-unresolved controversy about whether and/or when the DA should be closed (2, 33, 34).

Description of the interventions

There are three general classes of intervention for PDA: conservative measures, cyclo-oxygenase inhibitors and surgical closure.

Conservative measures include fluid restriction, diuretics, transfusion, permissive hypercapnia, elevated positive end expiratory pressure, use of minimal supplemental oxygen and avoidance or correction of metabolic acidosis (34). The effect of some of these therapies on the PDA has been included in Cochrane reviews of broader topics (36–38). These therapies are not included in this overview.

Both INDO and IBU are cyclo-oxygenase inhibitors and are used as specific medical therapies to effect ductal closure. These therapies have been used both prophylactically, to systematically close the DA in all premature infants in the first 24 hours after birth without proving its patency, and therapeutically, after the echocardiographic or clinical diagnosis of PDA beyond 24 hours of life. There are Cochrane Reviews of their use for prophylaxis which are not covered in this overview (39, 40). The use of these medications for therapeutic closure of the PDA is the subject of this overview.

Surgical closure can be accomplished either through ligation or application of a clip. There are Cochrane Reviews of primary surgical closure (41) as well as comparing surgery to medical management (42) which are not covered in this overview.

How the interventions might work

Various prostaglandins are important in maintaining patency of the DA in foetal life (43). Cyclo-oxygenase inhibitors block the conversion of arachidonic acid to these various prostaglandins thereby allowing the DA to close (11). There are two isoforms of cyclo-oxygenase and they are inhibited to different degrees by IBU and INDO (44). This may partially explain their differing short-term side effect profiles (45).

As stated previously, presence of a PDA is associated with numerous adverse outcomes; however, a

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causal relationship remains to be proven. Some of the postulated mechanisms by which the presence of a PDA may impact on these outcomes are briefly described here. Some investigators have found that left-to-right shunting through the PDA decreases lung compliance and this is reversed with medical closure (2). If compliance is decreased, there may be greater need for mechanical ventilation which is known to increase the risk of BPD (1). Overcirculation, as a result of the left-to-right shunt, may cause congestive heart failure with a resultant rise in pulmonary venous pressures which may lead to pulmonary haemorrhage (46). The associated renal insufficiency and NEC are postulated to arise as a result of 'ductal steal' whereby a large left-to-right shunt leads to decreased diastolic blood flow to distal organs, including the bowel and kidneys (47, 48). These findings are inconsistent in both humans and animal models and it remains to be proven that closure of the PDA ameliorates any of the associated outcomes (1).

Why it is important to do this overview

Despite the controversy concerning whether or not it is necessary, or appropriate, to close the PDA, given the lack of improvement in long-term outcomes, closure is currently a part of routine neonatal intensive care. There have been a large number of studies involving INDO and IBU in numerous different regimens and protocols for the therapeutic (as opposed to prophylactic) closure of the PDA. As a result, there are several Cochrane reviews on the subject leaving the clinician with multiple systematic reviews to consider in order to determine whether there is a 'most effective' or 'least harmful' therapeutic regimen. We aim to present the currently available evidence from the Cochrane Database of Systematic Reviews in such a way that the clinician who wishes to make an evidence-informed decision as to the optimal treatment regimen for a PDA has all of the evidence synthesized in one accessible source.

Objectives

The purpose of this overview is to critically evaluate the evidence available in the *Cochrane Database of Systematic Reviews* (CDSR) on the efficacy and safety of two pharmacological interventions, IBU and INDO, for the treatment of PDA in preterm and/or low birth weight infants.

Methods

Criteria for considering reviews for inclusion

All Cochrane reviews on pharmacological intervention with IBU or INDO for PDA in preterm infants were considered for inclusion. Reviews on other pharmacological treatments, surgical interventions and prevention were excluded.

Search methods for the identification of reviews

The term 'patent ductus arteriosus' was entered into the CDSR using the 'Title, Abstract or Keyword' search fields. The search was performed in January 2012. One author (MO) identified potentially relevant systematic reviews based on the criteria described above. The authors with clinical expertise (JH, TLM) made final decisions where inclusion was uncertain.

All reviews were considered for inclusion regardless of date of last assessment. If the date of completion was earlier than January 2010, we sought articles to update the review by rerunning the search strategy published in the review and restricting the date to after the last assessment was done. In addition, the Cochrane Neonatal Review Group was contacted to ensure that no relevant review was missed.

Types of outcome measures

The following outcomes were pre-specified for inclusion in this overview:

- Primary outcomes
  - Failure to close a PDA
  - Reopening of the ductus arteriosus after initial closure
  - Need for retreatment/need for surgical closure
  - Symptomatic PDA
- Secondary outcomes
  - Mortality/all cause mortality/neonatal mortality
  - Necrotizing enterocolitis (NEC)
  - Chronic lung disease (CLD)
  - Retinopathy of prematurity (ROP)
  - Intraventricular haemorrhage (IVH)
  - Periventricular leukomalacia (PVL)
  - Pulmonary haemorrhage
  - Pulmonary hypertension
  - Gastrointestinal perforation
  - Gastrointestinal haemorrhage

Other outcomes such as duration of assisted ventilation, duration of supplemental oxygen dependence, time to full enteral feeds, time to regain birth weight, sepsis, duration of hospital stay, changes in urine output, creatinine levels, cerebral blood flow, renal blood flow, blood urea nitrogen (BUN) level and mesenteric blood flow were not evaluated as they were considered to be less clinically meaningful.

Data collection and analysis

The following data was extracted by MO from the included reviews: inclusion criteria (population, intervention, comparison and outcomes), numerical data (results of original reviews) and methodological quality of included trials (as posted in the reviews). A

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second reviewer (Aireen Wingert) independently verified data extraction.

In the original reviews, Review Manager 5 was used to pool the data (49). Risk ratios (RR) with 95% confidence intervals (CI) were used to combine dichotomous data. Results were interpreted as statistically significant if the 95% CI did not cross 1.0. A fixed-effects model was used in all included reviews. Meta-analyses are presented with related I^2 values, which indicate statistical heterogeneity across trials. To quantify the treatment effect for outcomes that were statistically significant we calculated risk difference (RD), and number needed to treat (NNT) according to formulae below (50):

1. For harmful outcomes NNT = [1 − control group risk $(1 - \mathrm{OR}_{\mathrm{harm}})$]/[control group risk (1 − control group risk)$(1 - \mathrm{OR}_{\mathrm{harm}})$]
2. For beneficial outcomes NNT = [1 + control group risk $(\mathrm{OR}_{\mathrm{benefit}} - 1)$]/[control group risk (1 − control group risk)$(\mathrm{OR}_{\mathrm{benefit}} - 1)$]

In one instance, a composite outcome was presented in the review. For consistency with other reviews, we present an outcome that was not originally included in the review. For this, data from the trial included in the review were extracted and analysed using Review Manager 5.

Results

Description of included reviews

The search identified 37 reviews that were potentially relevant, 33 of which were excluded for the following reasons: 27 discussed interventions other than IBU/INDO and six focussed on prophylaxis. The remaining four reviews were included (51–54). No additional relevant review was suggested by the Cochrane Neonatal Review Group.

We performed literature searches for two reviews which were last updated in September 2002 (51) and November 2006 (53); we found no new relevant trials. The four included reviews contain 31 trials and 1739 participants. All studies included in the reviews were randomized controlled trials. Characteristics of the included reviews are shown in Table 1.

Search methods used in included reviews

All four included reviews searched MEDLINE, EMBASE and CENTRAL; all but one (53) searched CINAHL. One review (52) searched the ClinicalTrials.gov website for ongoing studies. Hand searching including references, abstracts and conference proceedings published in Pediatric Research was performed in three reviews (51, 52, 54). No language restrictions were applied.

Table I. Characteristics of the included reviews

Title of review	Date assessed as up to date	Population	Intervention	Comparison	Outcomes included in present overview
Indomethacin for asymptomatic patent ductus arteriosus in preterm infants (51)	September 2002	Preterm infants <37 weeks GA with asymptomatic PDA	INDO	Placebo or no treatment	Mortality; CLD; IVH; NEC; ROP; symptomatic PDA; need for surgical closure
Continuous infusion versus intermittent bolus doses of indomethacin for patent ductus arteriosus in symptomatic preterm infants (52)	January 2010	Preterm infants <37 weeks GA with symptomatic PDA	Continuous infusion of INDO	Bolus dose of INDO	Failure to close a PDA; reopening after treatment; neonatal mortality; IVH; NEC
Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants (53)	November 2006	Preterm infants <37 weeks GA with PDA	Long course of INDO (four of more doses)	Short course of INDO (three of less doses)	Failure to close a PDA; PDA reopening after treatment; need for retreatment; need for surgical closure; mortality; CLD; IVH; NEC; ROP
Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (54)	February 2010	Preterm infants <37 weeks GA or LBW infants (<2500 g) at 3 days of age with PDA	IBU oral or i.v.	INDO or placebo or no treatment	Failure to close a PDA mortality; NRC; IVH; PVL; ROP; CLD; reopening after treatment; need for surgical closure; need for retreatment; pulmonary hypertension; pulmonary haemorrhage; intestinal perforation; gastrointestinal haemorrhage

CLD: chronic lung disease; GA: gestational age; INDO: indomethacin; IVH: intraventricular haemorrhage; IBU: ibuprofen; PDA: patent ductus arteriosus; LBW: low birth weight; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.

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Interventions in included reviews

The four included reviews reported five unique comparisons. In two reviews (51, 54) active treatments (INDO and IBU, respectively) were compared to placebo; one review (54) included comparison of two different active treatments (IBU versus INDO); two reviews (52, 53) compared different administration regimens of the same medication (INDO).

Primary outcomes in included reviews

Three reviews specified their primary outcome as failure of PDA to close either after completion of allocated treatment (52, 53) or within a week of administration of the first dose of study drug (54); one review (51) did not specify a primary outcome. One review (54) presented a composite outcome as the primary outcome for one of its comparison.

Subgroup analyses in included reviews

Authors of all included reviews planned to conduct three or more subgroup analyses: GA (52–54), postnatal age (51), birth weight (52–54), dosing regimen (51–54), route of drug administration (51; 53; 54) and method of diagnosis (51–54). Only one subgroup analysis (route of administration) in one review (54) was performed, other subgroups analyses were not possible owing to insufficient data for each subgroup.

Methodological quality of included trials

Different aspects of the Risk of Bias tool (55) were used to evaluate methodological quality of included trials. All reviews assessed adequacy of allocation concealment, blinding and incomplete outcome data. One review (54) assessed selective reporting and other sources of bias; two reviews (53, 54) assessed sequence generation. Details of ratings are summarized in Table 2. The main source of bias in this set of studies was lack of blinding with 55% of studies being assessed as high risk of bias for this domain; a further 22% were unclear with respect to blinding and only 23% were considered low risk of bias. The other key potential sources of bias were unclear sequence generation (71%) and unclear (42%) or inadequate (3%) allocation concealment.

Effects of interventions

Indomethacin for asymptomatic PDA in preterm infants

One review (51) examined the efficacy of INDO versus placebo for asymptomatic PDA in preterm infants. In the three included studies, sample size ranged from 26 to 49 children. Premature newborn infants (less than 37 weeks GA) with asymptomatic PDA were included. Children received treatment after 24 hours of age. Asymptomatic PDA was identified clinically or by echocardiography; infants without clinical or radiological evidence of heart failure were randomized to receive either INDO (administered enterally or parenterally) or placebo.

The results are summarized in Table 3. No significant heterogeneity was observed in any of the outcomes presented. Two primary outcomes were included in this comparison: symptomatic PDA and need for surgical closure. A lower rate of occurrence of symptomatic PDA was observed in the group of children treated with INDO as compared with the group treated with placebo (RR 0.36, 95% CI 0.19 to 0.68; RD −0.35, 95% CI −0.52 to −0.17; NNT = 5). There was no statistically significant difference between the groups for the second primary outcome reported and

Table II. Details of risk of bias assessment for included trials

Risk of bias dimension	Low risk of bias (%)	Unclear risk of bias (%)	High risk of bias (%)	Number of trials assessed
Sequence generation	29	71	0	24
Allocation concealment	52	45	3	31
Blinding	23	22	55	31
Incomplete outcome data	74	7	19	31
Selective reporting	90	10	0	20
Other sources of bias	95	5	0	19

Table III. Indomethacin versus placebo for asymptomatic PDA

Outcome	Studies (participants)	Effect estimate RR (95% CI)	I^2 (%)	NNT (95% CI)
Symptomatic PDA	**3 (97)**	**0.36 (0.19, 0.68)**	**0**	**5 (3–11)**
Need for surgical closure	2 (73)	0.45 (0.17, 1.21)	n/a	—
Mortality	2 (73)	1.32 (0.45, 3.86)	0	—
CLD (at 28 days of life)	2 (45)	0.91 (0.62, 1.35)	24	—
IVH (all grades) 2	2 (75)	1.21 (0.62, 2.37)	0	—
NEC	1 (47)	0.41 (0.05, 3.68)	n/a	—
ROP (any stage) 3	2 (55)	0.68 (0.26, 1.78)	0	—

CI: confidence interval; CLD: chronic lung disease; IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; NNT: number needed to treat; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; RR: risk ratio. Statistically significant results are bold.

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Table IV. Prolonged versus short course of indomethacin for treatment of PDA

Outcome	Studies (participants)	Effect estimate RR (95% CI)	I^2 (%)	NNT (95% CI)
Failure to close a PDA	4 (361)	0.82 (0.51, 1.33)	67	—
PDA reopening after treatment	3 (322)	0.63 (0.39, 1.04)	0	—
Need for retreatment for PDA (INDO and/or surgical ligation)	5 (431)	0.95 (0.67, 1.34)	56	—
Need for surgical closure	4 (310)	0.86 (0.49, 1.51)	69	—
Mortality	5 (431)	1.36 (0.86, 2.15)	47	—
CLD (36 weeks of age)	2 (201)	1.35 (0.78, 2.36)	61	—
CLD (28 days of age)	1 (140)	0.97 (0.58, 1.64)	n/a	—
IVH (all grades)	2 (131)	0.83 (0.54, 1.28)	78	—
IVH (grade III–IV)	4 (310)	0.64 (0.36, 1.12)	0	—
NEC	**4 (310)**	**1.87 (1.07, 3.27)**	**4**	**16(7–175)**
ROP (any stage)	3 (240)	1.04 (0.57, 1.88)	11	—

CI: confidence interval; CLD: chronic lung disease; INDO: indomethacin; IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; NNT: number needed to treat; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; RR: risk ratio. Statistically significant results are bold.

need for surgical closure (RR 0.45, 95% CI 0.17 to 1.21). Other meta-analyses focused on mortality, episodes of CLD in survivors, all grades of IVH, NEC and all stages of ROP. None of these outcomes showed statistically significant differences between groups.

Duration of indomethacin therapy

One review (53) compared prolonged (four or more doses) versus short course (three or less doses) INDO administered by any route. The review included five studies and the sample size of these studies ranged from 39 to 140. Preterm infants (less than 37 weeks GA) with a PDA diagnosed clinically and/or echocardiographically were included. However, the review authors pointed out non-uniform inclusion criteria across trials.

The findings are summarized in Table 4. Insignificant or no heterogeneity was observed in four outcomes. Six outcomes showed moderate to considerable heterogeneity, for which we performed sensitivity analysis using a random effects model; no changes in statistical significance were observed.

None of the primary outcomes presented in this comparison show statistical significance: failure to close PDA (RR 0.82, 95% CI 0.51 to 1.33), PDA reopening after treatment (RR 0.63, 95% CI 0.39 to 1.04), need for retreatment (RR 0.95, 95% CI 0.67 to 1.34) and need for surgical closure (RR 0.86, 95% CI 0.49 to 1.51). A significant difference between prolonged and short course INDO, in favour of short course, was observed in the number of episodes of NEC (RR 1.87, 95% CI 1.07 to 3.27; RD 0.08, 95% CI 0.01 to 0.15; NNT = 15). There was no statistically significant difference between prolonged and short course INDO in the mortality ratio, episodes of CLD at 28 days of age and at 36 weeks corrected age, incidence of any grade or grade III–IV IVH, and episodes of all stages of ROP.

Continuous indomethacin infusion for symptomatic PDA

Two trials included in one review (52) compared the efficacy of continuous infusion versus intermittent bolus doses of no longer than 20 minutes duration in any dosing schedule of INDO for closure of PDA. The sample sizes were 32 and 18 patients; preterm infants less than 37 weeks GA with a symptomatic PDA were included. PDA was diagnosed clinically and/or echocardiographically in the first 28 days of life.

The findings are summarized in Table 5. Primary outcomes [failure to close PDA on day 2 (RR 1.57, 95% CI 0.54 to 4.60), failure to close PDA by day 5 (RR 2.77, 95% CI 0.33 to 23.14), and reopening of the DA (RR 2.77, 95% CI 0.33 to 23.14)] showed no statistical difference between continuous and bolus dose INDO. Similarly, no statistically significant differences were found for neonatal mortality rate and incidence of NEC. Two included trials assessed any grade of IVH but both reported that no episodes were found.

Table V. Continuous versus bolus INDO for symptomatic PDA

Outcome	Studies (participants)	Effect Estimate RR (95% CI)	I^2 (%)
Failure to close a PDA on day 2	2 (48)	1.57 (0.54, 4.60)	0
Failure to close a PDA on day ≤ 5	1 (25)	2.77 (0.33, 23.14)	n/a
Reopening of the ductus arteriosus	2 (43)	2.77 (0.33, 23.14)	n/a
Neonatal mortality	1 (32)	3.95 (0.20, 76.17)	n/a
IVH (all grades)	2 (50)	Not estimable	n/a
NEC	1 (22)	0.56 (0.03, 12.23)	n/a

CI: confidence interval; CLD: chronic lung disease; IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; NNT: number needed to treat; PDA: patent ductus arteriosus; RR: risk ratio.

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Table VI. Ibuprofen versus placebo for PDA treatment

Outcome	Studies (participants)	Effect Estimate RR [95% CI]	I^2 (%)	NNT (95% CI)
Infant deaths, infants who dropped out or required rescue treatment	**1 (136)**	**0.58 (0.38, 0.89)**	**n/a**	**8 (5–35)**
Need for retreatment with INDO before day 14*	**1 (136)**	**0.38 (0.19, 0.75)**	**n/a/**	**6 (4–16)**
NEC	1 (130)	1.00 (0.42, 2.36)	n/a	—
IVH (all grades)	1 (134)	1.00 (0.64, 1.55)	n/a	—
IVH (grade III–IV)	1 (134)	1.00 (0.47, 2.15)	n/a	—
PVL	1 (130)	0.11 (0.01, 2.02)	n/a	—
ROP (any stage)	1 (129)	1.19 (0.88, 1.62)	n/a	—
ROP (stage 3 or 4)	1 (129)	1.18 (0.38, 3.68)	n/a	—
ROP (plus disease)	1 (129)	1.31 (0.31, 5.63)	n/a	—
CLD (28 days of age)	1 (130)	1.09 (0.95, 1.26)	n/a	—
CLD (36 weeks of age)	1 (98)	0.99 (0.88, 1.11)	n/a	—
Pulmonary haemorrhage	1 (136)	0.25 (0.03, 2.18)	n/a	—
Pulmonary hypertension	1 (136)	2.00 (0.19, 21.54)	n/a	—
Mortality	1 (136)	0.80 (0.34, 1.90)	n/a	—

* Outcome not included in the original review.

CI: confidence interval; CLD: chronic lung disease; INDO: indomethacin; IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity; RR: risk ratio. Statistically significant results are bold.

Ibuprofen for early closure of an asymptomatic PDA

One study (56) included in Ohlsson's review (54) compared IBU versus placebo for the early closure of an asymptomatic PDA. In all 136 preterm infants (less than 30 weeks postmenstrual age) with ductal shunting echocardiographically confirmed within 72 hours of age were included; IBU was administered intravenously. The results are summarized in Table 6. The original review's primary outcome was a composite outcome assessing infant deaths and infants who dropped out or required rescue treatment. For this outcome a statistically significant difference was found in favour of IBU (RR 0.58, 95% CI 0.38 to 0.89; RD −0.22, 95% CI −0.38 to −0.06; NNT = 8). For consistency with other reviews, we present an outcome that was not originally included in the IBU versus placebo comparison: need for retreatment before day 14. For this, data from the included trial were extracted, analysed and added to Table 6. Fewer children needed a rescue treatment before day 14 in the IBU group compared with the placebo group (RR 0.38, 95% CI 0.19 to 0.75, RD −0.22, 95% CI −0.36 to −0.08; NNT = 6). No statistically significant differences between IBU and placebo were found in number of episodes of NEC, IVH (any grade and grade III–IV), incidences of PVL, ROP (any stage, stage 3 or 4, plus disease), CLD at 28 days of life and 36 weeks corrected, pulmonary haemorrhage and pulmonary hypertension.

Ibuprofen versus indomethacin

Twenty studies included in Ohlsson's review (54) compared the efficacy of IBU versus INDO; sample size ranged from 16 to 175. The inclusion criteria were not uniform: five trials did not specify GA or postmenstrual age, presence of PDA was not required in two trials and route of drug administration was not stated in two studies. In 18 trials, children with PDA were included but symptomatology (symptomatic versus nonsymptomatic) and method of diagnosis (echocardiography versus hemodynamically significant PDA) differed across studies. The findings are summarized in Table 7. None of the primary outcomes presented in this comparison showed statistically significant differences between IBU and INDO: failure to close PDA (RR 0.94, 95% CI 0.76 to 1.17), reopening of the DA (RR 1.28, 95% CI 0.48 to 3.38), need for surgical closure (RR 1.04, 95% CI 0.71 to 1.51), and need for retreatment (RR 1.20, 95% CI 0.76 to 1.90). A statistically significant difference was found for one outcome: a lower rate of NEC was observed in infants treated with IBU as compared with infants treated with INDO (RR 0.68, 95% CI 0.47 to 0.99; RD −0.04, 95% CI −0.08 to 0.00; NNT = 27); however, none of the 15 individual trials which reported this outcome found significant differences between groups.

Discussion

This overview presents the current Cochrane evidence concerning efficacy, safety and benefit of medical therapeutic closure of the PDA. Clinicians must still consider the necessity of effecting ductal closure; however, if a decision is made to proceed, the results of this overview will assist the clinician in their decisions around therapeutic regimen.

Summary of main results

The main findings from the included systematic reviews are synthesized in Table 8. Indomethacin significantly decreases subsequent symptomatic PDA and IBU decreases the need for retreatment compared to

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Table VII. Ibuprofen (any route of administration) versus indomethacin (any route of administration)

Outcome	Studies (participants)	Effect Estimate RR (95% CI)	I^2 (%)	NNT (95% CI)
Failure to close a PDA	19 (956)	0.94 (0.76, 1.17)	0	—
Failure to close PDA (oral IBU versus i.v. or oral INDO)	7 (189)	0.78 (0.49, 1.24)	0	—
Reopening of the ductus arteriosus	6 (204)	1.28 (0.48, 3.38)	0	—
Need for surgical closure	13 (848)	1.04 (0.71, 1.51)	0	—
Need for retreatment with INDO or IBU	7 (241)	1.20 (0.76, 1.90)	0	—
All cause mortality	8 (470)	0.77 (0.45, 1.29)	0	—
Neonatal mortality	4 (333)	1.12 (0.59, 2.11)	0	—
Pulmonary haemorrhage	3 (103)	1.23 (0.37, 4.10)	45	—
Pulmonary hypertension	1 (35)	3.53 (0.15, 81.11)	n/a	—
CLD (28 days of age)	4 (245)	1.22 (0.93, 1.59)	0	—
CLD (36 weeks of age)	3 (357)	1.12 (0.77, 1.61)	0	—
CLD (age not stated)	3 (128)	1.04 (0.83, 1.30)	0	—
IVH (all grades)	4 (144)	0.90 (0.44, 1.86)	0	—
IVH (grade III–IV)	8 (571)	1.21 (0.74, 1.98)	0	—
PVL	6 (573)	1.24 (0.67, 2.30)	0	—
NEC	**15 (865)**	**0.68 (0.47, 0.99)**	**0**	**27 (16 to 914)**
Intestinal perforation	5 (255)	0.48 (0.20, 1.14)	0	—
Gastrointestinal haemorrhage	6 (314)	1.11 (0.57, 2.15)	0	—
ROP (any stage)	5 (237)	0.86 (0.54, 1.38)	0	—

CI: confidence interval; CLD: chronic lung disease; IBU: ibuprofen; INDO: indomethacin; IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; NNT: number needed to treat; PDA: patent ductus arteriosus; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity; RR: risk ratio. Statistically significant results are bold.

Table VIII. Summary of main findings

Outcome	IBU versus placebo or none	IBU versus INDO	Prolonged versus short course of INDO	INDO versus placebo for asymptomatic PDA	Continuous versus bolus INDO for symptomatic PDA
Failure to close PDA	—	No difference	No difference	—	No difference
Reopening of DA after initial closure	—	No difference	No difference	—	No difference
Need for retreatment	**IBU better**	No difference	No difference	—	—
Symptomatic PDA	—	—	—	**INDO better**	—
Need for surgical ligation	—	No difference	No difference	No difference	—
Mortality/all cause mortality	No difference	No difference	No difference	No difference	—
Neonatal mortality	—	No difference	—	—	No difference
NEC	No difference	**IBU better**	**short course INDO better**	No difference	No difference
ROP (all stages)	—	No difference	No difference	No difference	—
ROP (stage 3 or 4)	No difference	—	—	—	—
ROP (plus disease)	No difference	—	—	—	—
IVH (all grades)	No difference	No difference	No difference	No difference	No difference
IVH (grade III or IV)	No difference	No difference	No difference	—	—
PVL	No difference	No difference	—	—	—
CLD (at 28 days of age)	No difference	No difference	No difference	No difference	—
CLD (at 36 weeks of age)	No difference	No difference	No difference	—	—
CLD (age not stated)	—	No difference	—	—	—
Pulmonary haemorrhage	No difference	No difference	—	—	—
Pulmonary hypertension	No difference	No difference	—	—	—
Gastrointestinal perforation	—	No difference	—	—	—
Gastrointestinal haemorrhage	—	No difference	—	—	—

(–) Outcome not assessed.
CLD: chronic lung disease; DA: ductus arteriosus; IBU: ibuprofen; INDO: indomethacin; IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity. Statistically significant results are bold.

placebo. When IBU and placebo are compared head to head, there are no differences in achieving ductal closure; however, IBU shows a small decrease in the occurrence of NEC. A short course of INDO has the advantage of fewer cases of NEC compared to a long course. These findings are based on small numbers of samples, which limits our confidence in the estimates of effect due to lack of precision (57).

With the exception of the effects on the rate of NEC, there were no differences between IBU, INDO and placebo, in any treatment regimen, on any important clinical outcomes including mortality.

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Limitations of the overview

One of the challenges in this overview was lack of consistency within the reviews in regards to inclusion criteria. Two reviews (53, 54) did not use uniform measures across trials. Included studies differ on symptomatology, method of diagnosis and route of drug administration. Furthermore, none of the studies included in the four reviews considered outcomes after hospital discharge which could be important to patients and families, for example neurosensory impairment or cerebral palsy. The outcomes measured also varied considerably between included studies and reviews making direct comparisons difficult in some cases. For example, the studies involving placebo and either IBU or INDO did not report on failure to close the ductus whereas this outcome is available for INDO compared to IBU and for different INDO regimens.

Another limitation was small to moderate sample size for many of the included trials. As a result, estimates for several outcomes were imprecise. In addition, results of a number of outcomes were derived from a single study; this can make it difficult to draw general conclusions applicable beyond the population studied. While there are considerably more trials of IBU for prophylaxis, there is a single report of IBU compared to placebo for treatment and the use of a composite outcome in this trial makes interpretation and comparison across studies difficult.

Authors' conclusions

Implications for practice

In practice, the most important, and difficult, decision remains whether or not to undertake ductal closure. Both IBU and INDO are known to close DA and the evidence provided in this overview shows no significant differences between IBU and INDO in achieving this end. Given this, there is a small advantage to the use of IBU as there are fewer cases of NEC, although this finding is based on a small number of samples. There is no proven advantage to a long course of INDO and if this drug is chosen, a short course should be prescribed.

In spite of the lack of proven long-term benefit from closing the ductus, treatment of the PDA remains a common practice in many NICUs and neonatologists can be pressured by other professionals, including respirologists, cardiologists and cardiovascular surgeons, to address and close the duct. Clinicians should consider the lack of proven benefit to ductal closure along with the risks of treatments when counselling parents and undertaking informed consent discussions. For a more detailed reflection on the controversy surrounding the advisability of ductal closure, readers are referred to the papers by Benitz and Laughon (2, 33, 34).

Implications for research

While there are a number of important clinical associations with the presence of a PDA, no significant benefit has been shown to its treatment. Perhaps the associated outcomes are not at all due to presence of a PDA but both the PDA and the adverse outcome are caused by something else – prematurity, inflammation, infection or some other common pathway (34, 35). Research efforts should be directed at determining the underlying causal associations such that appropriate prevention or treatment can be designed and tested.

It is possible that there is a subset of patients for whom there is benefit in ductal closure but that this effect is lost in the broader population included in past studies. Future studies should focus on determining the natural history of the PDA and identifying reliable and objective markers (clinical, echocardiographic and/or laboratory) to define those patients at greatest risk of potentially-related adverse outcome and highest risk of long-term patency. We would suggest that given the lack of proven benefit and the significant controversy surrounding ductal closure, there is enough clinical equipoise to support a prospective cohort study to examine the natural history of PDA and identify objective criteria that predict long-term patency or poor outcome. It would seem ethically appropriate to either withhold treatment altogether or at least to delay it until the second or third week of life or later. Once high-risk groups are identified, studies should be designed to determine whether there is benefit to medical or surgical closure in these subpopulations of patients. If there are improved outcomes following ductal closure in some patients, they may further benefit from research into safer and more efficient therapies to achieve closure. Modalities under study include miniaturized devices (58), non-invasive procedures (59) and therapies that target ductal tissue (60).

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Contributions of authors

All authors contributed in the overview preparation. MO did data extraction and analysis and wrote the Abstract, Plain Language Summary, Methods and Results sections. JH and TLM wrote the Background, Discussion and Conclusions sections. LH commented on various sections of the draft and coordinated the project. JH is the primary author of this overview. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of interest

The authors have no competing interests to declare.

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