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Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants (Review)

Ohlsson A, Shah PS

Ohlsson A, Shah PS.
Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants.
Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD010061.
DOI: 10.1002/14651858.CD010061.pub2.

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[Intervention Review]

Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 3, 2015.

Citation: Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD010061. DOI: 10.1002/14651858.CD010061.pub2.

ABSTRACT

Background

In preterm newborns, the ductus arteriosus frequently fails to close and the infants require medical or surgical closure of the patent ductus arteriosus (PDA). A PDA can be treated surgically or medically with one of two prostaglandin inhibitors, indomethacin or ibuprofen. Case reports suggest that paracetamol may be an alternative for the closure of a PDA. Concerns have been raised that in neonatal mice paracetamol may cause adverse effects on the developing brain, and an association between prenatal exposure to paracetamol and later development of autism or autism spectrum disorder has been reported.

Objectives

To determine the efficacy and safety of intravenous or oral paracetamol compared with placebo or no intervention, intravenous indomethacin, intravenous or oral ibuprofen, or with other cyclo-oxygenase inhibitors for closure of a PDA in preterm or low-birth-weight infants.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), MEDLINE, EMBASE and CINAHL. We searched abstracts from the meetings of the Pediatric Academic Societies and the Perinatal Society of Australia and New Zealand. We searched clinicaltrials.gov; controlled-trials.com; anzctr.org.au; World Health Organization International Clinical Trials Registry Platform at who.int/ictrp for ongoing trials and the Web of Science for articles quoting identified randomised controlled trials. We searched the first 200 hits on Google Scholar^{TM} to identify grey literature. All searches were conducted in December 2013. A repeat search of MEDLINE in August 2014 did not identify any new trials.

Selection criteria

We identified two randomised controlled trials (RCTs) that compared oral paracetamol to oral ibuprofen for the treatment of an echocardiographically diagnosed PDA in infants born preterm ($\leq$ 34 weeks postmenstrual age (PMA)).

Data collection and analysis

We performed data collection and analyses in accordance with the methods of the Cochrane Neonatal Review Group.

Main results

Two unmasked studies of treatment of PDA that enrolled 250 infants were included. The sequence of randomisation and the allocation to treatment groups were concealed in both studies. In one study the cardiologist assessing PDA closure was blinded to group allocation of the infant. In the other study it was not stated if that was the case or not. The quality of the trials, using GRADE, was low for the primary outcome of PDA closure and moderate for all other important outcomes. There was no significant difference between treatment with oral paracetamol versus oral ibuprofen for failure of ductal closure after the first course of drug administration (typical relative risk (RR) 0.90, 95% confidence interval (CI) 0.67 to 1.22; typical risk difference (RD) -0.04, 95% CI -0.16 to 0.08; I^2 = 0 % for RR and 23% for RD).

There were no significant differences between the paracetamol and the ibuprofen groups in the secondary outcomes except for 'duration for need of supplemental oxygen' (mean difference -12 days, 95% CI -23 days to -2 days; 1 study, n = 90) and for hyperbilirubinaemia (RR 0.57, 95% CI 0.34 to 0.97; RD -0.15, 95% CI -0.29 to -0.01; number needed to treat to benefit (NNTB) 7, 95% CI 3 to 100 in favour of paracetamol; 1 study, n = 160).

Authors' conclusions

Although a limited number of infants with a PDA have been studied in randomised trials of low to moderate quality according to GRADE, oral paracetamol appears to be as effective in closing a PDA as oral ibuprofen. In view of a recent report in mice of adverse effects on the developing brain from paracetamol, and another report of an association between prenatal paracetamol and the development of autism or autism spectrum disorder in childhood, long-term follow-up to at least 18 to 24 months postnatal age must be incorporated in any studies of paracetamol in the newborn population. Such trials are required before any recommendations for the use of paracetamol in the newborn population can be made.

PLAIN LANGUAGE SUMMARY

Paracetamol (acetaminophen) for patent ductus arteriosus in preterm and low-birth-weight infants

Background:

A common complication for very preterm (premature) or very small babies is a PDA (patent ductus arteriosus). PDA is an open channel between the lungs and heart. It should close after birth, but sometimes remains open because of the baby's premature stage of development. A PDA can lead to life-threatening complications. The usual treatment for PDA has been indomethacin or ibuprofen. Recently paracetamol (acetaminophen), a commonly used drug to treat fever or pain in children and infants, has been suggested as an alternative to ibuprofen, with potentially fewer side effects. A number of case reports and case series have suggested that paracetamol may be an attractive alternative for the closure of a PDA.

Study characteristics:

We identified two studies that enrolled 250 preterm infants and compared the effectiveness and safety of paracetamol versus ibuprofen in the treatment of a PDA in early life. The studies were conducted in Turkey and China.

Key findings:

When the results of the two studies were combined, the success rate for paracetamol to close a PDA was similar to that of ibuprofen. Adverse events were similar in both groups. However, in general the trends favoured infants who received paracetamol and additionally the adverse events were lower in the paracetamol group. Infants who were treated with paracetamol had a reduced duration of needing extra oxygen and a lower risk of hyperbilirubinaemia than those treated with ibuprofen.

Quality of the evidence:

Although the healthcare providers were not blinded to which drug the infants received (paracetamol versus ibuprofen) the quality of the studies was good.

Conclusions:

Paracetamol appears to be a promising new alternative to indomethacin and ibuprofen for the closure of a PDA with possibly fewer adverse effects.

Additional studies testing this intervention and including longer-term follow-up are needed before paracetamol can be recommended as standard treatment for a PDA in preterm infants. Several studies are ongoing that will eventually provide additional information.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Oral paracetamol compared to oral ibuprofen for patent ductus arteriosus in preterm or low-birth-weight infants

Patient or population: patients with patent ductus arteriosus in preterm or low-birth-weight infants
Settings: hospitals in China and Turkey
Intervention: oral paracetamol
Comparison: oral ibuprofen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral ibuprofen	Oral paracetamol				
Failure of ductal closure after the first course of treatment Echocardiogram	**Study population**		**RR 0.9** (0.67 to 1.22)	250 (2 studies)	⊕⊕◯◯ **low**	
	408 per 1000	**367 per 1000** (273 to 498)				
	Moderate					
	363 per 1000	**327 per 1000** (243 to 443)				
All-cause mortality during initial hospital stay Clinical assessment, no risk of bias	**Study population**		**RR 0.95** (0.52 to 1.72)	250 (2 studies)	⊕⊕⊕◯ **moderate**	
	152 per 1000	**144 per 1000** (79 to 261)				
	Moderate					
	153 per 1000	**145 per 1000** (80 to 263)				

Surgical closure of the PDA following treatment failure with paracetamol or ibuprofen Surgery	**Study population**		**RR 0.5** (0.05 to 5.32)	90 (1 study)	⊕⊕⊕○ **moderate**[1]	
	44 per 1000	**22 per 1000** (2 to 236)				
	Moderate					
	44 per 1000	**22 per 1000** (2 to 234)				
Severe IVH (Grade III-IV) Ultrasound	**Study population**		**RR 1** (0.3 to 3.37)	250 (2 studies)	⊕⊕⊕○ **moderate**	
	40 per 1000	**40 per 1000** (12 to 135)				
	Moderate					
	41 per 1000	**41 per 1000** (12 to 138)				
Necrotizing enterocolitis Clinical assessment and radiography	**Study population**		**RR 1.5** (0.43 to 5.18)	250 (2 studies)	⊕⊕⊕○ **moderate**	
	32 per 1000	**48 per 1000** (14 to 166)				
	Moderate					
	35 per 1000	**52 per 1000** (15 to 181)				
Oliguria (< 1 cc/kg/hr) Measurement of urine output	**Study population**		See comment	250 (2 studies)	⊕⊕⊕○ **moderate**[2]	Risks were calculated from pooled risk differences
	72 per 1000	**48 per 1000** (-8 to 112)				
	Moderate					

	56 per 1000	**38 per 1000** (-6 to 87)	
Serum levels of creatinine after treatment (mmol/L) Serum samples		The mean serum levels of creatinine after treatment mmol/l in the intervention groups was **1.05 lower** (5.32 lower to 3.21 higher)	250 (2 studies)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small sample size
[2] Small sample size

BACKGROUND

Description of the condition

The ductus arteriosus connects the pulmonary artery to the descending aorta (Clyman 2000). Normal fetal circulation is dependent on the placenta and the patency of the ductus arteriosus (PDA) (Mathew 1998). During fetal life it diverts most of the combined ventricular output away from the lungs (Clyman 2000). Following birth, and with the separation of the placenta and initiation of breathing, the circulation changes and the ductus closes (Mathew 1998). In full term newborns this happens within 24 to 48 hours after birth (Clyman 2000). In preterm newborns the ductus frequently fails to close. As a result, 70% of infants born before 28 weeks postmenstrual age (PMA) require medical or surgical closure of the PDA (Clyman 2000). The failure of the ductus arteriosus to constrict after birth is due to lower intrinsic tone, less ductal muscle fibre and fewer subendothelial cushions in preterm as compared to term infants (Hammerman 1995). The immature ductus arteriosus has higher sensitivity to the vasodilating effects of prostaglandins and nitric oxide (Hammerman 1995). This is aggravated by haemodynamic derangements due to respiratory distress syndrome and surfactant therapy (Hammerman 1995). The clinical consequences of a PDA are related to the degree of left to right shunting through the ductus. Despite the ability of the left ventricle, in preterm infants, to increase its output in the face of a left to right shunt, blood flow distribution to vital organs is altered due to a drop in diastolic pressure and localized vasoconstriction (Clyman 2000). The presence of a PDA is associated with reduced middle cerebral artery blood flow velocity (Weir 1999). The haemodynamic instability caused by the left to right shunt has been associated with gastrointestinal, cerebral and renal effects including spontaneous intestinal perforation and necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), decreased kidney function and bronchopulmonary dysplasia (BPD) and, if not managed, may lead to death.

In the two Cochrane reviews of prophylactic use of ibuprofen and indomethacin to close a PDA in preterm infants, the spontaneous closure rate in the control group was 58% and 57% respectively (Fowlie 2010; Ohlsson 2011).

Description of the intervention

A PDA can be treated surgically or medically with one of two prostaglandin inhibitors, indomethacin or ibuprofen. Surgical closure of a symptomatic PDA improves haemodynamics and lung compliance (Naulty 1978). However, medical treatment is still considered the treatment of choice because of the risks related to the surgery. In a large Canadian cohort (n = 3779) of very low-birth-weight infants, 28% required treatment for a PDA; 75% were treated with indomethacin alone, 8% with surgical ligation alone, and 17% required both indomethacin and surgical ligation (Lee 2000). Infants with lower birth weights were more likely to be treated surgically (Lee 2000). Prostaglandins play a significant role in keeping the ductus arteriosus patent (Mathew 1998). Inhibiting prostaglandin synthesis with non-selective blockers of both cyclo-oxygenase (COX) 1 and 2 is effective for the non-surgical closure of PDA (Clyman 2000). However, indomethacin use is associated with transient or permanent derangement of renal function, NEC, gastrointestinal haemorrhage or perforation, alteration of platelet function and impairment of cerebral blood flow or cerebral blood flow velocity (Edwards1990; Ohlsson 1993; Seyberth 1983; Wolf 1989).

Ibuprofen, a propionic acid derivative and non-selective COX inhibitor, is as effective as indomethacin in closing a PDA and reduces the risk of NEC (Ohlsson 2015). There is less evidence of transient renal insufficiency following treatment with ibuprofen compared to indomethacin (Ohlsson 2015).

Another non-steroidal anti-inflammatory drug, mefenamic acid, has been reported to close a PDA (Sakhalkar 1992), but no randomised controlled trials have been reported (Ohlsson 2011; Ohlsson 2015).

In the sheep fetus, Peterson (Peterson 1985) showed that acetaminophen has potent activity on the ductus arteriosus and produces a constriction in therapeutic analgesic quantities. In humans, Simbi 2002 reported on a pregnant woman near term who took nimesulide 400 mg and acetaminophen 500 mg twice daily for three days as a medication for pain. The women noticed diminished fetal movements and one day later ultrasound confirmed lack of fetal movements and breathing. A constricted ductus arteriosus was confirmed by fetal echocardiography. Following cesarean section the male infant presented with severe mixed acidosis. An echocardiogram showed an almost completely constricted ductus arteriosus. Following intensive care the infant improved and was discharged home on day 12 after birth. At three months follow-up the infant was doing well. Either nimesulide or acetaminophen, or both, could be responsible for ductal closure in this case.

The complications associated with the use of indomethacin and possibly ibuprofen have encouraged the search for an alternative drug to treat a PDA. In 2011 paracetamol was suggested as an alternative (Hammerman 2011). Hammerman reported on five preterm infants (PMA 26 to 32 weeks at birth and postnatal age of 3 to 35 days) with large, haemodynamically significant PDAs (Hammerman 2011). The infants had failed or had contraindications for treatment with ibuprofen. All infants were treated with oral paracetamol 15 mg/kg per dose every 6 hours. The treatment resulted in ductal closure in all infants within three days. No side effects were observed. The authors suggested that paracetamol could offer important therapeutic advantages over non-steroidal anti-inflammatory drugs (NSAIDs) (indomethacin and ibuprofen) as paracetamol has no peripheral vasoconstrictive effect, can be given to infants with clinical contraindications to NSAIDs, and appears to be effective after ibuprofen treatment

failure (Hammerman 2011).

Paracetamol is used to treat pain in infants. At the Astrid Lindgren Children's Hospital in Stockholm, Sweden, it is used for postoperative pain. An intravenous dose of paracetamol of 7.5 mg/kg every 8 hours for infants with a PMA of 28 to 32 weeks; 7.5 mg/kg every 6 hours for infants with a PMA of 33 to 36 weeks, and 10 to 15 mg/kg every 6 hours for infants with a PMA of 37 weeks or more is described in their protocol (Bartocci 2007).

In a survey of intravenous paracetamol use in neonates and infants under one year of age by UK anaesthetists, maintenance doses were either 7.5 mg/kg or 10 mg/kg with a dosing interval of six or eight hours in preterm infants (Wilson-Smith 2009).

In a study of the pharmacokinetics of intravenous acetaminophen, conducted in Australia, the postoperative dose given every 6 hours was 10 mg/kg for infants with a PMA of 28 to 32 weeks; 12.5 mg/kg for infants of a PMA of 32 to 36 weeks and 15 mg/kg for infants $\geq$ 36 weeks. Following the study the unit continues to use the reported doses based on PMA (Palmer 2008).

Unconjugated hyperbilirubinaemia impacts upon clearance of paracetamol (Palmer 2008). Acetaminophen-induced hepatic failure with encephalopathy has been described in a term newborn who received oral acetaminophen every four hours by the parents following circumcision (Walls 2007).

How the intervention might work

Paracetamol is an analgesic, antipyretic derivative of acetanilide with weak anti-inflammatory properties and is used as a common analgesic in all age groups, but may cause liver, blood cell and kidney damage (Drug Information Portal 2012). In low concentrations paracetamol stimulates and in high concentrations inhibits the synthesis of prostaglandins. In vivo (in adults) 500 mg of paracetamol causes a pronounced reduction of prostacyclin synthesis but has no effect on thromboxane synthesis (Grèen 1989). Because in vitro paracetamol is a weak inhibitor of both COX 1 and COX 2, the possibility exists that it inhibits a so far unidentified form of COX, perhaps a COX 3 (Botting 2000). In a murine model paracetamol was found to be less potent than indomethacin for construction of the mouse ductus arteriosus in vitro (El-Khuffash 2014).

Since the report in 2011 by Hammerman and co-workers (Hammerman 2011) there have been many case series of treatment of a PDA with paracetamol in preterm infants. In five recent case series (Kessel 2014; Nadir 2014; Sinah 2013; Terrin 2014; Yurttutan 2013) a total of 38 infants with different contraindications for the use of ibuprofen or indomethacin were included. Paracetamol was administered orally, intravenously or via nasogastric tube and the dose and duration of treatment varied; orally 15 mg/kg 8 hourly for 48 hours (Sinah 2013); 15 mg/kg 6 hourly for 3 days (Yurttutan 2013); 15 mg/kg 6 hourly for up to 7 days (Nadir 2014); via nasogastric tube 15 mg/kg 6 hourly for 3 to 7 days (Kessel 2014); or intravenously 7.5 to 15 mg/kg every 4 to 6 hours, with a maximum daily dose of 60 mg/kg (duration of treatment 3 days in 5 of 7 cases) (Terrin 2014). In these case reports the PDA closed in 33 of the 38 cases treated with paracetamol (86%). Kessel and co-workers (Kessel 2014) measured plasma paracetamol concentrations before the fifth dose and ninth dose and 24 hours after the last dose. Most measured paracetamol blood concentrations were comparable to those recommended for pain and fever control (10 to 20 mg/ml) (Arana 2001).

In the most recently published case series, El-Khuffash and co-workers (El-Khuffash 2014) retrospectively evaluated the clinical effectiveness of paracetamol on the closure of a PDA, and prospectively examined its effect on the in vitro term and preterm murine ductus arteriosus. A total of 21 infants were included in the study from the Mount Sinai Hospital, Toronto, Ontario, Canada and the Rotunda Maternity Maternity Hospital, Dublin, Ireland. At the Canadian site paracetamol was either given orally as a short course (15 mg/kg 6 hourly for 48 hours) or a long course of 15 mg/kg 6 hourly for 7 days. At the Irish site paracetamol was given intravenously, 15 mg/kg 6 hourly for a minimum of 48 hours until PDA closure was confirmed on echocardiography or up to a maximum of 6 days. In both centres, the decision to administer paracetamol treatment to neonates with a haemodynamically significant PDA was after failure of two courses of either ibuprofen or indomethacin or if there were contraindications to medical treatments (El-Khuffash 2014). No changes in PDA haemodynamics were seen in the five infants treated with a short course of paracetamol. In six of the seven infants treated with a long course the PDA closed. In eight of the nine infants treated with intravenous paracetamol the PDA closed (El-Khuffash 2014). Paracetamol drug levels were not ascertained. The authors concluded that the efficacy of paracetamol on PDA closure may depend on the duration of treatment and the mode of administration (El-Khuffash 2014). The inhibitory effect of paracetamol on prostaglandin E_2 (PGE_2) may not be present at lower gestational ages (El-Khuffash 2014).

Recently there have been concerns raised that prenatal or neonatal exposure, or both, to paracetamol could have adverse effects on brain development. Viberg and co-workers (Viberg 2014) examined whether neonatal paracetamol exposure in mice could affect the development of the brain, manifested as adult behaviour and cognitive deficits, as well as changes in the response to paracetamol. Ten day-old mice were administered a single dose of paracetamol (30 mg/kg body weight) or repeated doses of paracetamol (30 + 30 mg/kg body weight, 4 hours apart). Concentrations of paracetamol and brain-derived neurotrophic factor (BDNF) were measured in the neonatal brain and behavioural testing was done when animals reached adulthood. Acute neonatal exposure to paracetamol (2 x 30 mg) resulted in altered locomotor activity on exposure to a novel home cage arena and failure to acquire spatial learning in adulthood, without affecting thermal nociceptive responding or anxiety-related behaviour. However, mice exposed to paracetamol (2 x 30 mg) as neonates failed to exhibit paracetamol-induced antinociceptive and anxiogenic-like behaviour in adulthood. The

authors suggested that behavioural alterations in adulthood may, in part, be due to paracetamol-induced changes in BDNF levels in key brain regions at a critical time during development. They concluded that in mice exposure to and presence of paracetamol during a critical period of brain development can induce long-lasting effects on cognitive function and alter the adult response to paracetamol in mice (Viberg 2014).

In an ecological study conducted in humans and using country-level data for the period 1984 to 2005, prenatal use of paracetamol was correlated with autism or autism spectrum disorder (ASD) (Bauer 2013). To explore the relationship of early neonatal paracetamol exposure to autism and ASD, population weighted average male autism prevalence rates for all available countries and US states were compared to male circumcision rates, a procedure for which paracetamol has been widely prescribed since the mid-1990s. For studies including boys born after 1995, there was a strong correlation between country-level autism and ASD prevalence in males and a country's circumcision rate (r = 0.98) (Bauer 2013).

It is therefore of extreme importance that infants enrolled in trials of paracetamol either for pain relief or for closure of a PDA be followed long-term with conventional developmental tests and tests to diagnose autism and ASD (American Psychiatric Association 2013).

Why it is important to do this review

Currently there are at least three ongoing trials on this topic (NCT01938261; NCT01291654; NCT02002741). It is likely that several trials will be conducted in the near future and, with regular updates, this review will track the progress of the research in a timely fashion. It is expected that paracetamol will be compared with oral or intravenous ibuprofen or intravenous indomethacin for the efficacy of closing a PDA. In view of recent findings in mice of adverse effects on brain development following neonatal exposure to paracetamol and an association of neonatal exposure to paracetamol and autism or ASD it is important that long-term follow-up is included in individual studies and in this systematic review.

OBJECTIVES

To determine the efficacy and safety of intravenous or oral paracetamol compared with placebo or no intervention, intravenous indomethacin, intravenous or oral ibuprofen, or with other cyclo-oxygenase inhibitors for closure of a PDA in preterm or low-birth-weight infants.

Primary objectives

1. To determine the efficacy and safety of intravenous or oral paracetamol compared with placebo or no intervention for closure of a PDA in preterm or low-birth-weight infants
2. To determine the efficacy and safety of intravenous or oral paracetamol compared with intravenous indomethacin, for closure of a PDA in preterm or low-birth-weight infants
3. To determine the efficacy and safety of intravenous or oral paracetamol compared with intravenous ibuprofen for closure of a PDA in preterm or low-birth-weight infants
4. To determine the efficacy and safety of intravenous or oral paracetamol compared with oral ibuprofen for closure of a PDA in preterm or low-birth-weight infants
5. To determine the efficacy and safety of intravenous or oral paracetamol compared with other cyclo-oxygenase inhibitors (separate analyses for different cyclo-oxygenase inhibitors) for closure of a PDA in preterm or low-birth-weight infants

Secondary objectives

1. To determine in subgroup analyses the efficacy and safety of paracetamol for closure of a PDA in relation to postnatal ages of < 7 days, 7 to 14 days and > 14 days at the time of administration of the first dose of paracetamol.
2. To determine in subgroup analyses the efficacy and safety of paracetamol for closure of a PDA in relation to the following criteria:

i) gestational age (< 28 weeks, 28 to 32 weeks, 33 to 36 weeks);

ii) birth weight (< 1000 g, 1000 to 1500 g, 1501 to 2500 g).

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised and quasi-randomised controlled trials for inclusion.

Types of participants

Infants born preterm (< 37 weeks PMA) or with low birth weight (< 2500 g at birth) who had an echocardiographic diagnosis of a PDA regardless of their postnatal age were included. In the Cochrane review of ibuprofen for the treatment of a PDA all 20

included studies made the diagnoses of a PDA by echocardiography (Ohlsson 2015), and it is likely that would be the case in studies of the effectiveness of paracetamol in closing a PDA.

Types of interventions

Paracetamol (given via any route for the purpose of closure of PDA) in any dose versus placebo or no intervention or versus another prostaglandin inhibitor were included. If the intention for administration of paracetamol was not closure of PDA, the study would be excluded. Only data from the first course of paracetamol were included if the study reported on more than one course. Studies that used any therapeutic regimen of paracetamol were included.

Types of outcome measures

Primary outcomes

- Failure of PDA closure after the first course of paracetamol treatment (closure and failure of closure confirmed by echocardiographic criteria)
- Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardized and validated assessment tool or a child developmental specialist, or both) at any age reported (outcome data will be grouped at 12, 18, 24 months if available)
- Autism or autism spectrum disorder (ASD) in childhood (American Psychiatric Association 2013); this outcome was added at the full review stage

Secondary outcomes

- All-cause mortality during initial hospital stay
- Neonatal mortality (death during the first 28 days of life)
- Infant mortality (death during the first year of life)
- Re-opening of the ductus arteriosus (defined as echocardiographic evidence of closure followed by re-opening of PDA at later stage)
- Surgical closure of the PDA
- Treatment with indomethacin, ibuprofen or other prostaglandin inhibitor to close the PDA following treatment failure
- Duration of ventilator support (days)
- Duration of need for supplementary oxygen (O_2) (days)
- Pulmonary haemorrhage (blood stained liquid flowing from the trachea of the infant)
- Pulmonary hypertension (defined as an increased mean pulmonary arterial pressure of 25 mmHg at rest) (Van Loon 2011)
- Bronchopulmonary dysplasia (BPD) at 28 days (defined as O_2 requirement at 28 days postnatal age in addition to compatible clinical and roentgenographic findings)
- BPD at 36 weeks PMA (defined as O_2 requirement at 36 weeks PMA in addition to compatible clinical and roentgenographic findings)
- BPD defined according to the new criteria: mild BPD defined as a need for supplemental O_2 for $\geq$ 28 days but not at 36 weeks' PMA or discharge, moderate BPD as O_2 for $\geq$ 28 days plus treatment with < 30% O_2 at 36 weeks' PMA, and severe BPD as O_2 for $\geq$ 28 days plus $\geq$ 30% O_2 or positive pressure, or both, at 36 weeks' PMA (Ehrenkranz 2005)
- Intraventricular haemorrhage (IVH) (Grade I-IV)
- Severe IVH (Grade III-IV)
- Periventricular leukomalacia (PVL)
- Necrotizing enterocolitis (NEC) (any stage)
- Intestinal perforation
- Gastrointestinal bleed
- Retinopathy of prematurity (ROP) (according to the international classification of ROP); any stage and stage $\geq$ 3
- Decreased urine output (defined as < 1 cc/kg/hr) during treatment
- Sepsis (clinical symptoms and signs of sepsis and a positive blood bacterial culture); this outcome was added at the full review stage
- Serum or plasma levels of creatinine (mmol/L) after treatment
- Serum or plasma levels of aspartate transaminase (AST) (IU/L) following treatment
- Serum or plasma levels of alanine transaminase (ALT) (IU/L) following treatment
- Number of infants with AST or ALT levels > 100 IU/mL
- Serum bilirubin (mmol/L) following treatment
- Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and body weight)
- Incidence of liver failure; evidence of acute liver injury combined with either severe coagulopathy (International Normalized Ratio (INR) > 2.0 or prothrombin time (PT) > 20 seconds) or encephalopathy with moderate coagulopathy (INR $\geq$ 1.5 or PT $\geq$ 15 seconds) (Sundaram 2011)
- Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death) (days)
- Other side effects reported by the authors (not pre-specified)

Search methods for identification of studies

See: Cochrane Review Group search strategy.

Electronic searches

We used the standard search strategy of the Cochrane Neonatal Review Group as outlined in the Cochrane Library. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), MEDLINE (1966 to De-

cember 2013), EMBASE (1980 to December 2013) and CINAHL (1982 to December 2013). Ms Colleen Ovelman, Trials Search Co-ordinator, Cochrane Neonatal Review Group, conducted the searches modified as needed for the different databases. For MEDLINE the following search string was used: (paracetamol OR acetaminophen) AND (patent ductus arteriosus or PDA) AND ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])). Relevant reviews related to the topic were identified. No language restrictions were applied.

We conducted electronic searches of abstracts from the meetings of the Pediatric Academic Societies 2000 to 2013 and the Perinatal Society of Australia and New Zealand 2000 to 2013.

We searched the following clinical trials registries for ongoing or recently completed trials: clinicaltrials.gov; controlled-trials.com; anzctr.org.au; who.int/ictrp in December 2013. We searched the Web of Science for articles quoting identified RCTs in December 2013.

We searched the first 200 hits on Google Scholar^{TM} to identify grey literature. We limited the Google ScholarTM to the first 200 hits as in our experience the yield is poor after 200 hits.

We repeated the search of MEDLINE in August 2014 and did not identify any new trials.

Searching other resources

We performed manual searches of the reference lists of full-text versions of eligible articles (RCTs and reviews) identified in the primary search of the literature.

Data collection and analysis

Standard methods of The Cochrane Collaboration and its Neonatal Review Group were used.

Selection of studies

Two review authors independently assessed study eligibility for inclusion in this review according to the pre-specified selection criteria.

Data extraction and management

Two review authors independently extracted data from the full-text articles using a specifically designed spread sheet and customized form to manage information. We used these forms to decide trial inclusion and exclusion, extract data from eligible trials, and for requesting additional published information from authors of the original report. We entered and cross-checked data using RevMan 5.3 software (RevMan 2014). We compared the extracted data for any differences. If noted, we resolved differences by mutual discussion and consensus. We contacted the authors of the two identified trials and we obtained unpublished data from the Oncel group (Oncel 2013) and the Dang group (Dang 2013).

Assessment of risk of bias in included studies

The following headings and associated questions (based on the questions in the 'Risk of bias' table) were evaluated by the two review authors and entered into the 'Risk of bias' table.

Selection bias

(random sequence generation and allocation concealment)

Adequate sequence generation?

For each included study, we categorized the risk of selection bias.
Low risk: adequate (any truly random process e.g. random number table; computer random number generator).
High risk: inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number).
Unclear risk: no or unclear information provided.

Allocation concealment?

For each included study, we categorized the risk of bias regarding allocation concealment.
Low risk: adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes).
High risk: inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth).
Unclear risk: no or unclear information provided.

Blinding?

Performance bias

For each included study, we categorized the methods used to blind study personnel from knowledge of which intervention a participant received. As our study population consisted of neonates they would all be blinded to the study intervention.
Low risk: adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group).
High risk: inadequate, personnel aware of group assignment.
Uncelar risk: no or unclear information provided.

Detection bias

For each included study, we categorized the methods used to blind outcome assessors from knowledge of which intervention a participant received. As our study population consisted of neonates they would all be blinded to the study intervention. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods used with regards to detection bias.
Low risk: adequate, follow-up was performed with assessors blinded to group.
High risk: inadequate, assessors at follow-up were aware of group assignment.
Unclear risk: no or unclear information provided.

Incomplete data addressed?

Attrition bias

For each included study and for each outcome, we describe the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we planned to re-include missing data in the analyses. We categorized the methods with respect to the risk of attrition bias.
Low risk: adequate (< 10% missing data).
High risk: inadequate (> 10% missing data).
Unclear risk: no or unclear information provided.

Free of selective reporting?

Reporting bias

For each included study, we describe how we investigated the risk of selective outcome reporting bias and what we found. We assessed the methods as follows.
Low risk: adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported).
High risk: inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported).
Unclear risk: no or unclear information provided (the study protocol was not available).

Free of other bias?

Other bias

For each included study, we describe any important concerns we have about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias.
Low risk: no concerns of other bias raised.
High risk: concerns raised about multiple looks at the data with the results made known to the investigators; difference in number of patients enrolled in abstract and final publications of the paper.
Unclear: concerns raised about potential sources of bias that could not be verified by contacting the authors.

Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to assess the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses, see 'Sensitivity analysis'.
We used the GRADE approach (Guyatt 2011; Schünemann 2009) in order to assess the quality of the body of evidence relating to the following key outcomes for the only comparison of 'oral paracetamol versus oral ibuprofen'.
1. Failure of ductal closure after the first course of treatment.
2. All-cause mortality during initial hospital stay.
3. Surgical closure of the PDA following treatment failure with paracetamol or ibuprofen.
4. Severe IVH (Grade III-IV).
5. NEC.
6. Oliguria (< 1 cc/kg/hr)
7. Serum levels of creatinine after treatment (mmol/L).
We used GRADEprofiler (GRADEpro 2014) to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

We analysed treatment effects in the individual trials using RevMan 5.3 (RevMan 2014).

Dichotomous data

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

Continuous data

We reported continuous data using mean difference (MD) with 95% CI. If the authors had reported continuous data as median and range we would have estimated the mean and variance from the median, range and the size of the sample according to the formulas by Hozo 2005.

Unit of analysis issues

The unit of randomisation was the individual infant. We did not include cross-over or cluster randomised trials as those trial designs are unlikely for the intervention studied in this review. No cross-over or cluster randomised trials were identified. An infant was only considered once even if the infant may have been randomised twice by investigators. We planned to contact the authors in order to provide data resulting from the first randomisation. If we could not separate data from the first randomisation, the study was planned to be excluded.

Dealing with missing data

We requested additional data from the authors of each included trial when data on important outcomes were missing or needed clarification. We did receive clarifying information from the authors of both included trials (Dang 2013; Oncel 2013). The authors clarified that all the analyses that were published or they provided us with were intention-to-treat analyses.

Assessment of heterogeneity

We used RevMan 5.3 software to assess the heterogeneity of treatment effects between trials. We used the following two formal statistics described below.

1. The Chi^2 test, to assess whether observed variability in effect sizes between studies was greater than would be expected by chance. Since this test has low power when the number of studies included in the meta-analysis is small, we set the alpha probability at the 10% level of significance.

2. The I^2 statistic to ensure that pooling of data was valid. We graded the degree of heterogeneity as: none, low, moderate, and high for values of < 25%, ≥ 25% to 49%, 50% to 74%, and ≥ 75% respectively (Higgins 2003). There was no evidence of statistically significant heterogeneity for any of the analyses for which results from both the included trials were included (I^2 = 0 % for most analyses, and all results for I^2 < 25%, that is none).

Assessment of reporting biases

We identified the study protocols for both the trials we selected for inclusion (see the table 'Characteristics of included trials'). We planned to assess reporting and publication bias by examining the degree of asymmetry of a funnel plot in RevMan 5.3 provided that a sufficient number of studies (n = 10) were available (RevMan 2014). However, this was not feasible as only two trials were included in any one meta-analysis (Dang 2013; Oncel 2013).

Data synthesis

We performed statistical analyses according to the recommendations of the Cochrane Neonatal Review Group (http://neonatal.cochrane.org/en/index.html). We analysed all infants randomised on an intention-to-treat basis. We analysed treatment effects in the individual trials. We used a fixed-effect model in the meta-analysis to combine the data. Where substantial heterogeneity existed, the potential cause of heterogeneity would have been examined in subgroup and sensitivity analyses. There was no heterogeneity between the included study results (I^2 < 25%). When we judged meta-analysis to be inappropriate, we planned to analyse and interpret individual trials separately. For estimates of typical RR and RD, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. We would have used the standardized mean difference (SMD) to combine trials that measured the same outcome but used different scales.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were pre-specified:

- gestational age (< 28 weeks, 28 to 32 weeks, 33 to 36 weeks);

- birth weight (<1000 g, 1000 to 1500 g, 1501 to 2500 g).

Subgroup analyses to determine the efficacy and safety of paracetamol for closure of a PDA in relation to postnatal ages of < 7 days, 7 to 14 days and > 14 days at the time of administration of the first dose of paracetamol.

The data from the two included studies were not suitable for subgroup analyses according to the pre-specified categories.

Sensitivity analysis

A sensitivity analysis was planned to be performed to determine if the findings were affected by including only studies of adequate methodology, defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and < 10% losses to follow-up.
The two studies were of equal quality.

RESULTS

Description of studies

Results of the search

The literature searches in December 2013 identified three published studies (Dang 2013; Oncel 2013; Zarkesh 2013) and three ongoing studies (NCT01938261; NCT01291654; NCT02002741). The study by Zarkesh 2013 has been published in abstract form only and awaits further classification, leaving two studies for inclusion in this review.

Included studies

For details see the table 'Characateristics of included studies'.
Dang 2013 was a single centre study conducted in Changchun, China.

- Objective: to evaluate the efficacy and safety profiles of oral paracetamol to those of standard ibuprofen for PDA closure in preterm infants.
- Population: preterm infants with PMA ≤ 34 weeks with echocardiographically confirmed PDA; postnatal age ≤ 14 days.
- Intervention or contrast: the paracetamol group received 15 mg/kg of paracetamol orally every 6 hours for 3 days; the ibuprofen group received oral ibuprofen at an initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours.
- Outcomes assessed, primary outcome: rates of ductal closure after treatment confirmed by daily cardiography during treatment; secondary outcomes: oliguria (urine output < 1 cc/kg/hr), IVH, tendency to bleed, NEC, hyperbilirubinaemia, serum creatinine, death, BPD, PVL, NEC, ROP, sepsis.
- Notes: we contacted the authors in January 2014 to obtain unpublished information regarding outcomes, and we received information in April 2014.

Oncel 2013 was a single centre study conducted in Ankara, Turkey.

- Objective: to compare the efficacy and safety oral paracetamol and oral ibuprofen for the pharmacological closure of PDA in preterm infants.
- Population: preterm infants PMA ≤ 30 weeks, birthweight ≤ 1250 g with echocardiographically confirmed significant PDA; postnatal age 48 to 96 hours.
- Intervention or contrast: the paracetamol group received 15 mg/kg of paracetamol orally every 6 hours for 3 days; the ibuprofen group received oral ibuprofen at an initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours.
- Outcomes assessed, primary outcome: rates of ductal closure after treatment by echocardiography performed by a cardiologist who was blinded to the treatment group; secondary outcomes: all-cause mortality during initial hospital stay, neonatal mortality (first 28 days of life), infant mortality, re-opening of the ductus arteriosus, surgical closure of the PDA, duration of ventilatory support, duration of need for supplementary oxygen, pulmonary haemorrhage, pulmonary hypertension, BPD (at 28 days and at 36 weeks PMA, severe BPD at 36 weeks PMA), IVH (all grades and Grade III-IV), PVL, NEC, intestinal perforation, gastrointestinal bleeding, ROP (any stage, stage ≥ 3, ROP requiring laser treatment), oliguria (urine output < 1 cc/kg/hr), serum levels after treatment of creatinine, bilirubin, aspartate transaminase, alanine transaminase, liver failure, duration of hospital stay, sepsis.
- Notes: we contacted the authors and received unpublished information regarding several of the outcomes listed above, we received information in January 2014. The published report includes 80 patients who actually received the intervention whereas from the authors we received information on all outcomes for all 90 enrolled patients.

Excluded studies

No study was excluded but the study by Zarkesh 2013 was published in abstract form only and is awaiting classification before it can be included or excluded. There are at least three ongoing trials (NCT01938261; NCT01291654; NCT02002741) that we identified in clinical trials registries.

Risk of bias in included studies

For details see Figure 1 ('Risk of bias' graph) and Figure 2 ('Risk of bias' summary).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

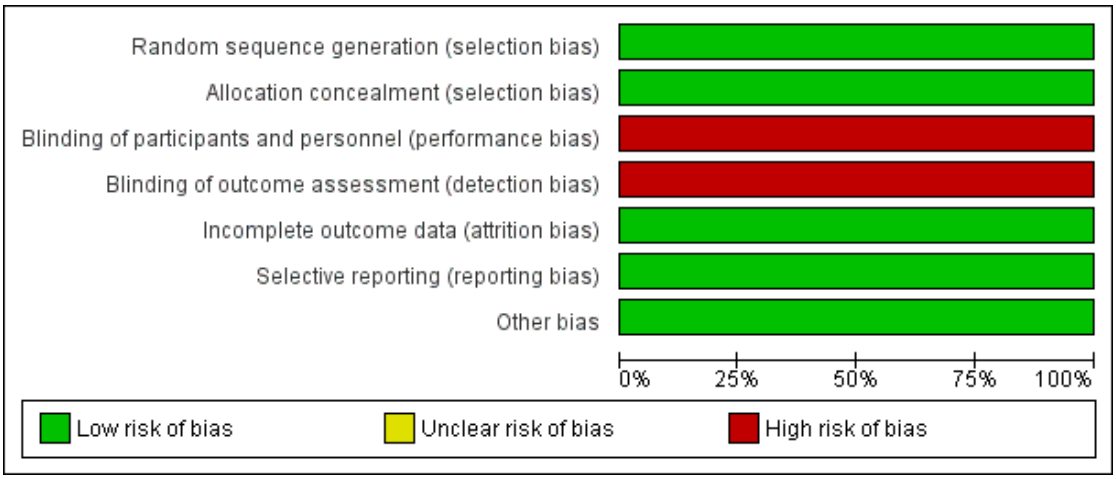
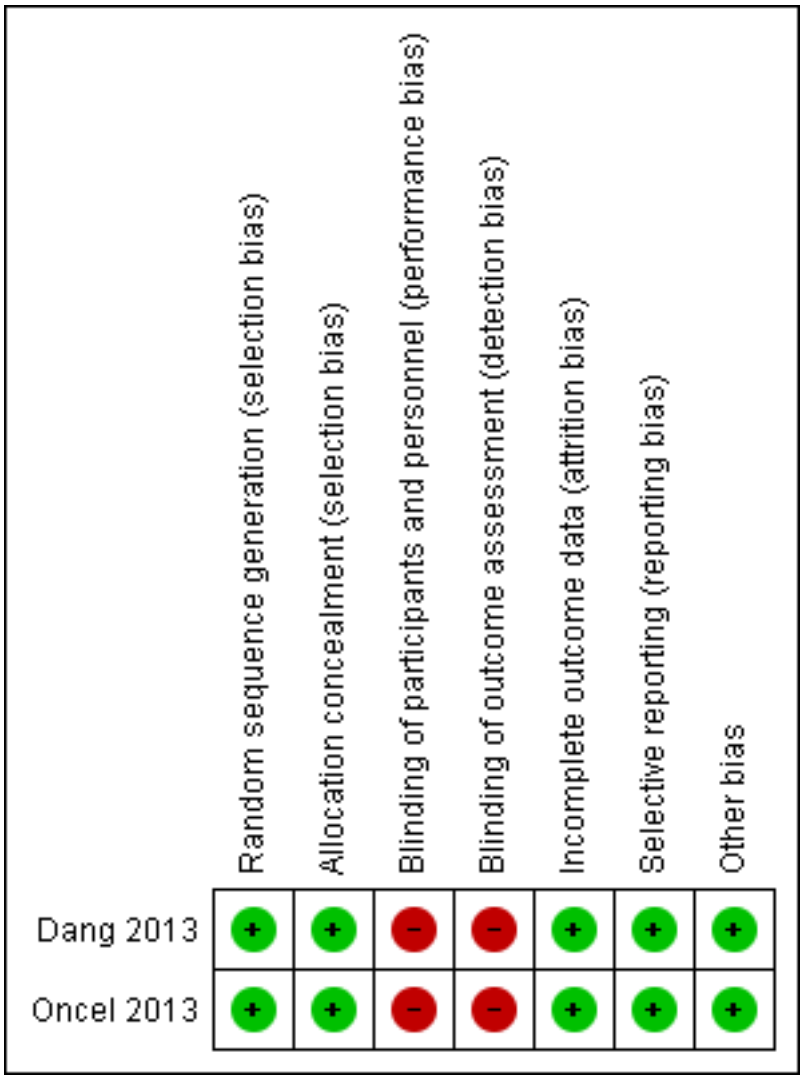


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



The randomisation sequence was computer generated in both studies.

Allocation

Both studies used sequentially numbered, sealed opaque envelopes for the allocation to the two treatment groups.

Blinding

In both studies (Dang 2013; Oncel 2013) the two study drugs were administered at different time points after the initial dose. Both studies administered paracetamol 15 mg/kg every 6 hours for 3 days and ibuprofen was given at an initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours. No placebo was administered at time points when no active drug was administered in one of the treatment groups, to try and mask what drug was given. Therefore, healthcare providers and researchers were not blinded to group allocation of the infants. Dang 2013 states "doctors and nurses were not blind". Oncel 2013 reports "....the intervention was not completely blinded because of the different number of doses per day of the drugs. However, the most important outcome-PDA closure-was made by a cardiologist, who was blinded to the treatment groups".

Incomplete outcome data

Outcome data reported for all pre-set outcomes and for all enrolled infants.

Selective reporting

The protocols for both studies were available to us as the trials were registered in the Chinese Clinical Trial Register (Dang 2013) and at ClinicalTrials.gov (Oncel 2013). We found no indication of selective reporting.

Other potential sources of bias

There were no other sources of bias identified.
We considered the overall risk of bias in the two studies to be low.

Effects of interventions

See: **Summary of findings for the main comparison** Oral paracetamol compared to oral ibuprofen for patent ductus arteriosus in preterm or low-birth-weight infants

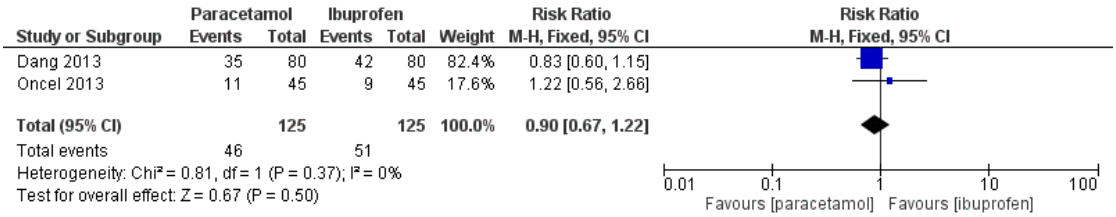
Oral paracetamol versus oral ibuprofen (Comparison 1)

Primary outcomes

Failure of PDA closure after the first course of paracetamol treatment (closure and failure of closure confirmed by echocardiographic criteria) (Outcome 1.1)

See Analysis 1.1. Figure 3

Figure 3. Forest plot of comparison: 1 Oral paracetamol versus oral ibuprofen, outcome: 1.1 Failure of ductal closure after the first course of treatment.



Both studies (n = 250 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in failure of PDA closure (typical RR 0.90, 95% 0.67 to 1.22; typical RD -0.04, 95% CI -0.16 to 0.08; I^2 = 0% for RR and I^2 = 23% for RD).

Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardized and validated assessment tool or a child developmental specialist, or both) at any age reported (outcome data will be grouped at 12, 18, 24 months if available)

No study has reported on this outcome.

Autism or autism spectrum disorder (ASD) in childhood

As defined by the American Psychiatric Association (American Psychiatric Association 2013).
No study has reported on this outcome.

Secondary outcomes

All-cause mortality during initial hospital stay (Outcome 1.2)

See Analysis 1.2
Both studies (n = 250 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in all-cause mortality during the initial hospital stay (typical RR 0.95, 95% CI 0.52 to 1.72; typical RD -0.01, 95% CI -0.10 to 0.08; I^2 = 0% (none) for both RR and RD).

Neonatal mortality (death during the first 28 days of life) (Outcome 1.3)

See Analysis 1.3
One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in neonatal mortality (RR 1.17, 95% CI 0.43 to 3.20; RD

0.02, 95% CI -0.12 to 0.17). The test for heterogeneity was not applicable.

Infant mortality (death during the first year of life) (Outcome 1.4)

See Analysis 1.4

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in infant mortality (RR 1.14, 95% CI 0.45 to 2.89; RD 0.02, 95% CI -0.13 to 0.18). The test for heterogeneity was not applicable.

Re-opening of the ductus arteriosus (defined as echocardiographic evidence of closure followed by re-opening of PDA at later stage) (Outcome 1.5)

See Analysis 1.5

Both studies (n = 143 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of re-opening of the ductus arteriosus (typical RR 1.04, 95% CI 0.50 to 2.18; typical RD 0.01, 95% CI -0.11 to 0.13; I^2 = 0% (none) for RR and I^2 = 1% (none) for RD).

Surgical closure of the PDA following treatment failure with paracetamol or placebo (Outcome 1.6)

See Analysis 1.6

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in surgical closure of the PDA following treatment failure (RR 0.50, 95% CI 0.05 to 5.32; RD -0.02, 95% CI -0.10 to 0.05). The test for heterogeneity was not applicable.

Treatment with indomethacin, ibuprofen or other prostaglandin inhibitor to close the PDA following treatment failure with paracetamol or placebo

This outcome was not reported in either of the two included studies.

Duration of ventilator support (days) (Outcome 1.7)

See Analysis 1.7

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the duration of ventilator support (mean difference (MD) -4.15 days, 95% CI -8.63 to 0.33). The test for heterogeneity was not applicable.

Pulmonary haemorrhage (blood stained liquid flowing from the trachea of the infant) (Outcome 1.8)

See Analysis 1.8

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of pulmonary haemorrhage (RR 1.00, 95% CI 0.21 to 4.69; RD 0.00, 95% CI -0.10 to 0.10). The test for heterogeneity was not applicable.

Pulmonary hypertension (defined as an increased mean pulmonary arterial pressure of 25 mmHg at rest) (Outcome 1.9)

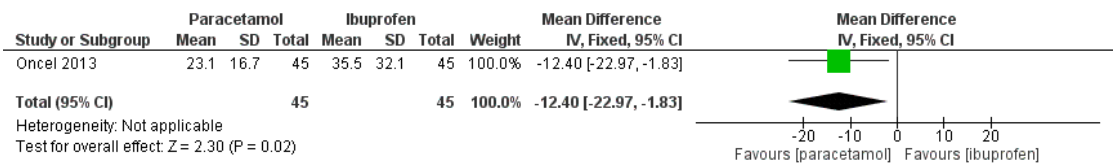
See Analysis 1.9

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in pulmonary hypertension (RR 0.33, 95% CI 0.01 to 7.97; RD -0.02, 95% CI -0.08 to 0.04). The test for heterogeneity was not applicable.

Duration of need for supplementary oxygen (days) (Outcome 1.10)

See Analysis 1.10, Figure 4

Figure 4. Forest plot of comparison: 1 Oral paracetamol versus oral ibuprofen, outcome: 1.10 Duration for need of supplementary oxygen (days).



One study (n = 90 infants) reported on this outcome. There was a significant difference between the paracetamol and the ibuprofen groups in the duration of need of supplementary oxygen (O_2) favouring the paracetamol treated group (MD -12.40 days, 95% CI -22.97 to -1.83). The test for heterogeneity was not applicable.

Bronchopulmonary dysplasia (BPD) at 28 days (defined as O_2 requirement at 28 days postnatal age in addition to compatible clinical and roentgenographic findings) (Outcome 1.11)

See Analysis 1.11

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of BPD at 28 days postnatal age (RR 0.79, 95% CI 0.46 to 1.35; RD -0.09, 95% CI -0.29 to 0.11). The test for heterogeneity was not applicable.

BPD at 36 weeks PMA (defined as O_2 requirement at 36 weeks PMA in addition to compatible clinical and roentgenographic findings) (Outcome 1.12)

See Analysis 1.12

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of BPD at 36 weeks PMA (RR 0.71, 95% CI 0.38 to 1.30; RD -0.11, 95% CI -0.30 to 0.08). The test for heterogeneity was not applicable.

Moderate to severe BPD according to the new criteria: moderate BPD defined as O_2 for ≥ 28 days plus treatment with < 30% O_2 at 36 weeks' PMA; and severe BPD as O_2 for ≥ 28 days plus ≥ 30% O_2 or positive pressure at 36 weeks' PMA, or both (Outcome 1.13)

See Analysis 1.13

One study (n = 160 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups (RR 0.80, 95% CI 0.22 to 2.87; RD -0.01, 95% CI -0.08 to 0.06). The test for heterogeneity was not applicable.

Severe BPD defined according to the new criteria: severe BPD defined as O_2 for ≥ 28 days plus ≥ 30% O_2 or positive pressure at 36 weeks' PMA, or both (Outcome 1.14)

See Analysis 1.14

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of severe BPD (RR 0.63, 95% CI 0.32 to 1.23; RD -0.13, 95% CI -0.32 to 0.05). The test for heterogeneity was not applicable.

Intraventricular haemorrhage (IVH) (Grade I-IV) (Outcome 1.15)

See Analysis 1.15

Both studies reported on this outcome, in 250 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of IVH (typical RR 0.92, 95% CI 0.73 to 1.15; typical RD -0.03, 95% CI -0.12 to 0.05; I^2 = 0% (none) for RR and for RD).

Severe IVH (Grade III-IV) (Outcome 1.16)

See Analysis 1.16

Both studies reported on this outcome, in 250 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of severe IVH (typical RR 1.00, 95% CI 0.30 to 3.37; typical RD 0.00, 95% CI -0.05 to 0.05; I^2 = 0% (none) for RR and for RD).

Periventricular leukomalacia (PVL) (Outcome 1.17)

See Analysis 1.17

Both studies reported on this outcome, in 250 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of PVL (typical RR 1.00, 95% CI 0.36 to 2.76; typical RD -0.00, 95% CI -0.06 to 0.06; I^2 = 0% (none) for RR and for RD).

Necrotizing enterocolitis (NEC) (any stage) (Outcome 1.18)

See Analysis 1.18

Both studies (n = 250 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of NEC (typical RR 1.50, 95% CI 0.43 to 5.18; typical RD 0.02, 95% CI -0.03 to 0.06; I^2 = 0% (none) for RR and for RD).

Intestinal perforation (Outcome 1.19)

See Analysis 1.19

One study (n = 90 infants) reported on this outcome. Intestinal perforation did not occur in any patients in either of the two groups. The RR was not estimable and there was no significant difference between the paracetamol and the ibuprofen groups (RD 0.00, 95% CI -0.04 to 0.04). The test for heterogeneity was not applicable.

Gastrointestinal bleed (Outcome 1.20)

See Analysis 1.20

Both studies (n = 250 infants) reported on gastrointestinal bleeding. There was no significant difference between the paracetamol

and the ibuprofen groups in the typical RR (typical RR 0.30, 95% CI 0.08 to 1.06; P = 0.06) but there was a significant difference in the typical RD (RD -0.06, 95% CI -0.11 to -0.00; P = 0.04) favouring paracetamol over ibuprofen (NNTB 17, 95% CI 9 to infinity; I^2 = 0% (none) for RR and 5% (none) for RD).

Retinopathy of prematurity (ROP) any stage (according to the international classification of ROP) (Outcome 1.21)

See Analysis 1.21

Both studies (n = 250 infants) reported on this outcome, in 250 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of developing ROP (typical RR 0.72, 95% CI 0.37 to 1.41; typical RD -0.04, 95% CI -0.12 to 0.04; I^2 = 0% (none) for RR and for RD).

ROP stage ≥ 3 (according to the international classification of ROP) (Outcome 1.22)

See Analysis 1.22

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the RR (RR 0.43, 95% CI 0.12 to 1.55) or in the RD (RD -0.09, 95% CI -0.22 to 0.04). The test for heterogeneity was not applicable.

ROP requiring laser therapy (Outcome 1.23)

See Analysis 1.23

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of developing ROP requiring laser therapy (RR 0.43, 95% CI 0.12 to 1.55; RD -0.09, 95% CI -0.22 to 0.04). The test for heterogeneity was not applicable.

Sepsis (clinical symptoms and signs of sepsis and a positive blood bacterial culture) (Outcome 1.24)

See Analysis 1.24

One study (n = 90 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in the risk of sepsis (RR 1.08, 95% CI 0.57 to 2.03; RD 0.02, 95% CI -0.17 to 0.21). The test for heterogeneity was not applicable.

Oliguria (decreased urine output (defined as < 1 cc/kg/hr) during treatment) (Outcome 1.25)

See Analysis 1.25

Both studies (n = 250 infants) reported on this outcome. Oliguria did not occur in any infant in the study by Oncel (Oncel 2013). There was no significant difference between the paracetamol and the ibuprofen groups in risk of oliguria (typical RR 0.67, 95% CI 0.25 to 1.79; typical RD -0.02, 95% CI -0.08 to 0.04; I^2 test not applicable for RR and 24% (none) for RD).

Serum or plasma levels of creatinine (mmol/L) after treatment (Outcome 1.26)

See Analysis 1.26

Two studies (n = 250 infants) reported on this outcome. There was no significant difference between the paracetamol and the ibuprofen groups in creatinine levels (typical weighted mean difference (WMD) -1.05 mmol/L, 95% CI -5.32 to 3.21; I^2 = 0% (none) for WMD).

Serum or plasma levels of aspartate transaminase (AST) (IU/L) following treatment (Outcome 1.27)

See Analysis 1.27

One study reported on this outcome, in 90 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the serum or plasma levels of AST (MD 4.20 IU/L, 95% CI -1.83 to 10.23). The test for heterogeneity was not applicable.

Number of infants with AST or alanine amino transaminase (ALT) levels > 100 IU/mL

No study reported on this outcome.

Serum or plasma levels of ALT (IU/L) following treatment (Outcome 1.28)

See Analysis 1.28

One study reported on this outcome, in 90 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the serum or plasma levels of ALT (MD 4.00 IU/L, 95% CI -3.58 to 11.58). The test for heterogeneity was not applicable.

Serum bilirubin (mmol/L) following treatment (Outcome 1.29)

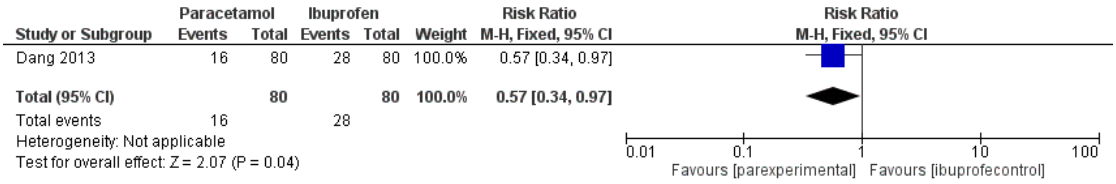
See Analysis 1.29

One study reported on this outcome, in 90 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the serum bilirubin (mmol/L) following treatment (MD -3.40 IU/L, 95% CI -15.74 to 8.94). The test for heterogeneity was not applicable.

Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and body weight) (Outcome 1.30)

See Analysis 1.30. Figure 5

Figure 5. Forest plot of comparison: 1 Oral paracetamol versus oral ibuprofen, outcome: 1.30 Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and body weight.



One study reported on this outcome, in 160 infants. There was a significant difference in hyperbilirubinaemia favouring the paracetamol groups (RR 0.57, 95% CI 0.34 to 0.97; RD -0.15, -0.29 to -0.01; NNTB 7, 95% CI 3 to 100).

Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death, in days) (Outcome 1.31)

Analysis 1.31

One study reported on this outcome, in 90 infants. There was no significant difference between the paracetamol and the ibuprofen groups in the duration of hospitalisation (MD -6.50 days, 95% CI -21.42 to 8.42). The test for heterogeneity was not applicable.

Incidence of liver failure; evidence of acute liver injury combined with either severe coagulopathy (International Normalized Ratio (INR) > 2.0 or prothrombin time (PT) > 20 seconds) or encephalopathy with moderate coagulopathy (INR ≥ 1.5 or PT ≥ 15 seconds)

One study (n = 90 infants) reported on this outcome. Liver failure did not occur in any infant enrolled in the study.

Other side effects reported by the authors (not pre-specified)

Oncel (Oncel 2013) reported that no other side effects were noted.

DISCUSSION

Summary of main results

The two studies completed to date have compared oral paracetamol to oral ibuprofen. Both studies used oral paracetamol at the dose of 15 mg/kg every 6 hours for 3 days and the comparison group received oral ibuprofen at the initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours.

There was no significant difference in the primary outcome of failure of PDA closure after the first course of paracetamol (closure and failure of closure confirmed by echocardiographic criteria), although the trend favoured paracetamol over ibuprofen.

Of the many secondary outcomes two reached statistical significance. The duration of need for supplementary oxygen reported in one study (n = 90) was reduced in favour of paracetamol (MD -12 days, 95% CI -23 to -2 days). Hyperbilirubinemia (serum bilirubin level higher than the exchange level according to the postnatal age and body weight) reported in one study (n = 160) showed a RR of 0.57 (95% CI 0.34 to 0.97), a RD of -0.15 (95% CI -0.29 to -0.01) and NNTB of 7 (95% CI 3 to 100).

There were no concerns in the results for mortality or common adverse neonatal outcomes.

Overall completeness and applicability of evidence

To date, 250 infants have been enrolled in two trials comparing the effectiveness and safety of paracetamol compared to ibuprofen for PDA closure in preterm infants. Larger trials are required to confirm the current promising evidence. Recently Viber and co-workers (Viberg 2014) reported that paracetamol administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. The dose of paracetamol used in mice was similar to that used in the two studies included in this review. In view of the possible negative impact of paracetamol on the developing brain reported in mice (Viberg 2014), the long-term effects of paracetamol used for PDA closure or prevention and treatment of pain need to be studied carefully. In addition, in an ecological study conducted in humans and using country-level data for the period 1984 to 2005, postnatal use of paracetamol was associated with autism or autism spectrum disorder (ASD) (Bauer 2013).

There are at least three ongoing trials that should provide additional evidence regarding this topic. The researchers should be encouraged to include pharmacokinetic data to determine optimal dosing regimen, duration of treatment and mode of administration (El-Khuffash 2014). Long-term follow-up should be planned to at least 18 to 24 months and preferably to school age.

Quality of the evidence

Although healthcare providers and researchers were aware of group assignment, we considered the two included trials to be of good quality as the random sequence was computer generated and allocation to the two study groups was by opaque, sequentially numbered and sealed envelopes. In addition, we were able to obtain unpublished data from both studies (Dang 2013; Oncel 2013) enabling us to report outcomes on all randomised infants (intention-to-treat analyses). The quality of the evidence, using GRADE, was low for the outcome 'failure of ductal closure after the first course of treatment' and moderate for six other important outcomes; 'all-cause mortality during initial hospital stay', ' surgical closure of the PDA following treatment failure with paracetamol or ibuprofen', 'severe IVH (Grade III-IV)', 'necrotizing enterocolitis', 'oliguria (< 1 cc/kg/hr)', and 'serum levels of creatinine after treatment in mmol/L'.

Potential biases in the review process

We are not aware of any biases in the review process.

Agreements and disagreements with other studies or reviews

We are not aware of any other published systematic reviews on the topic. Le and co-workers (Le 2015) recently published a narrative review of published case series and the two RCTs that we included (Dang 2013; Oncel 2013). They concluded: "Oral acetaminophen is an alternative to PDA therapy in preterm infants when indomethacin/ibuprofen is not effective or is contraindicated, and it may be considered before surgical ligation".

AUTHORS' CONCLUSIONS

Implications for practice

Further research regarding the effectiveness and safety of paracetamol to close a PDA is needed before recommendations for practice can be stated.

Implications for research

Additional larger trials are required to increase the precision of the point estimates for the primary and secondary outcomes included in this review. In view of the recent report in mice of adverse effects on the developing brain from paracetamol (Viberg 2014), and the association between postnatal use of paracetamol and autism and autism spectrum disorder (ASD) (Bauer 2013), long-term follow-up to 18 to 24 months postnatal age and preferably to school-age should be incorporated in any studies of paracetamol to close a PDA or to prevent or treat pain.

ACKNOWLEDGEMENTS

We are grateful to Ms Colleen Ovelman, Trials Search Co-ordinator, Cochrane Neonatal Review Group, who conducted the literature searches. We are thankful to Dr Mehmet Yekta Oncel, who provided us with unpublished data from their study (Oncel 2013). We are thankful to Dr Hui Wu, who provided us with unpublished information form their study (Dang 2013).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dang 2013

Methods	Randomised controlled trial conducted in the First Hospital of Jilin University. Study period 21 May 2012 to 30 March 2013
Participants	Inclusion criteria: PMA ≤ 34 weeks; postnatal age < 14 days; echocardiographic diagnosis of haemodynamically significant PDA. Exclusion criteria were: congenital heart disease which required PDA to maintain blood flow; life-threatening infection; recent (within the previous 24 hr) intraventricular haemorrhage, Grade 3-4; urine output < 1 mL/kg/hr during the preceding 8 hr; serum creatinine > 88.4 mmol/L; platelet count of < 50 x 10^9/L; hyperbilirubinaemia requiring exchange transfusion; active necrotizing enterocolitis (NEC) and/or intestinal perforation; liver dysfunction
Interventions	Eighty infants received oral paracetamol at the dose of 15 mg/kg every 6 hr for 3 days, and 80 infants received oral ibuprofen at the initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hr. Between doses of oral ibuprofen, infants of the ibuprofen group received the same volume of dextrose 5% in water (D5W) as that given for drug administration in the paracetamol group. Whether a subject received a second course of treatment depended on echocardiography evaluation after the first course. If only minor ductal shunting was present after two courses without the need of respiratory support, no further treatment was given
Outcomes	Failure of PDA closure, all-cause mortality, re-opening of the ductus arteriosus, BPD (according to NICHD criteria: Jobe 2001), IVH (Grade I-IV; Grade I-II, Grade III-IV) , PVL (diagnosed by cranial MRI), NEC (Bell staging criteria - Grade IIa and above) , gastrointestinal bleed, ROP (any stage), oliguria (< 1 cc/kg/hr), sepsis (positive blood culture), hyperbilirubinaemia according to Maisels 2003 - a serum bilirubin level higher than the exchange transfusion level according to the postnatal age and body weight), serum creatinine (μmol/L) following treatment
Notes	In the report, although references were provided for BPD and hyperbilirubinaemia, it was not possible to ascertain exactly what criteria the authors applied. Sepsis was not defined. We wrote to the authors requesting clarification. We received a response and their definitions are included for the outcomes listed above Funded by Jilin Department of Health

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table (according to the published protocol)
Allocation concealment (selection bias)	Low risk	"The participants were randomly assigned at a 1:1 ratio between oral paracetamol and

Dang 2013 (*Continued*)

		ibuprofen groups by using cards in sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"...doctors and nurses were not blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"...doctors and nurses were not blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported on an intention-to-treat basis which included patients who did not receive the complete course of treatment
Selective reporting (reporting bias)	Low risk	The study was entered in the Chinese Clinical Trial Register (http://www.chictr.org/cn/registration number: ChiCTR-TRC-12002177) and approved by the Hospital Ethics Committee of the First Hospital of Jilin University. There does not appear to be any deviations in study conduct between the study protocol and the publication
Other bias	Low risk	Appears free of other sources of bias

Oncel 2013

Methods	Randomised controlled trial conducted in the neonatal intensive care unit of Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey. Study period February to December 2012
Participants	Ninty infants with a gestational age $\leq$ 30 weeks, birthweight $\leq$ 1250 g, postnatal age 48 to 96 hours, and 1 of the following echocardiographic criteria: a duct size > 1.5 mm, a left atrium-to-aorta ratio > 1.5, end diastolic reversal of blood flow in the aorta, or poor cardiac function in addition to clinical signs of a PDA Exclusion criteria were: the presence of major congenital abnormalities, right-to-left ductal shunting, life-threatening infection, Grade III or Grade IV IVH, urine output of less than 1 mL/kg/hr during the preceding 8 hours, serum creatinine level > 1.6 mg/dL, platelet count < 60 000/mm^3, liver failure, hyperbilirubinaemia requiring exchange transfusion, and persistent pulmonary hypertension
Interventions	Forty-five infants received oral paracetamol at a dose of 15 mg/kg every 6 hours for 3 days and 45 infants received oral ibuprofen at an initial dose of 10 mg/kg followed by 5 mg/kg at 24 and 48 hours. Both paracetamol and ibuprofen were administered via an orogastric tube, which was flushed with 1 to 2 mL of sterile water to ensure delivery of the drug

Oncel 2013 (*Continued*)

Outcomes	Failure of PDA closure, all-cause mortality, surgical closure of the PDA, duration of ventilator support, pulmonary haemorrhage, increase in grade of IVH, NEC, gastrointestinal bleed, ROP (requiring laser treatment), oliguria (not defined), sepsis (clinical symptoms and signs of sepsis and a positive blood bacterial culture), serum creatinine, bilirubin, AST and ALT, duration of hospitalisation
Notes	We contacted Dr Oncel and he provided us with data for additional outcomes not reported in the published paper. In addition he provided outcome data for all 90 randomised infants

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequential numbers were generated at the computer centre of the NICU (information provided by the authors)
Allocation concealment (selection bias)	Low risk	The patients were randomly assigned to a treatment group by cards in sequentially numbered sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Paracetamol and ibuprofen were given according to different schedules and therefore it is likely that healthcare providers were not blinded to the drug the infant was given. The authors write: "....the intervention was not completely blinded because of the different number of doses per day of the drugs. However, the most important outcome-PDA closure-was made by a cardiologist who was blinded to the treatment groups. Second, safety outcomes should have been defined more clearly before the study started to prevent overestimation in evaluation"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Paracetamol and ibuprofen were given according to different schedules and therefore it is likely that health care providers were not blinded to the drug the infant was given. The authors write: "....the intervention was not completely blinded because of the different number of doses per day of the drugs. However, the most important outcome-PDA closure-was made by a cardiologist who was blinded to the treatment groups. Second, safety outcomes

Oncel 2013 (*Continued*)

		should have been defined more clearly before the study started to prevent overestimation in evaluation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 infants were randomised, and we received outcome data for the 10 infants (5 in ibuprofen group and 5 in paracetamol group) who died before the treatment was completed. Thus we received outcome data on an intention-to-treat basis for all 90 randomised infants
Selective reporting (reporting bias)	Low risk	The trial was registered at ClinicalTrials.gov NCT01536158 and there does not seem to be any deviations between the protocol and the full publication
Other bias	Low risk	Appears free of other bias

Characteristics of studies awaiting assessment *[ordered by study ID]*

Zarkesh 2013

Methods	Infants were randomly assigned to two groups; the prophylaxis group and the control group
Participants	A total of 32 preterm infants (PMA < 32 weeks, body weight ≤ 1500 g)
Interventions	The prophylaxis group received oral paracetamol at a dose of 60 mg/kg/day, in 4 divided doses, for a period of 2 days starting during the first 24 hours of life. No placebo was given to the control group. Echocardiography was performed 24 to 36 hours after the last given dose to prophylaxis group and on the fourth to fifth day in the control group
Outcomes	Rate of ductal closure, need for later treatment with ibuprofen
Notes	To date (December 2013) this study has been published in abstract form only. The abstract does not report how many infants were assigned to each group, preventing us from incorporating the results of the study in our review If this study is published as a full report, we will need to make a deviation from our protocol and report separately on the prophylactic use of paracetamol for PDA

Characteristics of ongoing studies *[ordered by study ID]*

NCT01291654

Trial name or title	Paracaetamol and patent ductus arteriosus (PDA)
Methods	Randomised controlled trial
Participants	Preterm infants with a haemodynamically significant PDA
Interventions	Group 1: paracetamol orally at a dose of 15 mg/kg every 6 hours x 3 days. Group 2: indomethacin intravenously 0.2 mg/kg/dose for three doses
Outcomes	Primary outcome: closure of the ductus within 3 days. Secondary outcomes: absence of peripheral vasoconstriction, Doppler flow velocity in the anterior cerebral artery, superior mesenteric artery and renal artery before and after pharmacological treatment, absence of hepatotoxicity
Starting date	February 6, 2011
Contact information	Cathy Hammerman, Shaare Zedek Medical centre, Israel. cathy@cc.huji.ac.il
Notes	ClinicalTrials.gov identifier: NCT01291654

NCT01938261

Trial name or title	The preterm infants' paracetamol study (PreParaS)
Methods	Randomised controlled, double-blind trial
Participants	Preterm infants < 32 weeks PMA
Interventions	Paracetamol infusion solution 10 mg/mL (Perfalgan®) or placebo, 0.45% saline solution. The loading dose is 20 mg/kg, and the maintenance dose 7.5 mg/kg every 6 hours for 4 days
Outcomes	Primary outcome: ductus diameter mm/kg at postnatal age 5 days. Cumulative dose of morphine at postnatal age 5 days. Secondary outcomes: number of patients who received any treatment for PDA prescribed by an attending clinician, postnatal age at closure of PDA, left atrium to aorta ratio, number of apneic periods/day, cumulative NIAPAS screening score/day up to 5 days postnatal age, duration of mechanical ventilation, long-term morbidity diagnoses, deaths, paracetamol side effects, paracetamol serum concentrations (up to 5 days postnatal age)
Starting date	August 22, 2013
Contact information	Outi Aikio, University of Oulu, Finland; outi.aikio@ppshp.fi
Notes	ClinicalTrials.gov identifier: NCT01938261

NCT02002741

Trial name or title	Adding paracetamol to ibuprofen for treatment of patent ductus arteriosus in preterm infants
Methods	Randomised double blind controlled trial
Participants	Preterm infants born at 24 to 37 weeks PMA, diagnosis of haemodynamically significant PDA, medical staff decided to treat with ibuprofen
Interventions	Group 1: ibuprofen + paracetamol (Ibuprofen 10mg/kg once, then 5 mg/kg twice, every 24 hr for a total of 3 doses and intravenous paracetamol loading dose 20 mg/kg then 10 mg/kg every 6 hr for a total of 12 doses) Group 2: ibuprofen + placebo (ibuprofen 10mg/kg once, then 5 mg/kg twice, every 24 h for a total of 3 doses and placebo (NaCl 0.9%), intravenous, at equal volume to the paracetamol in the paracetamol arm, total of 12 doses given every 6 hr)
Outcomes	Primary outcome: the incidence of patent ductus arteriosus closure 3 to 21 days after first dose of ibuprofen by echocardiography. The need for surgical ligation of PDA. Secondary outcomes: adverse effects until discharge home - renal and liver function, gastrointestinal complications
Starting date	February 2014
Contact information	o_hochwald@rambam.health.gov.il
Notes	ClinicalTrials.gov identifier: NCT02002741

DATA AND ANALYSES

Comparison 1. Oral paracetamol versus oral ibuprofen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of ductal closure after the first course of treatment	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.22]
2 All-cause mortality during initial hospital stay	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.52, 1.72]
3 Neonatal mortality (deaths during the first 28 days of life)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.43, 3.20]
4 Infant mortality (death during the first year of life)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.45, 2.89]
5 Re-opening of the ductus arteriosus	2	143	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.50, 2.18]
6 Surgical closure of the PDA following treatment failure with paracetamol or ibuprofen	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.32]
7 Duration of ventilator support (days)	1	90	Mean Difference (IV, Fixed, 95% CI)	-4.15 [-8.63, 0.33]
8 Pulmonary haemorrhage	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.69]
9 Pulmonary hypertension	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.97]
10 Duration for need of supplementary oxygen (days)	1	90	Mean Difference (IV, Fixed, 95% CI)	-12.40 [-22.97, -1.83]
11 BPD at 28 days	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.46, 1.35]
12 BPD at 36 weeks PMA	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.30]
13 Moderate to severe BPD (according to the new criteria)	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.22, 2.87]
14 Severe BPD (according to the new criteria)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.32, 1.23]
15 Intraventricular haemorrhage (grade I-IV)	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.15]
16 Severe IVH (Grade III-IV)	2	250	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.37]
17 Periventricular leukomalacia	2	250	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.76]
18 Necrotizing enterocolitis	2	250	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.43, 5.18]
19 Intestinal perforation	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Gastrointestinal bleed	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.08, 1.06]
21 Retinopathy of prematurity - any stage	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.37, 1.41]
22 Retinopathy of prematurity stage =/> 3	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.55]
23 Retinopathy of prematurity requiring laser therapy	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.55]
24 Sepsis	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.57, 2.03]
25 Oliguria (<1cc/kg/h))	2	250	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.08, 0.04]
26 Serum levels of creatinine after treatment mmol/L	2	250	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-5.32, 3.21]

27 Serum levels of aspartate transaminase (AST) IU/L	1	90	Mean Difference (IV, Fixed, 95% CI)	4.20 [-1.83, 10.23]
28 Serum levels of alanine aminotransferase (ALT) (IU/L)	1	90	Mean Difference (IV, Fixed, 95% CI)	4.0 [-3.58, 11.58]
29 Serum bilirubin following treatment (mmol/L)	1	90	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-15.74, 8.94]
30 Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and BW	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.34, 0.97]
31 Duration of hospitalisation (days)	1	90	Mean Difference (IV, Fixed, 95% CI)	-6.5 [-21.42, 8.42]

Analysis 1.1. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 1 Failure of ductal closure after the first course of treatment.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 1 Failure of ductal closure after the first course of treatment

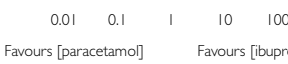
Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	35/80	42/80		82.4 %	0.83 [0.60, 1.15]
Oncel 2013	11/45	9/45		17.6 %	1.22 [0.56, 2.66]
Total (95% CI)	**125**	**125**		**100.0 %**	**0.90 [0.67, 1.22]**

Total events: 46 (Paracetamol), 51 (Ibuprofen)

Heterogeneity: $Chi^2 = 0.81$, df = 1 (P = 0.37); $I^2 = 0.0\%$

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable

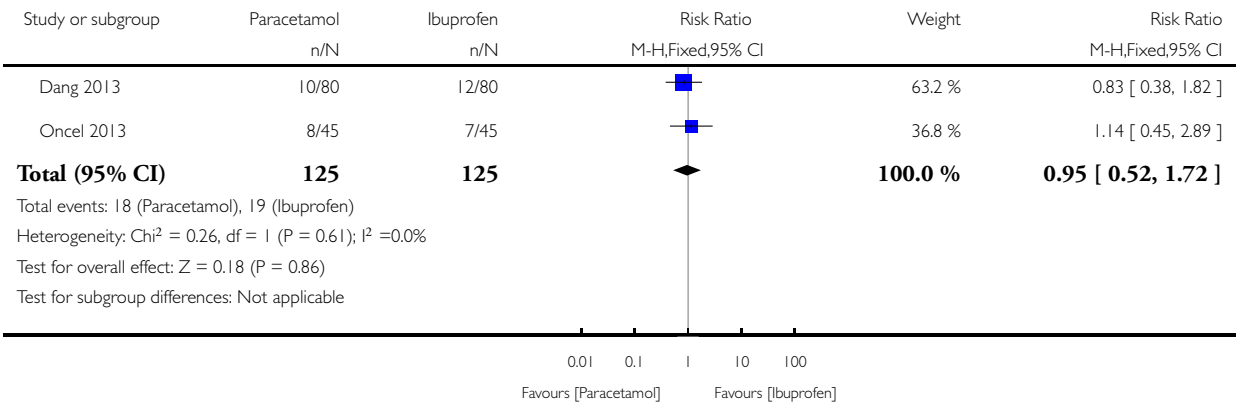


Analysis 1.2. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 2 All-cause mortality during initial hospital stay.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 2 All-cause mortality during initial hospital stay

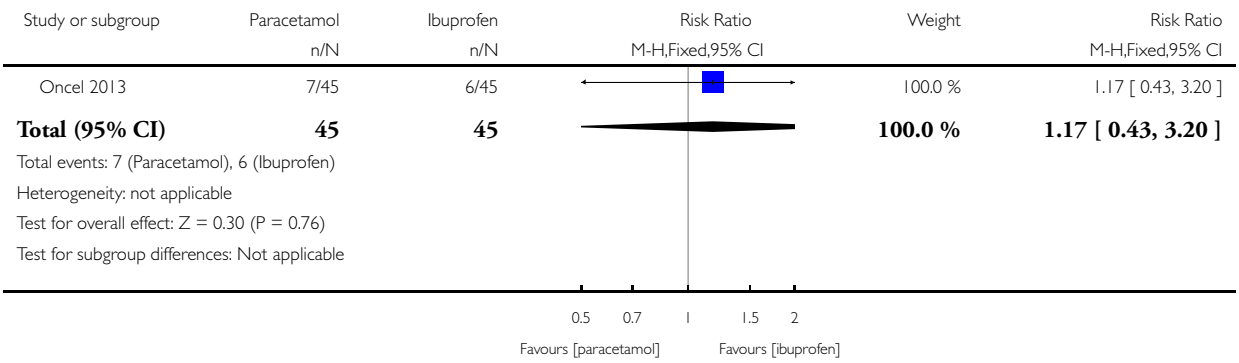


Analysis 1.3. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 3 Neonatal mortality (deaths during the first 28 days of life).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 3 Neonatal mortality (deaths during the first 28 days of life)

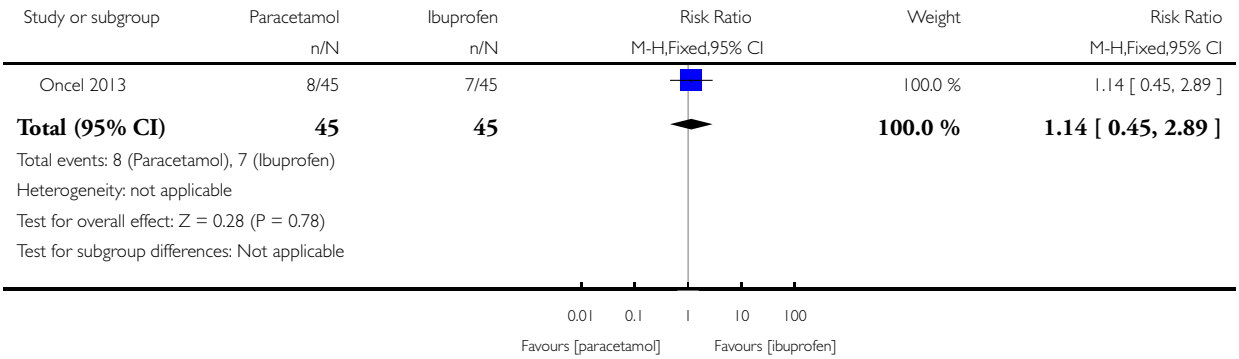


Analysis 1.4. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 4 Infant mortality (death during the first year of life).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 4 Infant mortality (death during the first year of life)



Analysis 1.5. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 5 Re-opening of the ductus arteriosus.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 5 Re-opening of the ductus arteriosus

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	5/45	6/38		57.4 %	0.70 [0.23, 2.13]
Oncel 2013	7/29	5/31		42.6 %	1.50 [0.53, 4.19]
Total (95% CI)	**74**	**69**		**100.0 %**	**1.04 [0.50, 2.18]**

Total events: 12 (Paracetamol), 11 (Ibuprofen)

Heterogeneity: $Chi^2 = 0.96$, df = 1 (P = 0.33); $I^2 = 0.0\%$

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 6 Surgical closure of the PDA following treatment failure with paracetamol or ibuprofen.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 6 Surgical closure of the PDA following treatment failure with paracetamol or ibuprofen

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Oncel 2013	1/45	2/45		100.0 %	0.50 [0.05, 5.32]
Total (95% CI)	**45**	**45**		**100.0 %**	**0.50 [0.05, 5.32]**

Total events: 1 (Paracetamol), 2 (Ibuprofen)

Heterogeneity: not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

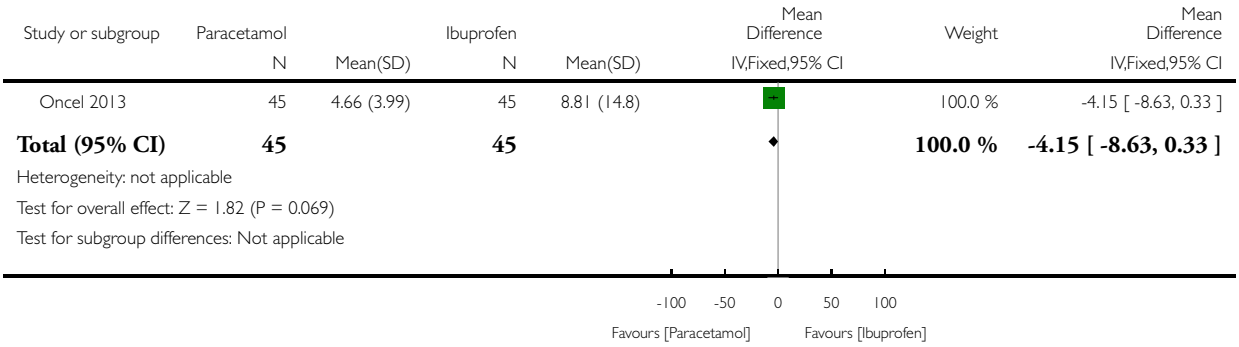
Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 7 Duration of ventilator support (days).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 7 Duration of ventilator support (days)

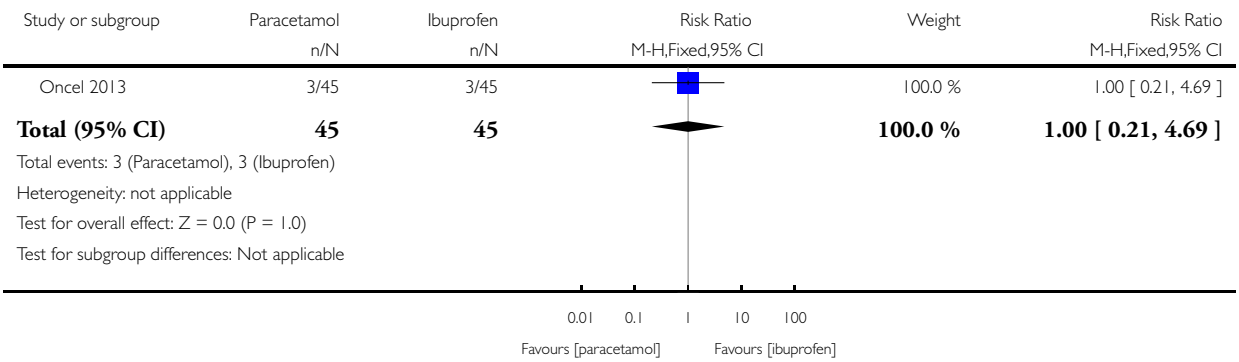


Analysis 1.8. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 8 Pulmonary haemorrhage.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 8 Pulmonary haemorrhage



Analysis 1.9. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 9 Pulmonary hypertension.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 9 Pulmonary hypertension

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Oncel 2013	0/45	1/45		100.0 %	0.33 [0.01, 7.97]
Total (95% CI)	**45**	**45**		**100.0 %**	**0.33 [0.01, 7.97]**

Total events: 0 (Paracetamol), 1 (Ibuprofen)
Heterogeneity: not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 10 Duration for need of supplementary oxygen (days).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 10 Duration for need of supplementary oxygen (days)

Study or subgroup	Paracetamol N	Mean(SD)	Ibuprofen N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Oncel 2013	45	23.1 (16.7)	45	35.5 (32.1)		100.0 %	-12.40 [-22.97, -1.83]
Total (95% CI)	**45**		**45**			**100.0 %**	**-12.40 [-22.97, -1.83]**

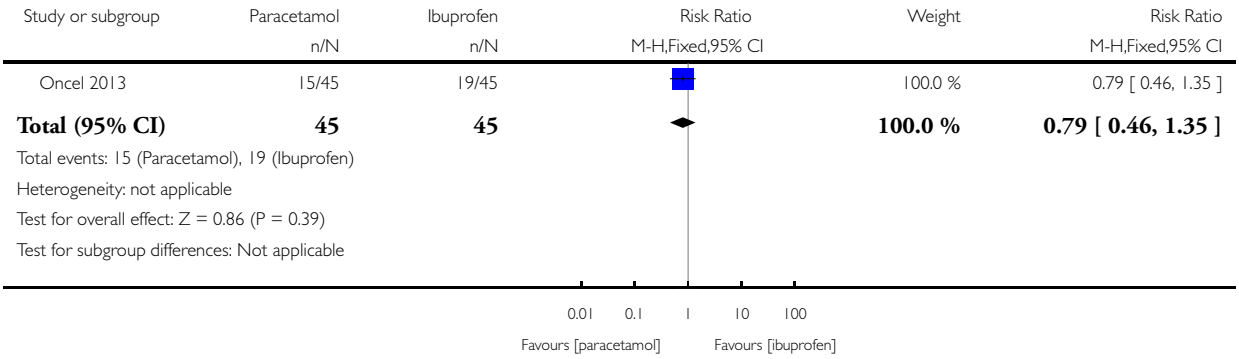
Heterogeneity: not applicable
Test for overall effect: Z = 2.30 (P = 0.022)
Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 11 BPD at 28 days.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 11 BPD at 28 days

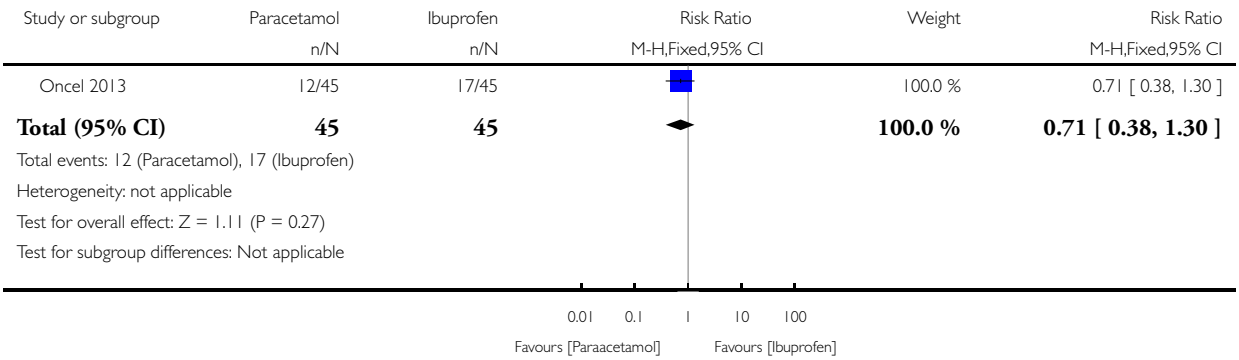


Analysis 1.12. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 12 BPD at 36 weeks PMA.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 12 BPD at 36 weeks PMA



Analysis 1.13. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 13 Moderate to severe BPD (according to the new criteria).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 13 Moderate to severe BPD (according to the new criteria)

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	4/80	5/80		100.0 %	0.80 [0.22, 2.87]
Total (95% CI)	**80**	**80**		**100.0 %**	**0.80 [0.22, 2.87]**
Total events: 4 (Paracetamol), 5 (Ibuprofen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
Test for subgroup differences: Not applicable					

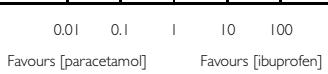
Analysis 1.14. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 14 Severe BPD (according to the new criteria).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 14 Severe BPD (according to the new criteria)

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Oncel 2013	10/45	16/45		100.0 %	0.63 [0.32, 1.23]
Total (95% CI)	**45**	**45**		**100.0 %**	**0.63 [0.32, 1.23]**
Total events: 10 (Paracetamol), 16 (Ibuprofen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Test for subgroup differences: Not applicable					



Analysis 1.15. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 15 Intraventricular haemorrhage (grade I-IV).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 15 Intraventricular haemorrhage (grade I-IV)

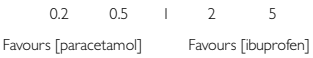
Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	9/80	10/80		20.4 %	0.90 [0.39, 2.10]
Oncel 2013	36/45	39/45		79.6 %	0.92 [0.77, 1.11]
Total (95% CI)	**125**	**125**		**100.0 %**	**0.92 [0.73, 1.15]**

Total events: 45 (Paracetamol), 49 (Ibuprofen)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 16 Severe IVH (Grade III-IV).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 16 Severe IVH (Grade III-IV)

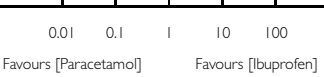
Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	3/80	3/80		60.0 %	1.00 [0.21, 4.81]
Oncel 2013	2/45	2/45		40.0 %	1.00 [0.15, 6.79]
Total (95% CI)	**125**	**125**		**100.0 %**	**1.00 [0.30, 3.37]**

Total events: 5 (Paracetamol), 5 (Ibuprofen)

Heterogeneity: $Chi^2 = 0.0$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

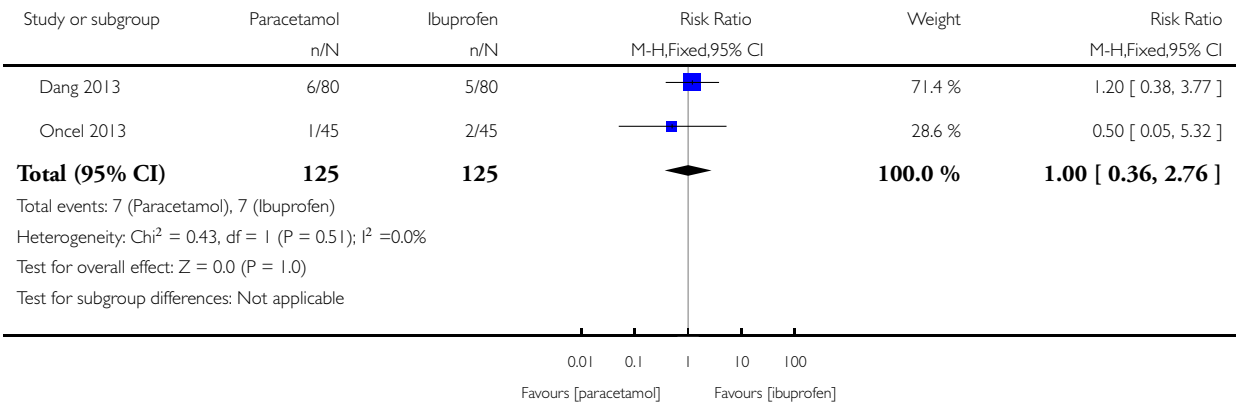


Analysis 1.17. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 17 Periventricular leukomalacia.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 17 Periventricular leukomalacia



Analysis 1.18. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 18 Necrotizing enterocolitis.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 18 Necrotizing enterocolitis

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	3/80	2/80		50.0 %	1.50 [0.26, 8.74]
Oncel 2013	3/45	2/45		50.0 %	1.50 [0.26, 8.55]
Total (95% CI)	**125**	**125**		**100.0 %**	**1.50 [0.43, 5.18]**
Total events: 6 (Paracetamol), 4 (Ibuprofen)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Not applicable					

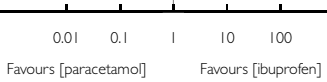
Analysis 1.19. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 19 Intestinal perforation.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 19 Intestinal perforation

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Oncel 2013	0/45	0/45			Not estimable
Total (95% CI)	**45**	**45**			**Not estimable**
Total events: 0 (Paracetamol), 0 (Ibuprofen)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 1.20. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 20 Gastrointestinal bleed.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 20 Gastrointestinal bleed

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	2/80	8/80		80.0 %	0.25 [0.05, 1.14]
Oncel 2013	1/45	2/45		20.0 %	0.50 [0.05, 5.32]
Total (95% CI)	**125**	**125**		**100.0 %**	**0.30 [0.08, 1.06]**

Total events: 3 (Paracetamol), 10 (Ibuprofen)

Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 1.86 (P = 0.062)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 21 Retinopathy of prematurity - any stage.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 21 Retinopathy of prematurity - any stage

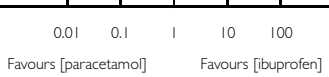
Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	7/80	9/80		50.0 %	0.78 [0.30, 1.99]
Oncel 2013	6/45	9/45		50.0 %	0.67 [0.26, 1.72]
Total (95% CI)	**125**	**125**		**100.0 %**	**0.72 [0.37, 1.41]**

Total events: 13 (Paracetamol), 18 (Ibuprofen)

Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable



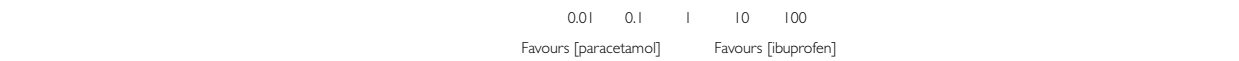
Analysis 1.22. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 22 Retinopathy of prematurity stage =/> 3.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 22 Retinopathy of prematurity stage =/> 3

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Oncel 2013	3/45	7/45		100.0 %	0.43 [0.12, 1.55]
Total (95% CI)	**45**	**45**		**100.0 %**	**0.43 [0.12, 1.55]**
Total events: 3 (Paracetamol), 7 (Ibuprofen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
Test for subgroup differences: Not applicable					

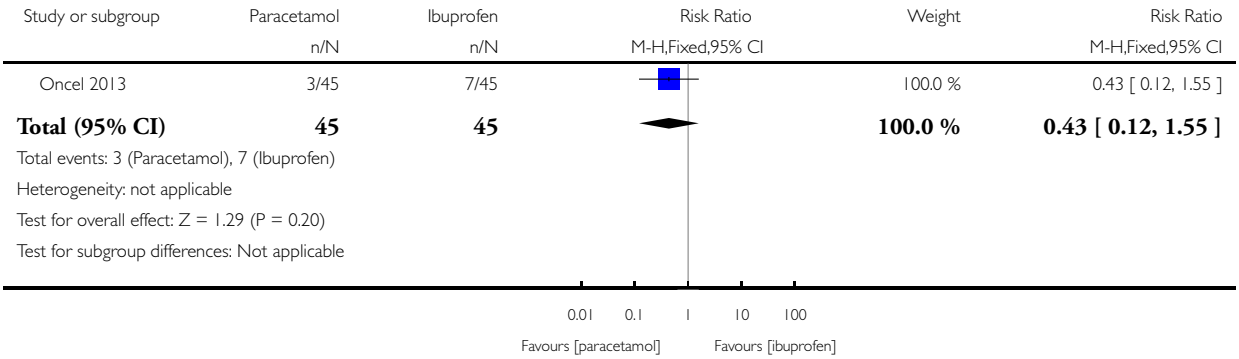


Analysis 1.23. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 23 Retinopathy of prematurity requiring laser therapy.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 23 Retinopathy of prematurity requiring laser therapy

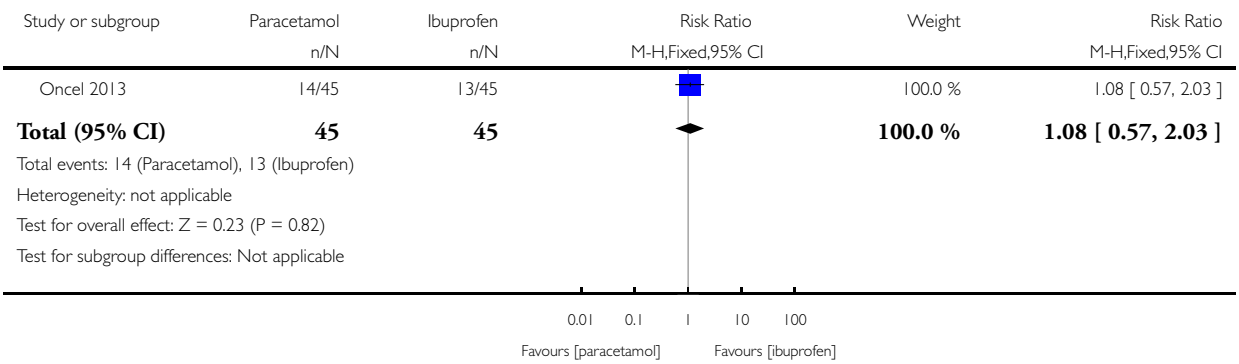


Analysis 1.24. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 24 Sepsis.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 24 Sepsis



Analysis 1.25. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 25 Oliguria (<1cc/kg/h)).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 25 Oliguria (<1cc/kg/h))

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Dang 2013	6/80	9/80		64.0 %	-0.04 [-0.13, 0.05]
Oncel 2013	0/45	0/45		36.0 %	0.0 [-0.04, 0.04]
Total (95% CI)	**125**	**125**		**100.0 %**	**-0.02 [-0.08, 0.04]**

Total events: 6 (Paracetamol), 9 (Ibuprofen)

Heterogeneity: Chi^2 = 1.32, df = 1 (P = 0.25); I^2 =24%

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 1.26. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 26 Serum levels of creatinine after treatment mmol/L.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

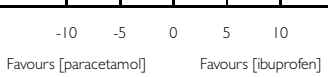
Outcome: 26 Serum levels of creatinine after treatment mmol/L

Study or subgroup	Paracetamol N	Mean(SD)	Ibuprofen N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dang 2013	80	61.62 (14.53)	80	62.4 (15.24)		85.5 %	-0.78 [-5.39, 3.83]
Oncel 2013	45	74.25 (23.8)	45	76.9 (30)		14.5 %	-2.65 [-13.84, 8.54]
Total (95% CI)	**125**		**125**			**100.0 %**	**-1.05 [-5.32, 3.21]**

Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 27 Serum levels of aspartate transaminase (AST) IU/L.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 27 Serum levels of aspartate transaminase (AST) IU/L

Study or subgroup	Paracetamol N	Mean(SD)	Ibuprofen N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Oncel 2013	45	44.3 (12.1)	45	40.1 (16.7)		100.0 %	4.20 [-1.83, 10.23]
Total (95% CI)	**45**		**45**			**100.0 %**	**4.20 [-1.83, 10.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.37 (P = 0.17)

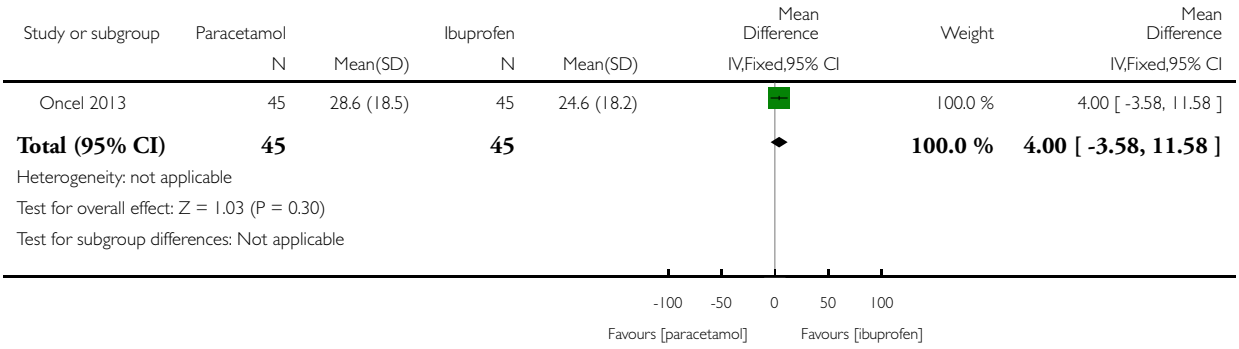
Test for subgroup differences: Not applicable

Analysis 1.28. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 28 Serum levels of alanine aminotransferase (ALT) (IU/L).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 28 Serum levels of alanine aminotransferase (ALT) (IU/L)

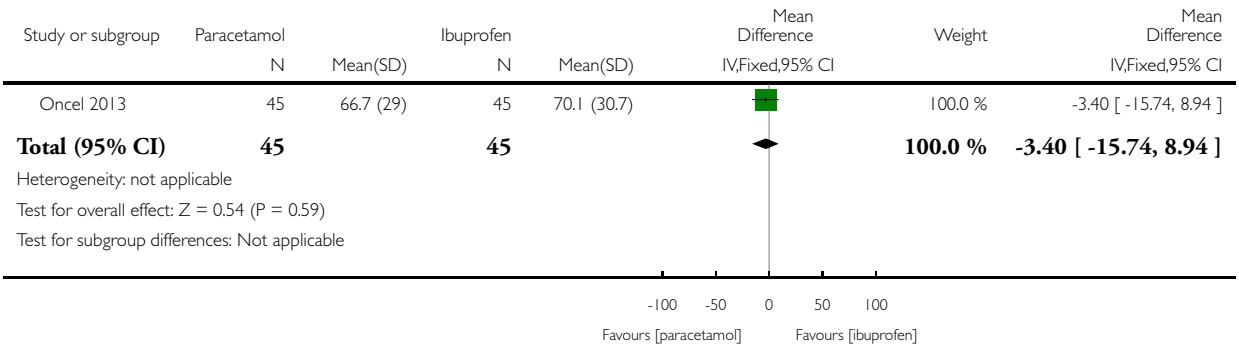


Analysis 1.29. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 29 Serum bilirubin following treatment (mmol/L).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 29 Serum bilirubin following treatment (mmol/L)



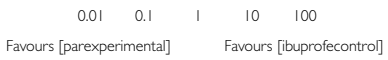
Analysis 1.30. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 30 Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and BW.

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 30 Hyperbilirubinaemia (serum bilirubin level higher than the exchange level according to the postnatal age and BW

Study or subgroup	Paracetamol n/N	Ibuprofen n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dang 2013	16/80	28/80		100.0 %	0.57 [0.34, 0.97]
Total (95% CI)	**80**	**80**		**100.0 %**	**0.57 [0.34, 0.97]**
Total events: 16 (Paracetamol), 28 (Ibuprofen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.07 (P = 0.039)					
Test for subgroup differences: Not applicable					



Analysis 1.31. Comparison 1 Oral paracetamol versus oral ibuprofen, Outcome 31 Duration of hospitalisation (days).

Review: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants

Comparison: 1 Oral paracetamol versus oral ibuprofen

Outcome: 31 Duration of hospitalisation (days)

Study or subgroup	Paracetamol N	Mean(SD)	Ibuprofen N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Oncel 2013	45	59.3 (37.3)	45	65.8 (34.9)		100.0 %	-6.50 [-21.42, 8.42]
Total (95% CI)	**45**		**45**			**100.0 %**	**-6.50 [-21.42, 8.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.85 (P = 0.39)							
Test for subgroup differences: Not applicable							

CONTRIBUTIONS OF AUTHORS

Both authors contributed to all sections of this review.

DECLARATIONS OF INTEREST

Arne Ohlsson - no conflict of interest to declare.

Prakeshkumar Shah - no conflict of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Pediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada, Other.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made some minor wording changes to the primary outcome. We changed from 'Failure of PDA closure within a week of administration of the first dose of paracetamol (closure and failure of closure confirmed by echocardiographic criteria)' to 'Failure of PDA closure after the first course of paracetamol (closure and failure of closure confirmed by echocardiographic criteria)'. We have added a few outcomes that the authors of the included studies reported on but that we had not anticipated. We have indicated this for the specific outcomes that were not pre-determined.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*administration & dosage; adverse effects]; Administration, Oral; Ductus Arteriosus, Patent [* drug therapy]; Ibuprofen [administration & dosage; adverse effects]; Indomethacin [administration & dosage]; Infant, Low Birth Weight; Infant, Premature; Oxygen Inhalation Therapy [utilization]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn