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Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

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ABSTRACT

Background

Patent ductus arteriosus (PDA) complicates the clinical course of preterm infants and increases the risk of intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), chronic lung disease (CLD) and death. The standard treatment to close a PDA is indomethacin. Indomethacin use is associated with renal, gastrointestinal and cerebral side-effects. Ibuprofen has been shown to be effective in closing a PDA without reducing blood flow velocity to the brain, gastrointestinal tract or kidneys.

Objectives

To determine the effectiveness and safety of prophylactic ibuprofen compared to placebo/no intervention or other cyclo-oxygenase inhibitor drugs in the prevention of PDA in preterm infants.

Search strategy

Randomized controlled trials comparing prophylactic ibuprofen use with placebo/no intervention/indomethacin were identified by searching in January 2009 the Cochrane Central Register of Controlled Trial, MEDLINE, CINAHL and EMBASE.

Selection criteria

Randomized or quasi-randomised controlled trials comparing use of ibuprofen with placebo/no intervention or other cyclo-oxygenase inhibitor drugs (indomethacin, mfenamic acid) for the prevention of PDA in preterm and/or low birth weight infants.

Data collection and analysis

Data regarding the clinical outcomes including presence of PDA on day three, need for surgical ligation, need for rescue treatment with cyclo-oxygenase inhibitors, mortality, IVH, renal, pulmonary and gastrointestinal complications were extracted. Meta-analyses were performed and treatment estimates are reported as typical weighted mean difference (WMD), relative risk (RR), risk difference (RD) and, if statistically significant, number needed to treat to benefit (NNTB) or number needed to treat to harm (NNTH) along with their 95% confidence intervals (CI).
Main results

Six studies comparing prophylactic ibuprofen with placebo or no medication qualified for inclusion in this updated review, including two additional trials identified at this update (n = 197). Ibuprofen significantly decreased the incidence of PDA on day three [typical RR 0.36 (95% CI 0.28, 0.46); typical RD -0.27 (95% CI -0.33, -0.23); NNT 4 (95% CI 3, 5); six trials, n = 869], decreased the need for rescue treatment with cyclo-oxygenase inhibitors, and decreased the need for surgical ligation. However, the PDA had closed spontaneously by day three in 58% of the neonates in the control group. Ibuprofen negatively affects renal function (oliguria, increased creatinine) and may increase the risk of sepsis. No significant differences in mortality, intraventricular haemorrhage, pulmonary or intestinal complications were found.

Authors’ conclusions

Prophylactic use of ibuprofen decreased the incidence of PDA, decreased the need for rescue treatment with cyclo-oxygenase inhibitors and decreased surgical closure. However, in the control group, the PDA closed spontaneously by day three in 58% of the neonates. Prophylactic treatment therefore exposes a large proportion of infants unnecessarily to a drug that has concerning renal side effects without conferring any important short-term benefits. Prophylactic treatment with ibuprofen is not recommended. Until long-term follow-up results are published from the trials included in this updated review, no further trials of prophylactic ibuprofen are recommended.

Plain Language Summary

Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Ibuprofen may prevent patent ductus arteriosus (PDA), a common complication for preterm or very small babies, but more research is needed into possible serious adverse effects. PDA is a common complication for very preterm (premature) or very small babies. PDA is an open vessel that channels blood from the lungs to the body. It should close after birth, but sometimes remains open because of the baby’s premature stage of development. PDA can lead to life-threatening complications. Indomethacin is successful in causing PDA closure, but can cause serious adverse effects. Another option is the drug ibuprofen, which can be given to try and prevent PDA. This updated review of trials found that ibuprofen can prevent PDA, but does not confer any other short-term or long-term benefits.

Background

Patent ductus arteriosus (PDA) often complicates the clinical course of preterm infants with or without respiratory distress syndrome (RDS) (Ramanathan 1997). In a large Canadian cohort (n = 3,779) of very-low-birth-weight infants (< 1500 g), the incidence of symptomatic PDA needing treatment was 28% (Lee 2000). The failure of the ductus arteriosus to constrict after birth is due to lower intrinsic tone, less ductal muscle fibres and fewer subendothelial cushions in the preterm infant as compared to the term infant (Hammerman 1995). The immature ductus arteriosus has higher sensitivity to the vasodilating effects of prostaglandins and nitric oxide (Hammerman 1995). This is aggravated by hemodynamic derangements due to respiratory distress syndrome and surfactant therapy (Hammerman 1995).

The clinical consequences of 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 face of a left to right shunt, blood flow distribution to vital organs is altered due to drop in diastolic pressure and localized vasoconstriction (Clyman 2000). Substantial left to right shunting through the ductus may increase the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), chronic lung disease (CLD), and death (Cotton 1979).

Inhibiting prostaglandin synthesis with non-selective blockers of both cyclo-oxygenases 1 and 2 is effective for the nonsurgical closure of PDA (Clyman 2000). Intravenous indomethacin is the standard pharmacological treatment for promoting closure of PDA in preterm infants and has been used since 1976 (Friedman 1976) with a reported efficacy of 66 - 80% (Gersony 1983; Van Overmeire 2000; Lago 2002).

The prophylactic use of indomethacin for the prevention of PDA has been shown to reduce the incidence of a symptomatic PDA, the need for surgical ligation, and the occurrence of pulmonary hemorrhage (Couser 1996; Domanico 1994). In a large trial, it
was shown that prophylactic use of indomethacin in extremely low birth weight infants reduces the frequency of PDA and severe intraventricular hemorrhage, but there was no evidence of effect on the rate of survival without neurosensory impairment at 18 months (Schmidt 2001). Similarly, a meta analysis of 19 eligible studies showed that prophylactic indomethacin reduces the incidence of symptomatic PDA, need for surgical ligation, and incidence of grade 3 and 4 IVH in preterm infants, but without evidence of effect on the incidence of long-term neurosensory impairment (Fowlie 2002).

However, the use of indomethacin may be followed by side effects such as decreased cerebral blood flow (Edwards 1990; Van Bel 1989; Ohlsson 1993), decreased cerebral blood volume and cerebral oxygen delivery (Patel 2000), oliguria or transient renal failure (Berkerur 1981; Gersony 1983; Lago 2002; Van Overmeire 2000), NEC, isolated bowel perforation or gastrointestinal hemorrhage (Gersony 1983; Grosfeld 1996). Concern regarding these complications potentially related to indomethacin use has tempered the enthusiasm for its use, encouraging many researchers to seek new, safer pharmacological strategies for the closure of a PDA. The only major side effect reported in the Cochrane review by Fowlie (Fowlie 2002) was an increased incidence of oliguria, but this was not associated with major renal impairment. In the same review there was no evidence of difference in rates of NEC, excessive clinical bleeding or sepsis.

Other cyclo-oxygenase inhibitors have been reported to close a PDA. In Japan, mefenamic acid is frequently used in the treatment of PDA (Sakhalkar 1992; Ito 1994; Niopas 1994).

Ibuprofen, another cyclo-oxygenase inhibitor drug, has been used for ductal closure in animals (Coceani 1979). Preliminary experimental and clinical studies (Varvarigou 1996; Van Overmeire 1997) have shown that ibuprofen is effective in closing PDA without reducing cerebral flow (Patel 2000; Mosca 1997) or affecting intestinal (Speziale 1999), or renal circulation (Pezzati 1999). Furthermore, ibuprofen enhances cerebral blood flow auto regulation (Chemtob 1990) and has been shown to protect neurological functions following an oxidative stress in a piglet model (Chemtob 1993). Trials reporting on the prophylactic use of ibuprofen in preterm neonates have been published over the years justifying the need for a Cochrane review.

This review aims to examine the role of prophylactic use of ibuprofen for the prevention of PDA in preterm infants by comparing it to indomethacin or other cyclo-oxygenase inhibitors.

**OBJECTIVES**

**Primary objectives**

1. To determine the effectiveness and safety of ibuprofen compared to placebo or no intervention in the prevention of PDA in preterm and/or low birth weight infants.
2. To determine the effectiveness and safety of ibuprofen compared to other cyclo-oxygenase inhibitor drugs (indomethacin, mefenamic acid) in the prevention of PDA in preterm and/or low birth weight infants.

**Secondary objectives**

To determine in subgroup analyses the effectiveness and safety of prophylactic ibuprofen to close a PDA in relation to the following criteria:

- Dose of ibuprofen used,
- Gestational age (< 28 weeks, 28 - 32 weeks, 33 - 37 weeks) or birth weight (< 1000 g, 1000 - 1500 g, > 1500 - < 2500 g).

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
Randomized or quasi-randomized controlled trials with or without blinding.

**Types of participants**
Preterm infants < 37 weeks gestational age or low-birth-weight infants (< 2500 g) in the neonatal period (< 28 days).

**Types of interventions**
Prophylactic use of ibuprofen for prevention of PDA compared to control infants who received no intervention, placebo, other cyclo-oxygenase inhibitor drugs (indomethacin, mefenamic acid) or rescue treatment with ibuprofen.

**Types of outcome measures**

**Primary outcome**
The presence of patent ductus arteriosus (clinically symptomatic or diagnosed by ECHO in response to clinical suspicion or diagnosed on routine screening by ECHO) by 72 hours (three days) of age

**Secondary outcomes**
- Neonatal mortality (death during the first 28 days of life)
All cause mortality during initial hospital stay
Mortality before 36 weeks postmenstrual age (PMA)
Infant mortality (death during the first year of life)
Need for rescue treatment with cyclo-oxygenase inhibitors for closure of PDA
Need for surgical closure of PDA
Duration of mechanical ventilation
Oxygen requirement (postnatal age at time of last day with need for supplemental oxygen)
Chronic lung disease (CLD) (defined as oxygen requirements at 28 days postnatal age in addition to compatible clinical and roentgenographic findings)
Chronic lung disease (CLD) (defined as oxygen requirements at 36 weeks postmenstrual age (PMA) in addition to compatible clinical and roentgenographic findings)
Chronic lung disease (CLD) (age at diagnosis not reported)
Pneumothorax
Pulmonary hypertension (PH)
Intraventricular haemorrhage (IVH) (Grade III,IV) (Papile 1978)
Intraventricular haemorrhage (IVH) (all grades)
Intraventricular haemorrhage (IVH) (Grade not stated)
Periventricular leukomalacia (PVL)
Necrotizing enterocolitis (NEC) (any stage) (Bell 1978)
Gastrointestinal haemorrhage
Gastrointestinal perforation (defined by presence of free air in peritoneal cavity on an abdominal x-ray)
Time to full enteral feeds (postnatal age at time of achieving full enteral feeds)
Urine output after treatment (ml/kg/hr)
Oliguria (decreased urine output defined as < 1 cc/kg/hr)
Serum creatinine levels after treatment
At least one episode of serum creatinine > 140 micromol/L (>1.5 mg/dl)
Retinopathy of prematurity (ROP) (according to the international classification of ROP) (ICROP 1984)
Definite sepsis (clinical symptoms and signs of sepsis and a positive bacterial culture in a specimen obtained from normally sterile fluids or tissue obtained at autopsy)
Probable sepsis (clinical symptoms and signs of sepsis and an abnormal findings on a laboratory screening test for infection)
At least one episode of severe hypoxaemia
Inhaled nitric oxide during first week of life
Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death)
Side effects not listed as an outcome above but reported by the authors as a side effect
Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardized and validated assessment tool and/or a child developmental specialist) at any age (outcome data will be grouped at 12, 18, 24 months if available)

Search methods for identification of studies
See: Cochrane Neonatal Review Group search strategy. MEDLINE database (1966 - January 2009) was searched using MeSH terms: cyclo-oxygenase inhibitors, ibuprofen or mefenamic acid, newborn, infant, premature (or preterm) or low birth weight infant, patent ductus arteriosus or PDA. The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2009), EMBASE (1980 - January 2009) and CINAHL (1982 - January 2009), abstracts (American Pediatric Society and European Society for Pediatric Research annual meetings) published in Pediatric Research (1990 - April Issue 2005) or electronically were searched. No new trials since the first publication of this review were identified in the searches undertaken in October 2004 (latest update of this review) but one trial previously published as an abstract (Van Overmeire 2004) and one trial previously published as a letter to the editors (Gournay 2004) were identified as full publications. The reference lists of identified trials were searched. References lists of published narrative and systematic reviews were reviewed. Unpublished data were not sought, but authors of published trials were contacted to clarify or provide additional information. No language restrictions were applied. The retrieved articles were screened by two review authors (SS, AO) to identify articles eligible for inclusion in the review. No language restrictions were applied. For this update there was only one review author (AO).

Data collection and analysis
The standardized review methods of the Cochrane Neonatal Review Group (CNRG) were used to assess the methodological quality of the studies. All abstracts and published full reports identified as potentially relevant by the literature search were assessed for the inclusion in the review by the two authors. Each author extracted data separately on to pre designed data abstraction forms, then compared
and resolved differences. One reviewer (AO) entered the data into RevMan 5.0 and the other (SS) cross checked the printout against his own data abstraction forms and errors were corrected by consensus. The current update was conducted by one reviewer (AO). Quality of included trials were evaluated independently by the review authors, using the following criteria: Blinding of randomisation? Blinding of intervention? Blinding of outcome measure assessment? Completeness of follow-up?

There were three potential answers to these questions - yes, can’t tell, no.

Information from the primary author was obtained if the published article provided inadequate information for the review. Retrieved articles were assessed and data were abstracted independently by the review authors. Independent quality assessments were conducted by the two review authors, who were not blinded to authors, institution or journal of publication.

The statistical analyses followed the recommendations of the Cochrane Neonatal Group. A weighted treatment effect was calculated using the RevMan 5.0 package. The treatment effect estimates included typical relative risk (RR), typical risk difference (RD), number needed to treat to benefit (NNNT) or number needed to treat to harm (NNTH) for dichotomous outcomes, and weighted mean difference (WMD) for continuous outcomes. All estimates of treatment effects were reported with 95% confidence intervals (CI). A fixed effect model was used for meta-analyses. Heterogeneity tests including the I-squared test (I²) were performed to assess the appropriateness of pooling the data. Planned subgroup analyses were performed according to the criteria listed under objectives. No sensitivity analyses were performed.

**RESULTS**

**Description of studies**

See: Characteristics of included studies.

Six studies comparing prophylactic ibuprofen with placebo or no medication qualified for inclusion in this updated review (Van Overmeire 2004; Dani 2000; De Carolis 2000; Gournay 2004; Dani 2005; Sangrawesin 2006). The addition of two newly published studies (Dani 2005; Sangrawesin 2006) published since the last version of this review increased the total number enrolled in trials by 197 to 869. All have been published as full text articles. Rubaltelli published an abstract in 1998 which reported an interim analysis of Dani 2000. The dose and duration of prophylactic ibuprofen was similar in all the studies, but the age at which ibuprofen was started varied from two to 24 hours in the different studies. In one study oral ibuprofen was used (Sangrawesin 2006) and in all other studies ibuprofen was administered IV. PDA at 72 hours was diagnosed using echocardiographic criteria was reported as an outcome in all studies. Echocardiographic criteria of a significant PDA were similar between the studies. Back-up medical treatment with cyclo-oxygenase inhibitors (indomethacin or ibuprofen) was permitted in the presence of significant PDA (after initial trial of ibuprofen, placebo or no medication) in all trials (Dani 2000; De Carolis 2000; Gournay 2004; Van Overmeire 2004; Dani 2005; Sangrawesin 2006). Further details can be found in “Table of Included Studies.” No study of ibuprofen vs. other cyclo-oxygenase inhibitors was identified.

Dani 2000 - This trial enrolled 80 preterm neonates with gestational age < 34 weeks with RDS requiring either continuous positive airway pressure (CPAP) with fractional inspired oxygen concentration (FiO₂) > 0.3 or mechanical ventilation (synchronized intermittent mandatory ventilation or high frequency ventilation). The infants were randomised to receive intravenous ibuprofen lysine (10 mg/kg, followed by 5 mg/kg after 24 and 48 hours) either within 24 hours of life (prophylactic) or after echocardiographic diagnosis of PDA (selective). When PDA was still present after the first course of ibuprofen, a second course was administered. Failure to respond to ibuprofen was an indication for surgical ligation. Primary outcome was incidence of significant PDA as determined by echocardiographic analysis. Echocardiographic evaluation was performed on day three, seven and 21 of life. Other studied variables were ventilatory support, renal function, biochemical and hematological profiles, frequency of CLD at 36 weeks PMA, IVH, NEC, ROP and time to reach full feeds.

De Carolis 2000 - The trial enrolled 50 preterm neonates with gestational age < 31 weeks. The infants were randomly assigned at two hours of age to prophylaxis group or control group. Two infants in each group died during the first 24 hours after birth and were not included by the authors in the final analysis. The prophylaxis group (n = 23) received intravenous (i.v.) treatment with ibuprofen lysine (10 mg/kg) followed by 5 mg/kg after 24 and 48 hours. No placebo was given to the control group (n = 23). In the presence of a significant PDA at the completion of the ibuprofen cycle, treatment with indomethacin (three times 0.2 mg/kg at 12 hourly intervals, administered by i.v. infusion over 20 minutes) was carried out. The same treatment was administered to infants in the control group who had a significant PDA on day three of life. Failure to respond to medical treatment was an indication for surgical treatment. Primary outcome was incidence of significant PDA as determined by echocardiographic analysis. Echocardiographic evaluation was performed immediately after birth, on day three of life and whenever there was a clinical suspicion of PDA. Other studied variables were ventilatory support, renal function, biochemical and hematological profiles, need for surgical ligation for PDA, frequency of CLD at 28 days, IVH, NEC, ROP and time to reach full feeds.

Gournay 2004 - This multicenter trial enrolled 135 infants < 28 weeks gestational age and postnatal age < 6 hours. The infants were randomly assigned to prophylactic ibuprofen or placebo group.
both of which were given as three successive doses 24 hours apart. The initial dose of ibuprofen was 10 mg/kg, and the two following doses were 5 mg/kg, infused iv over 20 minutes. The primary outcome was need for surgical ligation. Other outcomes included: mortality, PDA on day three by echocardiogram, need of back-up treatment with indomethacin, PVL, grade III or IV IVH, NEC, intestinal perforation, duration of mechanical ventilation, CLD at 36 weeks PMA, renal function, actuarial curve of survival during the study period. Occurrence of pulmonary hypertension within one hour of administration of ibuprofen was reported in three infants < 27 weeks and < 1000 g. The trial was stopped prematurely after enrolment of 135 infants due to this adverse effect.

Van Overmeire 2004 - In this multicentre trial 415 preterm infants < 31 weeks of gestation were randomized to receive either three doses of intravenous ibuprofen lysine (10 mg/kg followed by 5 mg/kg after 24 and 48 hours interval) or saline (1 ml/kg as initial dose, 0.5 ml/kg as subsequent doses). The initial dose of medication was given within six hours after birth and subsequent doses were given at 24 and 48 hours interval after the initial dose. Two hundred five infants received ibuprofen (10 mg/ml) while 210 received saline. Cerebral and cardiac ultrasound were performed before and after treatment. The trial was conducted double blind. Perinatal characteristics and possible side-effects were registered. The primary outcome variable was IVH grade 3 or 4. Secondary outcomes included: echocardiographically confirmed PDA after day three of life and the need for its pharmacological rescue treatment or surgical ligation, occurrence of renal dysfunction measured by urine production, NEC and death.

Dani 2005 - This multicenter study enrolled 155 infants < 28 weeks gestational age and postnatal age < 6 hours in seven tertiary neonatal care units in Italy. Infants were assigned randomly to the treatment or the control group using sealed envelopes. Envelopes were prepared centrally and distributed to the different units. Infants in the prophylactic ibuprofen group received 3 doses of ibuprofen lysine (Arfen, Lisapharma, Erba, Italy; 10 mg/kg within 6 hours after birth, followed by 5 mg/kg after 24 and 48 hours. Infants in the control group received indistinguishable placebo. The medications were infused continuously iv over 15 minutes. The primary outcome was IVH (grade 2 to 4) at seven days of life. Other outcomes included IVH at days 15, 30 and at 40 weeks' PMA, PVL, PDA on day 3 (defined as echocardiographic evidence of a haemodynamically significant PDA), mortality, CLD at 36 weeks' PMA, NEC, sepsis (confirmed with positive blood culture), urine output after treatment, oliguria, increased serum creatinine levels after treatment, length of hospital stay and ROP.

Sangtwasesin 2006 - This single center trial enrolled 42 infants of 28 - 32 weeks gestational age and birth weight < 1500 g and postnatal age < 24 hours. The infants were randomly assigned to ibuprofen or control group by block randomisation. The prophylaxis group received ibuprofen suspension (Junifen, Boots Company, Thailand) at a dosage of 10 mg/kg via an orogastric tube, followed by 0.5 ml of distilled water. The first dose was given within the first 24 hours of life. The second and third doses were given within 24 and 48 hours after the first dose respectively. The patients in the control group were given three doses of an orange starch suspension as placebo that looked like ibuprofen. The primary outcome was presence of a PDA (defined as echocardiographic evidence of a haemodynamically significant PDA) on day three of treatment. Additional outcomes included neonatal mortality, duration of mechanical ventilation, pulmonary hypertension, NEC, gastrointestinal haemorrhage, time to full enteral feeds, ROP (grades not stated), length of hospital stay, CLD (age at diagnosis not stated), days of supplemental oxygen therapy, days of mechanical ventilation, IVH (grades not stated), need for rescue treatment with indomethacin or ibuprofen or surgical closure of the PDA and PH.

Risk of bias in included studies

Dani 2000 - This was a randomised controlled trial involving two centres in Italy. Randomization was performed using sealed envelopes. There was no blinding of intervention or assessment. Follow-up was complete and outcomes were reported for all infants enrolled in the study. An intention to treat analysis was performed.

De Carolis 2000 - This was a randomised controlled trial involving a single centre in Italy. Method of randomisation is unclear. We quote the authors. “Randomization was carried out at birth by random permuted blocks for both prophylaxis and control groups, envisaging 25 neonates in each”. There was no blinding of the intervention. There was blinding of outcome measurement. An intention to treat analysis was not performed.

Gournay 2004 - This was a multicentre, randomised double blind, placebo-controlled trial conducted in 11 tertiary neonatal intensive care centres in France. The allocation was concealed. One hundred thirty five infants were included. However, four patients were not randomly assigned because of errors in study drug allocation [three mistakenly received open-label ibuprofen prepared for the curative part of the study during their prophylactic course, and one 10-day-old patient diagnosed with PDA was mistakenly given two doses of the randomised test drug (placebo) instead of curative ibuprofen]. The per protocol analyses were performed on 131 infants. No patient was lost to follow-up. The trial was closed earlier than planned after three episodes of refractory hypoxaemia with pulmonary hypertension happened after the first prophylactic injection in three different centres. The Agence Francaise du Medicament was notified and requested unblinding of the treatment received in these three cases. The treatment was ibuprofen in all three cases and the recruitment was closed on December 14, 2001. This study was industry sponsored. The sponsor of the study was involved in study design, data management, data analysis, and data interpretation. The study sponsor had no role in writing the report or the decision to submit the report for publication. All final data analyses were done by the sponsor and double checked by the first author who had free access to the raw data.
Van Overmeire 2004 - Multicentre randomised controlled trial involving seven centres in Belgium. Randomization was done independently by the chief pharmacist at each hospital. The trial was conducted double blind and saline was used as placebo. Follow-up was complete and outcomes were reported for all infants enrolled in the study. An intention to treat analysis was performed. The study was published as an abstract when 358 infants had been enrolled. There is no mention of this interim analysis in the final publication.

Dani 2005 - This was a multi-centre double-blind placebo-controlled randomised trial conducted in seven tertiary neonatal care units in Italy. The infants were assigned randomly to treatment groups with the sealed-envelope technique. Envelopes were prepared at Careggi University Hospital of Florence and then distributed to participating hospitals. The authors did not state how the randomisation sequence was created. Five infants were excluded after randomisation because of incomplete data collection (four in the ibuprofen group and one in the placebo group).

Sangtawesin 2006 - This was a single-centre placebo-controlled randomised trial. Patients were randomly assigned into the study and control group by block randomisation. It is not clear whether the allocation to study groups was concealed or not. The authors do not state how the randomisation sequence was created. The outcomes for all 42 patients who were randomised are reported.

Effects of interventions

Primary outcome

**IBUPROFEN VS. PLACEBO OR NONE (COMPARISON 1)**

The presence of patent ductus arteriosus (diagnosed on routine screening by ECHO) by 72 hours (three days) of age (Outcome 1.1): This was reported in all six trials (n = 869) (Van Overmeire 2004; Dani 2000; De Carolis 2000; Gournay 2004; Dani 2005; Sangtawesin 2006). Each of the trials noted a statistically significant decrease in the incidence of PDA on day three in the group receiving prophylactic ibuprofen. In the meta-analysis, there was a statistically significant decrease in the incidence of PDA on day three in the prophylactic ibuprofen group as compared to the placebo group. The typical estimates were RR 0.36 (95% CI 0.28, 0.46); RD -0.27 (95% CI -0.33, -0.22); NNT 4 (95% CI 3, 5). There was no statistically significant between study heterogeneity for this outcome (p = 0.20; I² 31% for RR and p = 0.12; I² 42% for RD).

In subgroup analyses including two studies (Van Overmeire 2004; Dani 2005) for the gestational age group <= 28 weeks (n = 420) the RR was 0.41 (95% CI 0.29, 0.58); RD -0.23 (95% CI -0.31, -0.15); NNT 4 (95% CI 3, 7) (Outcome 1.28). There was no significant heterogeneity for this outcome RR p = 0.40, I² = 0%; RD p = 0.62; I² 0%. For the gestational age group 29-30 weeks (n = 150) the RR was 0.29 (95% CI 0.13, 0.64); RD -0.23 (95% CI -0.35, -0.10); NNT 4 (95% CI 3, 10) (Outcome 1.29). For the birth weight group <= 1000 g (n = 196) the RR was 0.37 (95% CI 0.23, 0.61); RD -0.28 (95% CI -0.40, -0.16); NNT 4 (95% CI 3, 6) (Outcome 1.30). For the birth weight group 1001 - 1500 g (n = 185) the RR was 0.47 (95% CI 0.27, 0.81); RD -0.18 (95% CI -0.30, -0.06); NNT 6 (95% CI 3, 17) (Outcome 1.31). All secondary analyses were statistically significant.

Secondary outcomes

**Neonatal mortality (at < 28 days of age) (Outcome 1.2):** Mortality at < 28 days was reported in three trials (n = 172) (Dani 2000; De Carolis 2000; Sangtawesin 2006). There was no statistically significant difference in the mortality between the groups in either trial. In the meta-analysis, there was no statistically significant difference in the mortality between the two groups. The typical estimates were RR 1.28 (95% CI 0.49, 3.33); RD 0.02 (95% CI -0.06, 0.10). There was no statistically significant heterogeneity for this outcome (RR p = 0.56; I² 0%; RD p = 0.30; I² 17%).

**All cause mortality during initial hospital stay (Outcome 1.3):** This was reported in four trials (n = 700) (Van Overmeire 2004; Dani 2000; De Carolis 2000; Dani 2005). None of the trials found a significant difference in the mortality between the groups. In the meta-analysis, there was no statistically significant difference in the incidence of mortality. The typical estimates were RR 0.90 (95% CI 0.62, 1.30) and RD -0.01(95% CI -0.06, 0.03). There was no statistically significant heterogeneity for this outcome (RR p = 0.68; I² = 0%; RD p = 0.72, I² = 0%).

**Mortality before 36 weeks PMA (Outcome 1.4):** This was reported in one trial (n = 131) (Gournay 2004). The relative risk was 0.96 (95% CI 0.56, 1.66) and the RD was -0.01 (95% CI -0.17, 0.14), neither of which were statistically significant.

Infant mortality (death during the first year of life): This outcome was not reported by any of the authors.

**Need for rescue medical treatment with cyclo-oxygenase inhibitors for closure of PDA (Outcome 1.5):** This outcome was reported in five trials (n = 714) (Dani 2000; De Carolis 2000; Gournay 2004; Van Overmeire 2004; Sangtawesin 2006) and all found a statistically significantly reduced need for rescue medical treatment in the prophylaxis group based on RD. Dani et al (Dani 2000) used ibuprofen for rescue treatment and De Carolis et al (De Carolis 2000) used indomethacin for rescue treatment. Van Overmeire et al (Van Overmeire 2004) used either indomethacin or ibuprofen. Gournay et al (Gournay 2004) initiated rescue treatment with ibuprofen and if this failed used indomethacin. Sangtawesin (Sangtawesin 2006) used indomethacin and/or ibuprofen. In the meta-analysis, there was decreased need for rescue medical treatment in the group receiving prophylactic ibuprofen. The typical estimates were RR 0.16 (95% CI 0.10, 0.26), RD -0.28 (95% CI -0.33, -0.22); NNT 4 (95%CI 3, 5). There was statistically significant between study heterogeneity for RD for this outcome (p < 0.00001; I² = 90%) but not for RR (p = 0.06; I² 56%).
Need for surgical closure of PDA (Outcome 1.6):
This outcome was reported in five trials (n = 714) (Dani 2000; De Carolis 2000; Gournay 2004; Van Overmeire 2004; Sangtawesin 2006) and all trials found no significant difference between the groups. In the meta-analysis there was a statistically significant decrease in the need for surgical ligation between the two groups. The typical estimates from the meta-analysis were RR 0.34 (95% CI 0.14, 0.81), RD -0.04 (95% CI -0.06, -0.01).and NNT 25 (95% CI 17, 100). There was no statistically significant heterogeneity for this outcome (RR p = 0.45, I² = 0%; RD p = 0.21, I² = 31%).

Duration of mechanical ventilation (days) (Outcome 1.7):
Duration of mechanical ventilation was reported in three trials (n = 253) (Dani 2000; Gournay 2004; Sangtawesin 2006) and there was no statistically significant difference between the groups in either trial. The typical WMD was 0.67 days (95% CI -3.42, 4.76). There was no statistically significant heterogeneity for this outcome (p = 0.61, I² = 0%). Van Overmeire (n = 415) (Van Overmeire 2004) also reported on this outcome but as medians and inter-quartile ranges. For the ibuprofen group the results were four (2 - 10) days and in the placebo group four (1 - 8) days; p = 0.49.

Pneumothorax:
No trial reported on this outcome.

Pulmonary hypertension (Outcome 1.11):
Pulmonary hypertension was reported in three trials (n = 328) (Gournay 2004; Dani 2005; Sangtawesin 2006). In the study by Gournay 2004 three infants in the ibuprofen group (n = 65) developed PH within one hour of administration of the drug which was responsive to inhaled nitric oxide, as compared to none of the infants in placebo group (n = 66). In the other two studies no cases of PH developed. The typical RR was 7.11 (95% CI 0.37, 134.91), RD 0.02 (95% CI -0.01, 0.05). Test for heterogeneity not applicable for RR; for RD p = 0.21, I² = 37%.

Intraventricular haemorrhage (Grade III, IV) (Papile 1978) (Outcome 1.12):
IVH grade 3 or 4 was reported in five trials (n = 827) (Dani 2000; De Carolis 2000; Gournay 2004; Van Overmeire 2004; Dani 2005). There was no significant difference in the incidence of IVH between the groups in any of the trials. In the meta-analysis there was no statistically significant difference in the incidence of grade 3 or 4 IVH between the two groups. The typical estimates from the meta-analysis were RR 0.82 (95% CI 0.54, 1.26), and RD -0.02 (95% CI -0.06, 0.02) There was no between study heterogeneity for this outcome (RR p = 0.44; I² = 0%; RD p = 0.38, I² = 5%).

Intraventricular haemorrhage (All grades) (Outcome 1.13):
IVH (all grades) were reported in 4 trials (n = 781). The RR was 1.01 (95% CI 0.82, 1.25) and the RD was -0.00 (95% CI -0.06, 0.07). There was no statistically significant heterogeneity for this outcome (RR p = 0.63, I² = 0%; RD p = 0.63. I² = 0%).

Intraventricular haemorrhage (Grades not stated) (Outcome 1.14) was reported in one study (n = 40) (Sangtawesin 2006). The RR was 0.45 (95% CI 0.09, 2.20). The RD was -0.12 (95% CI -0.34, 0.11). Test for heterogeneity not applicable.

Periventricular leukomalacia (PVL) (Outcome 1.15):
PVL was reported in four trials (n = 747) (De Carolis 2000; Gournay 2004; Van Overmeire 2004; Dani 2005) and there was no statistically significant difference in the incidence of PVL between the groups in the individual trials. The typical estimates were RR 1.19 (95% CI 0.64, 2.18), RD 0.01 (95% CI -0.02, 0.04). There was no statistically significant heterogeneity for this outcome (RR p = 0.62, I² = 0%; RD p = 0.71, I² = 0%).

Necrotizing enterocolitis (NEC) (any stage) (Bell 1978) (Outcome 1.16):
This was reported in all six trials (n = 869) (Dani 2000; De Carolis 2000; Gournay 2004; Van Overmeire 2004; Dani 2005; Sangtawesin 2006) and one of the trials (Gournay 2004) found a significant difference in the incidence of NEC between the groups for RR but not for RD. In the meta-analysis there was no statistically significant difference in the incidence of NEC. The typical
estimates were RR 1.08 (95% CI 0.65, 1.79), RD 0.00 (95% CI -0.03, 0.04). There was no statistically significant difference between study heterogeneity for this outcome for RR (p = 0.11; I² = 47%) and for RD (p = 0.08, I² = 49%).

**Gastrointestinal haemorrhage (Outcome 1.17):**
This outcome was reported in two trials (n = 122) (Dani 2000; Sangtawesin 2006) and there was no statistically significant difference between the groups. The typical estimates were RR 1.91 (95% CI 0.89, 4.06) and RD 0.10 (95% CI -0.01, 0.21). Test for heterogeneity showed no statistically significant heterogeneity for this outcome for RR (p = 0.76, I² = 0%) but for RD (p = 0.01, I² = 83%).

**Gastrointestinal perforation (defined by presence of free air in peritoneal cavity on an abdominal x-ray) (Outcome 1.18):**
This outcome was reported in one trial (n = 151) (Gournay 2004) and there was no statistically significant difference between the groups. The relative risk was 5.08 (95% CI 0.61, 42.28) and the RD was 0.06 (95% CI -0.01, 0.13). Test for heterogeneity not applicable.

**Time to reach full enteral feeds (days) (Outcome 1.19):**
This was reported in two trials (n = 122) (Dani 2000; Sangtawesin 2006) and there was no statistically significant difference between the groups. The typical estimate was mean difference 0.00 days (95% CI -3.96, 3.96). There was no statistically significant heterogeneity for this outcome (p = 0.65, I² = 0%).

**Urine output after treatment (ml/kg/hr on day 3) (Outcome 1.20):**
Urine output after treatment was reported in three trials (n = 650) (Dani 2000; Van Overmeire 2004; Dani 2005) and there was no statistically significant difference between the groups. The typical WMMD was -0.05 mL/kg/hr (95% CI -0.26, 0.15). There was no statistically significant heterogeneity for this outcome (p = 0.46, I² = 0%). De Carolis et al (De Carolis 2000) reported urine output on day three as median (range) in the ibuprofen group 3.3 (1.3-4.6) ml/kg/hr and in the control group 2.3 (1.1-4.9) ml/kg/hr.

**Renal complications - Oliguria (urine output < 1 cc/kg/hr) (Outcome 1.21):**
Two studies (n = 286) (Gournay 2004; Dani 2005) reported on this outcome. The RR was 1.23 (95% CI 0.71, 2.12) and the RD was 0.03 (95% CI -0.05, 0.11) (Outcome 1.21.2). One study (n = 415) Van Overmeire 2004 reported on oliguria defined as < 0.5 ml/kg/hour (Outcome 1.21.1). The statistically significant RR was 1.54 (95% CI 1.01, 2.34) and the RD of (borderline statistical significance) was 0.08 (95% CI 0.00, 0.15). Combining the three studies (n = 701) (Outcome 1.21) the typical RR was statistically significantly increased at 1.42 (95% CI 1.02, 1.98) and the typical RD was of borderline statistical significance at 0.06 (95% CI 0.00, 0.11). There was no statistically significant heterogeneity for the meta-analysis of the three studies (RR p = 0.60, I² = 0%; RD p = 0.70, I² = 0%).

**Serum creatinine levels (mg/dL)(Outcomes 1.22 and 1.23):**
Serum creatinine levels after treatment (Outcome 1.22) were reported in three trials (n = 650) (Van Overmeire 2004; Dani 2000; Dani 2005). In the meta-analysis, there was a statistically significant increase in the serum creatinine levels on day three in the group receiving ibuprofen as compared to the group receiving placebo. The typical estimate was WMD 0.11 mg/dL (95% CI 0.07, 0.16). There was significant between study heterogeneity (p = 0.02) I² = 80.4%. De Carolis et al (De Carolis 2000) reported serum creatinine levels on day three as median (range) in the ibuprofen group 1.3 (0.8-1.7) mg/dl and in the control group 1.2 (0.8-1.5) mg/dl, Gournay (Gournay 2004) and Dani (Dani 2005) reported on “at least one episode of serum creatinine > 140 micromol/L (1.6 mg/dl)” (Outcome 1.23). The RR was 3.70 (95% CI 1.05, 12.98); RD 0.06 (95% CI 0.01, 0.11); Number needed to harm (NTH) was 17 (95% CI 9, 100); 2 trials, n = 285. There was statistically significant heterogeneity for this outcome (RR p = 0.21, I² = 36%; RD p = 0.05, I² = 73%).

**Retinopathy of prematurity (ROP) (according to the international classification of ROP) (ICROP 1984) (Outcome 1.24):**
ROP was reported in three trials (n = 275) (Dani 2000; Dani 2005; Sangtawesin 2006) and there was no statistically significant difference between the groups. The estimates were typical RR 1.07 (95% CI 0.76, 1.51), RD 0.02 (95% CI -0.08, 0.13). there was no statistically significant heterogeneity for this outcome (RR p = 0.54, I² = 0%; RD p = 0.52, I² = 0%).

**Definite sepsis (clinical symptoms and signs of sepsis and a positive bacterial culture in a specimen obtained from normally sterile fluids or tissue obtained at autopsy) (Outcome 1.25):**
The incidence of sepsis was reported in two trials (n = 201) (De Carolis 2000; Dani 2005) and there was a statistically significant difference between the groups. The estimates were typical RR 2.70 (95% CI 1.10, 6.59), RD 0.10 (95% CI 0.02, 0.19); NNTH 10 (95% CI 5, 50).Test for heterogeneity (RR p = 0.45, I² = 0%; RD p = 0.08, I² 68%). Probable sepsis (clinical symptoms and signs of sepsis and an abnormal findings on a laboratory screening test for infection) This outcome was not reported.

**At least one episode of severe hypoxaemia (Outcome 1.26):**
One trial reported on this outcome (n = 131) (Gournay 2004). The RR was 1.69 (95% CI 0.80, 3.59); RD 0.09 (95% CI -0.04, 0.23). Test for heterogeneity not applicable.

**Inhaled nitric oxide use during first week of life (Outcome 1.27):**
This outcome was reported in one study (n = 131) (Gournay 2004). The RR was 1.89 (95% CI 0.80, 4.42) and the RD 0.09 (95% CI -0.03, 0.22) (neither reached statistical significance). Test for heterogeneity not applicable.
Length of hospital stay (total length of hospitalisation from birth to discharge home or death in days) (Outcome 1.32): This was reported in three trials (n = 277) (Dani 2000; Dani 2005; Sangtawesin 2006) and there was no statistically significant difference between the groups. The estimates were typical WMD -2.53 days (95% CI -8.26, 3.19). There was no statistically significant heterogeneity for this outcome (p = 0.39; I² = 0%).

Side effects not listed as an outcome above but reported by the authors as a side effect:
Reported side effects are all included under the specific headings above.
Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardized and validated assessment tool and/or a child developmental specialist) at any age (outcome data will be grouped at 12, 18, 24 months if available): No data were available for long-term neurodevelopment outcome.

Subgroup analyses specified a priori could not be performed for the following reasons:
1. Dose of ibuprofen used was similar in all the studies.
2. Echocardiographic criteria were used to diagnose PDA in all the studies.
3. Demographic and outcome data were available separately for the different birth weight or GA categories in the study by Dani (Dani 2005) and in the study by Van Overmeire (Van Overmeire 2004) but did not completely correspond to our preset cut off points. However as they were close we included them as subgroup analyses under the outcome of “The presence of patent ductus arteriosus (clinically symptomatic or diagnosed by ECHO in response to clinical suspicion or diagnosed on routine screening by ECHO) by 72 hours (three days) of age” (see above).

We were not able to identify any randomised controlled trials comparing prophylactic ibuprofen to prophylactic indomethacin or any trials for the use of mefenamic acid for the prevention of PDA.

**DISCUSSION**

This update of our review, including two additional studies enrolling an additional 197 infants for a total of 869 infants, confirms the findings of the previous versions of this review published in 2003 and 2006. Several of the estimates of effect size have become more precise due to the increase in sample size. This review confirmed that prophylactic ibuprofen is effective in reducing the incidence of PDA on day three, reducing the need for rescue treatment with cyclo-oxygenase inhibitors and reducing the need for surgical ligation of a PDA. There was statistically significant between study heterogeneity for the outcomes; need for rescue treatment with cyclo-oxygenase inhibitors, NEC and serum creatinine levels after treatment but for no other outcomes. This review did not find evidence of a statistically significant difference in mortality, duration of hospitalisation, CLD at 28 days or 36 weeks PMA, duration of mechanical ventilation, IVH, PVL, NEC, GI haemorrhage, intestinal perforation, time to reach full enteral feeds or ROP between ibuprofen and placebo groups. In this update of the review there was a statistically significant increased risk of proven sepsis between ibuprofen and placebo groups. This outcome was reported only in two trials (n = 201) resulting in wide CIs around the point estimates. There was a statistically significant increase in the serum creatinine levels on day three of treatment in the prophylactic ibuprofen group as compared to the placebo group. The occurrence of “at least one episode of serum creatinine > 140 micromol/L” was statistically significantly increased. However, there was statistically significant heterogeneity for this outcome. The occurrence of oliguria was statistically significantly increased using RR but of borderline statistical significance using RD. There was no statistically significant heterogeneity for this outcome. In our previous review, one trial (Gournay 2004) reported the occurrence of PH within one hour of administration of ibuprofen to three infants < 27 weeks and < 1000 g. The trial was stopped prematurely after enrolment of 135 infants due to this adverse effect. The authors postulated that this could be due to early administration of ibuprofen (< 6 hours) preventing the normal fall in pulmonary vascular resistance, acidification of their ibuprofen solution (buffered with tromethamine) causing precipitation and micro-embolism in the lungs or due to a specific effect of ibuprofen. This adverse effect was not reported in the two trials included in this updated review (Dani 2005; Sangtawesin 2006) nor in the trials using ibuprofen for treatment of PDA (Van Overmeire 2000; Lago 2002; Mosca 2002). Gournay et al (Gournay 2004) concluded that prophylactic ibuprofen should not be preferred to early curative ibuprofen.

In the current review, there was a statistically significant increase in the need for rescue treatment with cyclo-oxygenase inhibitors (indomethacin or ibuprofen) in the placebo group as compared to prophylactic ibuprofen group. This is an expected event and reflects common clinical practice in the neonatal intensive care units for the management of a symptomatic PDA. In the study by Dani et al (Dani 2000), the infants were randomised to prophylactic ibuprofen or rescue group. In this respect the trial was different from rest of the trials which randomised infants to prophylactic ibuprofen or placebo group. However, the back-up management protocol in four other studies (De Carolis 2000; Gournay 2004; Van Overmeire 2004; Sangtawesin 2006) and the rescue protocol in the study by Dani et al (Dani 2000) were similar in that each was based on the detection of a significant PDA by echocardiography performed at regular predetermined intervals. Hence, for practical purposes, we considered the rescue ibuprofen group in the study by Dani et al (Dani 2000) to be comparable to the placebo group in other studies as far as management of PDA is concerned.
We did not find any trials comparing prophylactic ibuprofen with prophylactic indomethacin. Prophylactic indomethacin (Fowlie 2002) has been shown to reduce need for surgical ligation of PDA and grade 3 and 4 IVH. In that review there was no significant effect on the long-term neurodevelopmental outcomes. It is of note that ibuprofen does not impact on IVH. It is presently unknown whether preventing IVH with the use of indomethacin is preferable to preventing ischaemias with the use of ibuprofen.

In the present update of our review, prophylactic ibuprofen was effective in reducing the incidence of PDA, the need for rescue treatment with cyclo-oxygenase inhibitors and the need for surgical ligation, but did not confer any substantial clinical advantages in the short-term. Ibuprofen prophylaxis has a negative effect on kidney function. As 58% of the infants in the control group had closed the duct by three days of life a large proportion of neonates would be exposed to ibuprofen unnecessarily if used as prophylaxis. There are still no long-term neurodevelopmental follow-up studies available.

In 2005 Coceani et al. (Coceani 2005) proposed that "... an mPGES (membrane bound prostaglandin E synthase) inhibitor, once developed for therapeutic use, could become the agent of choice for PDA treatment, particularly in those instances in which prematurity is complicated by infectious or inflammatory conditions" (Coceani 2005).

AUTHORS’ CONCLUSIONS

Implications for practice

Prophylactic use of ibuprofen reduces the incidence of PDA, the need for rescue treatment with cyclo-oxygenase inhibitors and surgical closure. However, in the control group, the PDA had closed spontaneously by day three in 58% of the neonates. Prophylactic treatment exposes a large proportion of infants unnecessarily to a drug that has important side effects without conferring any important short-term benefit on outcomes. There was an increase in the serum creatinine levels in the ibuprofen group and in the risk of oliguria. There were no statistically significant differences in mortality, grade 3 or 4 IVH, CLD at 28 days or 36 weeks PMA, NEC, gastrointestinal haemorrhage or time to reach full feeds. The prophylactic use of ibuprofen has been associated with severe PH in one of the trials included in the review but did not occur in the two most recent trials included in this updated review. Current evidence does not support the use of ibuprofen for prophylaxis of PDA.

Implications for research

Until long-term follow-up results are published from the trials included in this review no further trials of prophylactic ibuprofen are recommended.

ACKNOWLEDGEMENTS

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Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants (Review)

Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants (Review)

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**References to other published versions of this review**

**Shah 2003**

**Shah 2006**

* Indicates the major publication for the study
# Characteristics of included studies

**Dani 2000**

| Methods  | Two-centre, randomised, controlled trial without the use of a placebo.  
|          | I. Blinding of randomisation - yes  
|          | II. Blinding of intervention - no  
|          | III. Complete follow-up - yes  
|          | IV. Blinding of outcome measurement(s) - no  |

| Participants | Study period not stated.  
|             | 2 centres, Italy  
|             | Inclusion criteria:  
|             | 1. GA < 34 weeks  
|             | 2. Treatment with nasal continuous positive airway pressure with FiO2 > 30% or with synchronized mechanical ventilation or high frequency ventilation because of RDS.  
|             | 3. Platelet count = or > 75000/cmm, serum creatinine = or < 1.5 mg/dl, absence of clinical manifestation of abnormal clotting function.  
|             | 4. absence of grade III or IV IVH before randomisation.  
|             | Enrolled within first 24 hours after birth.  
|             | Demographic data:  
|             | Values presented as mean ± SD or as appropriate  
|             | Prophylactic ibuprofen group  
|             | n = 40  
|             | Gestational age (weeks): 29.2 ± 2.4  
|             | Birth weight (g): 1231 ± 445  
|             | Rescue ibuprofen group  
|             | n = 40  
|             | Gestational age (weeks): 29.6 ± 5.6  
|             | Birth weight (g): 1226 ± 505  |

| Interventions | Group A (prophylactic ibuprofen group; n = 40) received intravenous ibuprofen lysine (Arfen, Lisa-pharma, Italy) 10 mg/kg, within first 24 hours of life, followed by 5 mg/kg after 24 and 48 hours.  
|               | Group B (rescue ibuprofen group; n = 40) received the same pharmacological treatment after echocardiographic diagnosis of PDA.  
|               | When significant PDA was still present after the first course of ibuprofen, a second course was administered. Failure to respond to ibuprofen was an indication for surgical ligation  |

| Outcomes | Echocardiographic diagnosis (Toshiba, Sonolayer SSH 140A with 7.5 MHz transducer) of PDA on day 3, 7 and 21 of life.  
|          | A diagnosis of significant PDA was made by echocardiographic demonstration of a ductal left to right shunt, with left atrial to aortic root ratio > 1.3 or a ductal size > 1.5 mm  
|          | Further endpoints were severity of RDS, CLD at 36 weeks CGA, IVH, ROP, NEC, need for surgical ligation of PDA, mortality, length of hospital stay, time to reach full feeds, renal function, biochemical and hematological profile and any significant adverse effects  |
Patients enrolled in this study are the same as in the abstract of Rubaltelli 1998. This information was provided by Dr Dani and Dr Rubaltelli

### Risk of bias

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### Dani 2005

**Methods**

- Study period
- Multi-center randomised double-blind trial with the use of placebo
- I. Blinding of randomisation - yes
- II. Blinding of intervention - yes
- III. Complete follow-up - yes
- IV. Blinding of outcome measurement(s) - yes

**Participants**

155 infants < 28 weeks gestational age and postnatal age < 6 hours in 7 tertiary neonatal care units in Italy

**Interventions**

Infants were assigned randomly to the treatment or the control group using sealed envelopes. Envelopes were prepared centrally and distributed to the different units. Infants in the prophylactic ibuprofen group received 3 doses of ibuprofen lysine (Arfen, Lisapharma, Erba, Italy; 10 mg/kg within 6 hours after birth, followed by 5 mg/kg after 24 and 48 hours. Infants in the control group received indistinguishable placebo. The medications were infused continuously iv over 15 minutes

**Outcomes**

The primary outcome was IVH (grade 2 to 4) at 7 days of life. Other outcomes included IVH at days 15, 30 and at 40 weeks' postconceptual age, PDA on day 3 (defined as echocardiographic evidence of a haemodynamically significant PDA), BPD at 36 weeks' postconceptual age, NEC, sepsis (confirmed with positive blood culture) and ROP

### Risk of bias

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De Carolis 2000

| Methods | Single-centre, randomised, controlled trial without the use of a placebo.  
I. Blinding of randomisation - Can't tell  
II. Blinding of intervention - no  
III. Complete follow-up - yes  
IV. Blinding of outcome measurement(s) - yes for the primary outcome |
|---|---|
| Participants | Fifty infants < 2 hours of age and with GA < 31 weeks. Two infants in each group died within 24 hours after birth and were not considered in the final analysis.  
Single centre study, Italy. April 1, 1996 - July 30th 1997  
Assignment was performed within 2 hours after birth.  
Demographic data: values presented as mean ± SD or as number (percentage)  
Prophylaxis group  
n = 25  
Gestational age (weeks): 28.1 ± 1.1  
Birth weight (g): 934 ± 288  
Control group  
n = 25  
Gestational age (weeks): 28.0 ± 1.9  
Birth weight (g): 993 ± 308 |
| Interventions | 25 neonates received 10 mg ibuprofen lysine/kg i.v. over 20 minutes within 2 hrs of life, and 5 mg/kg of ibuprofen lysine at 24 and 48 hrs of life.  
25 neonates received no placebo/control treatment. Two neonates in each group died within 24 hours of life and were not considered in the final evaluation  
In the presence of significant PDA at the completion of ibuprofen cycle, treatment with indomethacin (three times 0.2 mg/kg at 12 hourly interval, administered by i.v. infusion over 20 minutes was carried out. The same treatment was administered to control neonates having significant PDA on 3rd day of life. Failure to respond to medical treatment was an indication for surgical ligation |
| Outcomes | PDA at 72 hours of age, need for treatment with indomethacin after 72 hours, surgical ligation, time to full oral feeds, mortality to 28 days of age, CLD at 28 days of age among survivors, sepsis. In addition a number of outcomes during the first 3 days of life were reported as median and range and not as mean and SD  
Echocardiographic evaluation (Esaote Biomedica SPR 8000 ultrasound imaging system, using 5 MHz probe incorporating pulsed and colour-flow doppler) was performed by the same investigator who was blinded to the treatment schedule. Neonates were studied immediately after birth, on day 3 of life, and then whenever clinical suspicion of PDA occurred. PDA was defined symptomatic in the presence of heart murmur, bounding pulses, hyperactive precordium, decrease in diastolic arterial pressure, tachypnoea, increasing FiO2 or ventilatory requirements. Diagnosis of PDA was always confirmed by colour doppler echocardiography and PDA was considered haemodynamically significant when the left atrial:aortic root ratio > 1.3 |
| Notes | “Randomization was carried out at birth by random permuted blocks for both prophylaxis and control groups, envisaging 25 neonates in each.” No further information is provided regarding the randomisation and allocation process.  
Out of the 50 randomised infants, 2 in each group died in the first 24 hours following birth and were not considered in the final analyses by the authors, but were included by us in the analyses reported in this review |
### Gournay 2004

**Methods**
- Randomized, double blinded, controlled trial.
- I. Blinding of randomization - yes
- II. Blinding of intervention - yes
- III. Complete follow up - No (see notes)
- IV. Blinding of outcome measurement(s): yes

**Participants**
- Study period: March 2001 - Dec 2001
- Multicentre trial in 11 NICUs in France
- Inclusion criteria:
  1. GA < 28 weeks
  2. Postnatal age < 6 hours
- Exclusion criteria:
  1. Congenital malformations
  2. Shock or right to left ductal shunt evidenced by differential cyanosis
  3. Cerebral complications
  4. Bleeding disorders
- Demographic data: values presented as mean ± SD
  - Prophylaxis group
    - N = 65
    - GA 26.3 (0.9) weeks
    - BW 844 (181) g
  - Placebo group
    - GA 26.0 (0.9) weeks
    - BW 851 (164) g

**Interventions**
- One hundred and thirty five infants were enrolled in the trial and 131 were randomized to receive either ibuprofen (n = 65) or placebo (n = 66).
- Both ibuprofen or placebo were given as 3 doses, 24 hours apart with the first dose being given within first 6 hours of life. The initial dose of ibuprofen was 10 mg/kg and the 2 following doses were 5 mg/kg, infused i.v. continuously over 20 minutes

**Outcomes**
- Decreased need for surgical ligation based on the presence of a significant PDA on echocardiogram
- Mortality
- PDA on day 3 by echocardiogram
- Need of back-up treatment with indomethacin
- PVL
- Grade III or IV IVH
- NEC
- Intestinal perforation
- Duration of mechanical ventilation

---

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
### Gournay 2004

(Continued)

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
</table>
| BPD at 36 weeks corrected GA  
Renal function  
Actuarial curve of survival during the study period |

| 135 infants were included.  
However, four patients were not randomly assigned because of errors in study drug allocation (3 mistakenly received open-label ibuprofen prepared for the curative part of the study during their prophylactic course, and one 10-day-old patient diagnosed with PDA was mistakenly given 2 doses of the randomised test drug (placebo) instead of curative ibuprofen. The per protocol analyses were performed on 131 infants. No patient was lost to follow-up.  
The trial was closed earlier than planned after 3 episodes of refractory hypoxemia with pulmonary hypertension happened after the first prophylactic injection in three different centres. The Agence Francaise du Medicament was notified and requested unblinding of the treatment received in these 3 cases. The treatment was ibuprofen in all three cases and the recruitment was closed on December 14, 2001.  
The study was supported by the industry (Orphan Europe, Paris, France) |

<table>
<thead>
<tr>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
</tr>
<tr>
<td>Allocation concealment?</td>
</tr>
</tbody>
</table>

### Sangtawesin 2006

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
</table>
| I. Blinding of randomisation - yes; The infants were randomly assigned to ibuprofen or control group by block randomisation.  
II. Blinding of intervention - yes  
III. Complete follow-up - yes  
IV. Blinding of outcome measurement(s) - yes |

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
</table>
| Study period July 2003 - April 2004  
This single center trial conducted in Thailand enrolled 42 infants of 28-32 weeks gestational age and birth weight < 1500 g and postnatal age < 24 hours. |

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>The prophylaxis group received ibuprofen suspension (Junifen, Boots Company, Thailand) at a dosage of 10 mg/kg via an orogastric tube, followed by 0.5 ml of distilled water. The first dose was given within the first 24 hours of life. The second and third doses were given within 24 and 48 hours after the first dose respectively. The patients in the control group were given 3 doses of an orange starch suspension as placebo that looked like ibuprofen</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>The primary outcome was presence of a PDA (defined as echocardiographic evidence of a haemodynamically significant PDA) on day 3 of treatment. Additional outcomes included neonatal mortality, duration of mechanical ventilation, pulmonary hypertension, NEC, gastrointestinal haemorrhage, time to full enteral feeds, ROP (grades not stated), length of hospital stay, BPD (age at diagnosis not stated), days of supplemental oxygen therapy, days of mechanical ventilation, IVH (grades not stated), need for rescue treatment with indomethacin or ibuprofen, and PPHN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
</table>
### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Van Overmeire 2004

**Methods**
- Seven-centre, randomized, double blinded, controlled trial
  - Blinding of randomization - Yes
  - Blinding of intervention - Yes
  - Blinding of outcome measurement(s) - Yes
  - Complete follow-up - Yes

**Participants**
- Study period: February 1, 1999 - September 30, 2001
- 7 centres, Belgium
- Inclusion criteria: gestational age 24-30 weeks
- Exclusion criteria: Major congenital malformation or chromosomal anomaly, intraventricular hemorrhage higher than grade 1 already detected during baseline cranial ultrasonography, an Apgar score at 5 minutes less than 5, signs of congenital infection or life-threatening septicemia, uncontrolled hypotension, contraindications for administration of ibuprofen
- Demographic data: values presented as mean ± SD or as number (percentage)
  - **Prophylaxis group**
    - N = 205
    - GA = 28.1 (1.7) weeks
    - BW = 1048 (315) g
  - **Placebo group**
    - N = 210
    - GA = 28.1 (1.6) weeks
    - BW = 1065 (324) g

**Interventions**
- 205 infants received ibuprofen and 210 infants received placebo (saline). First dose of medication was given within 6 hours of birth and 2nd and 3rd doses were given at 24 hours and 48 hours after the first dose. The dose of ibuprofen used was 10 mg/kg for first dose and 5 mg/kg for subsequent doses. The dose of saline was 1 ml/kg for first dose and 0.5 ml/kg for subsequent doses

**Outcomes**
- The primary outcome variable was IVH grade 3 or 4. Secondary outcomes included: echocardiographically confirmed PDA after day three of life and the need for its pharmacological rescue treatment or surgical ligation, occurrence of renal dysfunction measured by urine production, NEC and death

**Notes**
- The study was published as an abstract when 358 infants had been enrolled. There is no mentioning of this interim analysis in the final publication

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Allocation concealment?  Unclear  B - Unclear

Abbreviations:
BW = birth weight
g = gram
GA = gestational age
IgG = immunoglobulin
i.v. = intravenous(ly)
IVIG = intravenous immunoglobulin
kg = kilogram
LBW = low birth weight (< 2.5kg)
mg = milligram
SEM = standard error of the mean
SD = standard deviation
FiO2 = Fraction of inspired oxygen concentration
### Comparison 1. Ibuprofen vs placebo or none

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of PDA on 3rd day of life (72 hours of age)</td>
<td>6</td>
<td>869</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.36 [0.28, 0.46]</td>
</tr>
<tr>
<td>Neonatal mortality (during first 28 days of life)</td>
<td>3</td>
<td>172</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.28 [0.49, 3.33]</td>
</tr>
<tr>
<td>Mortality during hospital stay</td>
<td>4</td>
<td>700</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.90 [0.62, 1.30]</td>
</tr>
<tr>
<td>Mortality before 36 weeks after conception</td>
<td>1</td>
<td>131</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.56, 1.66]</td>
</tr>
<tr>
<td>Need for rescue medical treatment with cyclo-oxygenase inhibitors</td>
<td>5</td>
<td>714</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.16 [0.10, 0.26]</td>
</tr>
<tr>
<td>Need for surgical closure of PDA</td>
<td>5</td>
<td>714</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.34 [0.14, 0.81]</td>
</tr>
<tr>
<td>Duration of ventilator (days)</td>
<td>3</td>
<td>253</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.67 [-3.42, 4.76]</td>
</tr>
<tr>
<td>CLD at 28 days of life among survivors</td>
<td>1</td>
<td>41</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.88 [0.32, 2.42]</td>
</tr>
<tr>
<td>CLD at 36 weeks corrected GA</td>
<td>4</td>
<td>781</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.87, 1.25]</td>
</tr>
<tr>
<td>CLD (age at diagnosis not stated)</td>
<td>1</td>
<td>41</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.33 [0.78, 14.17]</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3</td>
<td>328</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>7.11 [0.37, 134.91]</td>
</tr>
<tr>
<td>IVH grade III - IV</td>
<td>5</td>
<td>827</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.82 [0.54, 1.26]</td>
</tr>
<tr>
<td>IVH all grades</td>
<td>4</td>
<td>781</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.01 [0.82, 1.25]</td>
</tr>
<tr>
<td>IVH (grades not stated)</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.45 [0.09, 2.20]</td>
</tr>
<tr>
<td>PVL</td>
<td>4</td>
<td>747</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.19 [0.64, 2.18]</td>
</tr>
<tr>
<td>NEC</td>
<td>6</td>
<td>869</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.08 [0.65, 1.79]</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>2</td>
<td>122</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.91 [0.89, 4.06]</td>
</tr>
<tr>
<td>Isolated intestinal perforation</td>
<td>1</td>
<td>131</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.08 [0.61, 42.28]</td>
</tr>
<tr>
<td>Time to full enteral feeds (days)</td>
<td>2</td>
<td>122</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Urine output after treatment (mL/kg/hr)</td>
<td>3</td>
<td>650</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.05 [-0.26, 0.15]</td>
</tr>
<tr>
<td>Oliguria</td>
<td>3</td>
<td>701</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.42 [1.02, 1.98]</td>
</tr>
<tr>
<td>Oliguria &lt; 0.5 ml/kg/hour</td>
<td>1</td>
<td>415</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.54 [1.01, 2.34]</td>
</tr>
<tr>
<td>Oliguria &lt; 1.0 ml/kg/hour</td>
<td>2</td>
<td>286</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.23 [0.71, 2.12]</td>
</tr>
<tr>
<td>Serum creatinine levels after treatment</td>
<td>3</td>
<td>650</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.11 [0.07, 0.16]</td>
</tr>
<tr>
<td>At least one episode of serum creatinine &gt; 140 micromol/L (&gt;1.5 mg/dl)</td>
<td>2</td>
<td>285</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.70 [1.05, 12.98]</td>
</tr>
<tr>
<td>ROP</td>
<td>3</td>
<td>725</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.07 [0.76, 1.51]</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>201</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.70 [1.10, 6.59]</td>
</tr>
<tr>
<td>At least one episode of severe hypoxemia</td>
<td>1</td>
<td>131</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.69 [0.80, 3.59]</td>
</tr>
</tbody>
</table>
27 Nitric oxide during first week of life

28 Presence of PDA on 3rd day of life in infants <\= 28 weeks gestation at birth

29 Presence of PDA on 3rd day of life in infants 29-30 weeks gestation at birth

30 Presence of PDA on 3rd day of life in infants <\= 1000 g

31 Presence of a PDA on 3rd day of life in infants 1001 - 1500 g

32 Length of hospital stay (days)

---

Analysis 1.1. Comparison 1 Ibuprofen vs placebo or none, Outcome 1 Presence of PDA on 3rd day of life (72 hours of age).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 1 Presence of PDA on 3rd day of life (72 hours of age)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Dani 2000</td>
<td>3/40</td>
<td>21/40</td>
<td>11.4 %</td>
<td>0.14 [ 0.05, 0.44 ]</td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>7/77</td>
<td>23/78</td>
<td>12.4 %</td>
<td>0.31 [ 0.14, 0.68 ]</td>
<td></td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>3/23</td>
<td>14/23</td>
<td>7.6 %</td>
<td>0.21 [ 0.07, 0.65 ]</td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>18/65</td>
<td>36/66</td>
<td>19.4 %</td>
<td>0.51 [ 0.32, 0.80 ]</td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>1/22</td>
<td>7/20</td>
<td>4.0 %</td>
<td>0.13 [ 0.02, 0.97 ]</td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>33/205</td>
<td>84/210</td>
<td>45.1 %</td>
<td>0.40 [ 0.28, 0.57 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>432</td>
<td>437</td>
<td>100.0 %</td>
<td>0.36 [ 0.28, 0.46 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 65 (Ibuprofen), 185 (Control)

Heterogeneity: Chi² = 7.27, df = 5 (P = 0.20); I² = 31%

Test for overall effect: Z = 8.18 (P < 0.00001)
**Analysis 1.2. Comparison 1 Ibuprofen vs placebo or none, Outcome 2 Neonatal mortality (during first 28 days of life).**

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 2 Neonatal mortality (during first 28 days of life)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>0/40</td>
<td>1/40</td>
<td>22.9 % 0.33 [ 0.01, 7.95 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>5/25</td>
<td>4/25</td>
<td>61.1 % 1.25 [ 0.38, 4.12 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>3/22</td>
<td>1/20</td>
<td>16.0 % 2.73 [ 0.31, 24.14 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>87</strong></td>
<td><strong>85</strong></td>
<td><strong>100.0 %</strong> <strong>1.28 [ 0.49, 3.33 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 8 (Ibuprofen), 6 (Control)

Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² = 0.0%

Test for overall effect: Z = 0.50 (P = 0.62)

Favours prophylactic Favours control
**Analysis 1.3. Comparison 1 Ibuprofen vs placebo or none, Outcome 3 Mortality during hospital stay.**

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 3 Mortality during hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>0/40</td>
<td>1/40</td>
<td></td>
<td>3.0 %</td>
<td>0.33 [0.01, 7.95]</td>
</tr>
<tr>
<td>Dani 2005</td>
<td>15/77</td>
<td>20/78</td>
<td></td>
<td>39.7 %</td>
<td>0.76 [0.42, 1.37]</td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>6/25</td>
<td>4/25</td>
<td></td>
<td>8.0 %</td>
<td>1.50 [0.48, 4.68]</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>23/205</td>
<td>25/210</td>
<td></td>
<td>49.3 %</td>
<td>0.94 [0.55, 1.61]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>347</strong></td>
<td><strong>353</strong></td>
<td></td>
<td>100.0 %</td>
<td>0.90 [0.62, 1.30]</td>
</tr>
</tbody>
</table>

Total events: 44 (Ibuprofen), 50 (Control)

Heterogeneity: Chi² = 1.50, df = 3 (P = 0.68); I² = 0.0%

Test for overall effect: Z = 0.58 (P = 0.56)

---

**Analysis 1.4. Comparison 1 Ibuprofen vs placebo or none, Outcome 4 Mortality before 36 weeks after conception.**

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 4 Mortality before 36 weeks after conception

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gournay 2004</td>
<td>18/65</td>
<td>19/66</td>
<td></td>
<td>100.0 %</td>
<td>0.96 [0.56, 1.66]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>65</strong></td>
<td><strong>66</strong></td>
<td></td>
<td>100.0 %</td>
<td>0.96 [0.56, 1.66]</td>
</tr>
</tbody>
</table>

Total events: 18 (Ibuprofen), 19 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.14 (P = 0.89)
Analysis 1.5. Comparison 1 Ibuprofen vs placebo or none, Outcome 5 Need for rescue medical treatment with cyclo-oxygenase inhibitors.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 5 Need for rescue medical treatment with cyclo-oxygenase inhibitors

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>0/40</td>
<td>19/40</td>
<td>16.6 % 0.03 [0.00, 0.41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>3/23</td>
<td>16/23</td>
<td>13.6 % 0.19 [0.06, 0.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>2/65</td>
<td>34/66</td>
<td>28.7 % 0.06 [0.01, 0.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>0/22</td>
<td>6/20</td>
<td>5.8 % 0.07 [0.00, 1.17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>13/205</td>
<td>42/210</td>
<td>35.3 % 0.32 [0.18, 0.57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>355</strong></td>
<td><strong>359</strong></td>
<td><strong>100.0 % 0.16 [0.10, 0.26]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 18 (Ibuprofen), 117 (Control)
Heterogeneity: Chi² = 9.00, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 7.71 (P < 0.00001)
### Analysis 1.6. Comparison 1 Ibuprofen vs placebo or none, Outcome 6 Need for surgical closure of PDA.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 6 Need for surgical closure of PDA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>0/40</td>
<td>0/40</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>1/23</td>
<td>3/23</td>
<td>15.5 % 0.33 [0.04, 2.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>0/65</td>
<td>6/66</td>
<td>33.4 % 0.08 [0.00, 1.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>0/22</td>
<td>0/20</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>5/205</td>
<td>10/210</td>
<td>51.1 % 0.51 [0.18, 1.47]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>355</strong></td>
<td><strong>359</strong></td>
<td><strong>100.0 % 0.34 [0.14, 0.81]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Ibuprofen), 19 (Control)

Heterogeneity: Chi² = 1.60, df = 2 (P = 0.45); I² = 0.0%

Test for overall effect: Z = 2.43 (P = 0.015)
### Analysis 1.7. Comparison 1 Ibuprofen vs placebo or none, Outcome 7 Duration of ventilator (days).

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 7 Duration of ventilator (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dani 2000</td>
<td>40 12.6 (17.9)</td>
<td>40 12.2 (13.6)</td>
<td>-0.40</td>
<td>34.5 %</td>
<td>(-0.65, 7.37)</td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>65 18.4 (19)</td>
<td>66 19.6 (18.5)</td>
<td>-1.20</td>
<td>40.5 %</td>
<td>(-7.62, 5.22)</td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>22 11.66 (12.49)</td>
<td>20 7.59 (14.36)</td>
<td>4.07</td>
<td>25.0 %</td>
<td>(-4.11, 12.25)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>127</td>
<td>126</td>
<td>0.67</td>
<td>100.0 %</td>
<td>(-3.42, 4.76)</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.00, df = 2 (P = 0.61); I² = 0.0%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable

### Analysis 1.8. Comparison 1 Ibuprofen vs placebo or none, Outcome 8 CLD at 28 days of life among survivors.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 8 CLD at 28 days of life among survivors

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>5/20</td>
<td>6/21</td>
<td>0.88</td>
<td>100.0 %</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>20</td>
<td>21</td>
<td>0.88</td>
<td>100.0 %</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Total events: 5 (Ibuprofen), 6 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.26 (P = 0.80)
## Analysis 1.9. Comparison 1 Ibuprofen vs placebo or none, Outcome 9 CLD at 36 weeks corrected GA.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 9 CLD at 36 weeks corrected GA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Dani 2000</td>
<td>2/40</td>
<td>3/40</td>
<td></td>
<td>2.2 %</td>
<td>0.67 [ 0.12, 3.78 ]</td>
</tr>
<tr>
<td>Dani 2005</td>
<td>16/77</td>
<td>22/78</td>
<td></td>
<td>16.1 %</td>
<td>0.74 [ 0.42, 1.29 ]</td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>19/65</td>
<td>15/66</td>
<td></td>
<td>11.0 %</td>
<td>1.29 [ 0.72, 2.31 ]</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>103/205</td>
<td>97/210</td>
<td></td>
<td>70.7 %</td>
<td>1.09 [ 0.89, 1.33 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>387</td>
<td>394</td>
<td></td>
<td>100.0 %</td>
<td>1.04 [ 0.87, 1.25 ]</td>
</tr>
</tbody>
</table>

Total events: 140 (Ibuprofen), 137 (Control)

Heterogeneity: Chi$^2$ = 2.39, df = 3 (P = 0.50); $I^2$ =0.0%

Test for overall effect: Z = 0.46 (P = 0.64)

## Analysis 1.10. Comparison 1 Ibuprofen vs placebo or none, Outcome 10 CLD (age at diagnosis not stated).

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 10 CLD (age at diagnosis not stated)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>7/21</td>
<td>2/20</td>
<td></td>
<td>100.0 %</td>
<td>3.33 [ 0.78, 14.17 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>21</td>
<td>20</td>
<td></td>
<td>100.0 %</td>
<td>3.33 [ 0.78, 14.17 ]</td>
</tr>
</tbody>
</table>

Total events: 7 (Experimental), 2 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.63 (P = 0.10)

Test for subgroup differences: Not applicable
Analysis 1.11. Comparison 1 Ibuprofen vs placebo or none, Outcome 11 Pulmonary hypertension.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 11 Pulmonary hypertension

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2005</td>
<td>0/77</td>
<td>0/78</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>3/65</td>
<td>0/66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>0/22</td>
<td>0/20</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 164 164 100.0% 7.11 [0.37, 134.91]

Total events: 3 (Ibuprofen), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

Analysis 1.12. Comparison 1 Ibuprofen vs placebo or none, Outcome 12 IVH grade III - IV.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 12 IVH grade III - IV

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>0/40</td>
<td>0/40</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>8/77</td>
<td>8/78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>2/23</td>
<td>1/23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>7/65</td>
<td>15/66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>17/205</td>
<td>18/210</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 410 417 100.0% 0.82 [0.54, 1.26]

Total events: 34 (Ibuprofen), 42 (Control)

Heterogeneity: CHI² = 2.70, df = 3 (P = 0.44); I² = 0.0%

Test for overall effect: Z = 0.88 (P = 0.38)
### Analysis 1.13. Comparison 1 Ibuprofen vs placebo or none, Outcome 13 IVH all grades.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 13 IVH all grades

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dani 2000</td>
<td>3/40</td>
<td>1/40</td>
<td>0.9%</td>
<td>3.00 [0.33, 27.63]</td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>20/77</td>
<td>19/78</td>
<td>16.4%</td>
<td>1.07 [0.62, 1.84]</td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>25/65</td>
<td>30/66</td>
<td>25.9%</td>
<td>0.85 [0.56, 1.27]</td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>67/205</td>
<td>66/210</td>
<td>56.8%</td>
<td>1.04 [0.79, 1.38]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|          | 387       | 394       | 100.0%     | 1.01 [0.82, 1.25] |

Total events: 115 (Ibuprofen), 116 (Control)

Heterogeneity: $\chi^2 = 1.74, \text{df} = 3 (P = 0.63); I^2 = 0.0$

Test for overall effect: $Z = 0.10 (P = 0.92)$

Test for subgroup differences: Not applicable

---

0.05 0.2 1 5 20

Favours prophylactic Favours control
### Analysis 1.14. Comparison 1 Ibuprofen vs placebo or none, Outcome 14 IVH (grades not stated).

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 14 IVH (grades not stated)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>2/21</td>
<td>4/19</td>
<td>100.0%</td>
<td>0.45 [0.09, 2.20]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 21/19  100.0%  0.45 [0.09, 2.20]

Total events: 2 (Experimental), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable

---

### Analysis 1.15. Comparison 1 Ibuprofen vs placebo or none, Outcome 15 PVL.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 15 PVL

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>3/77</td>
<td>4/78</td>
<td>22.3%</td>
<td>0.76 [0.18, 3.28]</td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>2/23</td>
<td>2/23</td>
<td>11.2%</td>
<td>1.00 [0.15, 6.51]</td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>6/65</td>
<td>7/66</td>
<td>38.9%</td>
<td>0.87 [0.31, 2.45]</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>10/205</td>
<td>5/210</td>
<td>27.7%</td>
<td>2.05 [0.71, 5.89]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 370/377  100.0%  1.19 [0.64, 2.18]

Total events: 21 (Ibuprofen), 18 (Control)

Heterogeneity: Chi² = 1.76, df = 3 (P = 0.62); I² = 0.0%

Test for overall effect: Z = 0.55 (P = 0.58)
### Analysis 1.16. Comparison 1 Ibuprofen vs placebo or none, Outcome 16 NEC.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 16 NEC

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Dani 2000</td>
<td>0/40</td>
<td>0/40</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>2/78</td>
<td>2/78</td>
<td>7.8 %</td>
<td>1.00 [ 0.14, 6.92 ]</td>
<td></td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>0/23</td>
<td>2/23</td>
<td>9.8 %</td>
<td>0.20 [ 0.01, 3.95 ]</td>
<td></td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>11/65</td>
<td>3/66</td>
<td>11.7 %</td>
<td>3.72 [ 1.09, 12.73 ]</td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>8/21</td>
<td>6/20</td>
<td>24.1 %</td>
<td>1.27 [ 0.54, 3.01 ]</td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>6/205</td>
<td>12/210</td>
<td>46.5 %</td>
<td>0.51 [ 0.20, 1.34 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>432</strong></td>
<td><strong>437</strong></td>
<td>100.0 %</td>
<td><strong>1.08 [ 0.65, 1.79 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 27 (Ibuprofen), 25 (Control)

Heterogeneity: $\chi^2 = 7.57$, df = 4 ($P = 0.11$); $I^2 = 47\%$

Test for overall effect: $Z = 0.29$ ($P = 0.77$)
Analysis 1.17. Comparison 1 Ibuprofen vs placebo or none, Outcome 17 Gastrointestinal hemorrhage.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 17 Gastrointestinal hemorrhage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>1/40</td>
<td>0/40</td>
<td>7.4 % 3.00 [0.13, 71.51]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>12/22</td>
<td>6/20</td>
<td>92.6 % 1.82 [0.84, 3.93]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 62 60 100.0 % 1.91 [0.89, 4.06]

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

Test for overall effect: Z = 1.67 (P = 0.095)

Analysis 1.18. Comparison 1 Ibuprofen vs placebo or none, Outcome 18 Isolated intestinal perforation.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 18 Isolated intestinal perforation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gournay 2004</td>
<td>5/65</td>
<td>1/66</td>
<td>100.0 % 5.08 [0.61, 42.28]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 65 66 100.0 % 5.08 [0.61, 42.28]

Heterogeneity: not applicable

Test for overall effect: Z = 1.50 (P = 0.13)
Analysis 1.19. Comparison 1 Ibuprofen vs placebo or none, Outcome 19 Time to full enteral feeds (days).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 19 Time to full enteral feeds (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Dani 2000</td>
<td>40 15.5 (9.1)</td>
<td>40 15.8 (9.9)</td>
<td>-0.30 [-4.47, 3.87]</td>
<td>90.2 %</td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>22 29.71 (17.9)</td>
<td>20 26.94 (23.29)</td>
<td>2.77 [-9.88, 15.42]</td>
<td>9.8 %</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td>60</td>
<td>0.00 [-3.96, 3.96]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0.0%
Test for overall effect: Z = 0.00 (P = 1.0)
Test for subgroup differences: Not applicable

Analysis 1.20. Comparison 1 Ibuprofen vs placebo or none, Outcome 20 Urine output after treatment (mL/kg/hr).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 20 Urine output after treatment (mL/kg/hr)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Dani 2000</td>
<td>40 2.5 (0.9)</td>
<td>40 2.4 (0.8)</td>
<td>0.10 [-0.27, 0.47]</td>
<td>29.9 %</td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>77 2.9 (1.3)</td>
<td>78 2.9 (1.1)</td>
<td>0.00 [-0.38, 0.38]</td>
<td>28.9 %</td>
<td></td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>205 3.8 (1.7)</td>
<td>210 4 (1.6)</td>
<td>-0.20 [-0.52, 0.12]</td>
<td>41.2 %</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>322</td>
<td>328</td>
<td>-0.05 [-0.26, 0.15]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.54, df = 2 (P = 0.46); I² = 0.0%
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable
Analysis 1.21. Comparison 1 Ibuprofen vs placebo or none, Outcome 21 Oliguria.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 21 Oliguria

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>1 Oliguria &lt; 0.5 ml/kg/hour</td>
<td>45/205</td>
<td>30/210</td>
<td></td>
<td>61.1 %</td>
<td>1.54 [1.01, 2.34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subtotal (95% CI)</td>
<td>205</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 2.00 (P = 0.045)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Oliguria &lt; 1.0 ml/kg/hour</td>
<td>7/77</td>
<td>4/78</td>
<td></td>
<td>8.2 %</td>
<td>1.77 [0.54, 5.81]</td>
</tr>
<tr>
<td></td>
<td>16/65</td>
<td>15/66</td>
<td></td>
<td>30.7 %</td>
<td>1.08 [0.59, 2.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subtotal (95% CI)</td>
<td>142</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² =0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total (95% CI)</td>
<td>347</td>
<td>354</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total events: 68 (Ibuprofen), 49 (Control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Chi² = 1.01, df = 2 (P = 0.60); I² =0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 2.05 (P = 0.040)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.2 0.5 1 2 5
| Favours treatment | Favours control |
Analysis 1.22. Comparison 1 Ibuprofen vs placebo or none, Outcome 22 Serum creatinine levels after treatment.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 22 Serum creatinine levels after treatment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
</tr>
<tr>
<td>Dani 2000</td>
<td>40</td>
<td>1 (0.42)</td>
<td>40</td>
<td>1.1 (0.5)</td>
<td>-0.10 [ -0.30, 0.10 ]</td>
</tr>
<tr>
<td>Dani 2005</td>
<td>77</td>
<td>1.11 (0.39)</td>
<td>78</td>
<td>1.1 (0.47)</td>
<td>0.01 [ -0.13, 0.15 ]</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>205</td>
<td>1.14 (0.28)</td>
<td>210</td>
<td>1 (0.22)</td>
<td>0.14 [ 0.09, 0.19 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>322</strong></td>
<td></td>
<td><strong>328</strong></td>
<td></td>
<td><strong>100.0 % 0.11 [ 0.07, 0.16 ]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 7.65, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 5.03 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 1.23. Comparison 1 Ibuprofen vs placebo or none, Outcome 23 At least one episode of serum creatinine > 140 micromol/L (>1.5 mg/dl).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen vs placebo or none

Outcome: 23 At least one episode of serum creatinine > 140 micromol/L (>1.5 mg/dl)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Dani 2005</td>
<td>3/77</td>
<td>2/77</td>
<td></td>
<td>66.8 %</td>
<td>1.50 [ 0.26, 8.73 ]</td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>8/65</td>
<td>1/66</td>
<td></td>
<td>33.2 %</td>
<td>8.12 [ 1.05, 63.13 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>142</strong></td>
<td><strong>143</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>3.70 [ 1.05, 12.98 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 11 (Treatment), 3 (Control)
Heterogeneity: Chi² = 1.57, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 2.04 (P = 0.04)

Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants (Review) 36

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### Analysis 1.24. Comparison 1 Ibuprofen vs placebo or none, Outcome 24 ROP.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 24 ROP

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2000</td>
<td>10/40</td>
<td>13/40</td>
<td>31.0% 0.77 [0.38, 1.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>32/77</td>
<td>27/78</td>
<td>64.0% 1.20 [0.80, 1.80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>3/21</td>
<td>2/19</td>
<td>5.0% 1.36 [0.25, 7.27]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)** 138 137 100.0% 1.07 [0.76, 1.51]

Total events: 45 (Ibuprofen), 42 (Control)

Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0.0%

Test for overall effect: Z = 0.41 (P = 0.68)
### Analysis 1.25. Comparison 1 Ibuprofen vs placebo or none, Outcome 25 Sepsis.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Outcome:** 25 Sepsis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Dani 2005</td>
<td>15/77</td>
<td>5/78</td>
<td></td>
<td>83.2%</td>
<td>3.04 [ 1.16, 7.95 ]</td>
</tr>
<tr>
<td>De Carolis 2000</td>
<td>1/23</td>
<td>1/23</td>
<td></td>
<td>16.8%</td>
<td>1.00 [ 0.07, 15.04 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100</strong></td>
<td><strong>101</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.70 [ 1.10, 6.59 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 16 (Ibuprofen), 6 (Control)

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² =0.0%

Test for overall effect: Z = 2.18 (P = 0.030)

---

### Analysis 1.26. Comparison 1 Ibuprofen vs placebo or none, Outcome 26 At least one episode of severe hypoxemia.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Outcome:** 26 At least one episode of severe hypoxemia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Gournay 2004</td>
<td>15/65</td>
<td>9/66</td>
<td></td>
<td>100.0%</td>
<td>1.69 [ 0.80, 3.59 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>65</strong></td>
<td><strong>66</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.69 [ 0.80, 3.59 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 15 (Ibuprofen), 9 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.37 (P = 0.17)
### Analysis 1.27. Comparison 1 Ibuprofen vs placebo or none, Outcome 27 Nitric oxide during first week of life.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 27 Nitric oxide during first week of life

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gournay 2004</td>
<td>13/65</td>
<td>7/66</td>
<td></td>
<td>100.0%</td>
<td>1.89 [0.80, 4.42]</td>
</tr>
</tbody>
</table>

Total (95% CI) 65 66 100.0% 1.89 [0.80, 4.42]

Total events: 13 (Ibuprofen), 7 (Control)

**Heterogeneity:** not applicable

**Test for overall effect:** Z = 1.46 (P = 0.14)

---

### Analysis 1.28. Comparison 1 Ibuprofen vs placebo or none, Outcome 28 Presence of PDA on 3rd day of life in infants <= 28 weeks gestation at birth.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 28 Presence of PDA on 3rd day of life in infants <= 28 weeks gestation at birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani 2005</td>
<td>7/77</td>
<td>23/78</td>
<td></td>
<td>28.0%</td>
<td>0.31 [0.14, 0.68]</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>26/130</td>
<td>60/135</td>
<td></td>
<td>72.0%</td>
<td>0.45 [0.30, 0.67]</td>
</tr>
</tbody>
</table>

Total (95% CI) 207 213 100.0% 0.41 [0.29, 0.58]

Total events: 33 (Treatment), 83 (Control)

**Heterogeneity:** Chi² = 0.72, df = 1 (P = 0.40); I² = 0.0%

**Test for overall effect:** Z = 4.96 (P < 0.00001)
### Analysis 1.29. Comparison 1 Ibuprofen vs placebo or none, Outcome 29 Presence of PDA on 3rd day of life in infants 29-30 weeks gestation at birth.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 29 Presence of PDA on 3rd day of life in infants 29-30 weeks gestation at birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>7/75</td>
<td>24/75</td>
<td>100.0 %</td>
<td>0.29 [ 0.13, 0.64 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>75</strong></td>
<td><strong>75</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.29 [ 0.13, 0.64 ]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 7 (Treatment), 24 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.10 (P = 0.0019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 1.30. Comparison 1 Ibuprofen vs placebo or none, Outcome 30 Presence of PDA on 3rd day of life in infants <= 1000 g.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 30 Presence of PDA on 3rd day of life in infants <= 1000 g

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>16/97</td>
<td>44/99</td>
<td>100.0 %</td>
<td>0.37 [ 0.23, 0.61 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>97</strong></td>
<td><strong>99</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.37 [ 0.23, 0.61 ]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 16 (Treatment), 44 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.89 (P = 0.000099)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 1.31. Comparison 1 Ibuprofen vs placebo or none, Outcome 31 Presence of a PDA on 3rd day of life in infants 1001 - 1500 g.

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 31 Presence of a PDA on 3rd day of life in infants 1001 - 1500 g

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Van Overmeire 2004</td>
<td>15/94</td>
<td>31/91</td>
<td>100.0 % 0.47 [ 0.27, 0.81 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>94</strong></td>
<td><strong>91</strong></td>
<td><strong>100.0 % 0.47 [ 0.27, 0.81 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (Treatment), 31 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.73 (P = 0.0064)

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### Analysis 1.32. Comparison 1 Ibuprofen vs placebo or none, Outcome 32 Length of hospital stay (days).

**Review:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

**Comparison:** 1 Ibuprofen vs placebo or none

**Outcome:** 32 Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ibuprofen</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
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<tr>
<td>Dani 2000</td>
<td>40</td>
<td>52.9 (28.9)</td>
<td>-3.50 [-15.55, 8.55 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dani 2005</td>
<td>77</td>
<td>82.7 (21.9)</td>
<td>-4.20 [-11.29, 2.89 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangtawesin 2006</td>
<td>22</td>
<td>61.9 (28.97)</td>
<td>8.25 [-8.20, 24.70 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>139</strong></td>
<td><strong>138</strong></td>
<td><strong>100.0 % -2.53 [-8.26, 3.19 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.89, df = 2 (P = 0.39); I² =0.0%

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable
**WHAT'S NEW**

Last assessed as up-to-date: 27 February 2009.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
</table>
| 28 February 2009    | New search has been performed| This updates the review “Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants” published in The Cochrane Library, Issue 1, 2006 (Shah 2006)  
Updated search identified two additional trials for inclusion in this review  
No change to the conclusion of the review. |

**HISTORY**

Review first published: Issue 2, 2003

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 September 2005</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
</tbody>
</table>

**CONTRIBUTIONS OF AUTHORS**

Ohlsson A - contributed to all stages of the review and conducted the updates in July 2005 and February 2009.

Shah S - contributed to all stages of the protocol and the original review.

**DECLARATIONS OF INTEREST**

None

**SOURCES OF SUPPORT**

Internal sources

- Department of Paediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada.
External sources

• No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)
*Infant, Low Birth Weight; *Infant, Premature; Cyclooxygenase Inhibitors [*therapeutic use]; Ductus Arteriosus, Patent [*prevention & control]; Enzyme Inhibitors [*therapeutic use]; Ibuprofen [*therapeutic use]; Infant, Newborn; Randomized Controlled Trials as Topic

MeSH check words

Humans