

PATENT DUCTUS ARTERIOSUS

Supporting information

In premature infants with patent ductus arteriosus (PDA), does early treatment with indometacin improve outcomes?

A randomised prospective trial in 127 infants (van Overmeire, 2001) compared early (day 3, n = 64) with late (day 7, n = 63) iv indometacin treatment (3 x 0.2 mg/kg 12 hrly). PDA closure rate was higher in the “early” group at both 6 (73% vs 44%, p = .0008) and 9 days of age (91% vs 78%, p = .047). More adverse events (including death, lower urinary output, higher serum creatinine, necrotising enterocolitis, extension of haemorrhage and cystic leukomalacia) occurred in the “early” group, however.

Evidence on the duration of indometacin therapy is unclear. A randomised trial in 61 premature infants (Tammela, 1999) compared 31 given a short course (3 doses: 0.2/0.1/0.1 mg/kg in 24 hours) to 30 given a long course (0.1 mg/kg every 24 hours for 7 days). Primary PDA closure occurred more often in the short course group (94% vs 67%, p = .011), but the sustained closure rates were not significantly different (74% vs 60%). The short course patients suffered fewer adverse effects. The authors concluded that a prolonged, low-dosage regimen offered no advantage over a standard-dosage short course.

A similar conclusion was reached by a Cochrane review of 5 trials in a total of 431 infants (Herrera, 2007).

In a more recent retrospective cohort study (Quinn, 2002), 313 infants with PDA were divided, after an initial 3 doses of indometacin into “clinically closed” (n = 214), “partially closed” (n = 69) and “nonresponder” (n = 30) groups. The 69 partial responders were then investigated, using a hierarchical regression model, to identify factors associated with permanent closure. Only gestational age and duration of indometacin treatment were significantly and independently associated, with long course (6 dose rather than 3) recipients also having decreased incidence of symptomatic reopening (OR 0.19, 95% CI 0.04-0.96) and ductus ligation (OR 0.14, 95% CI 0.03-0.68).

A small retrospective study in 46 infants (Dumas de la Roque, 2002) found that omitting the initial bolus of indometacin and giving 0.1 mg/kg daily until the ductus arteriosus was closed was as effective as the standard protocol. Initial success rate was 84.7%, of which 6.5% reopened. The mean cumulative dose of indometacin was 0.35 mg/kg.

Dumas de la Roque E, Fayon M, Babre F, et al. Minimal effective dose of indomethacin for the treatment of patent ductus arteriosus in preterm infants. *Biol Neonate* 2002;81:91-4

Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD003480

Patel J, Roberts I, Azzopardi D, et al. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. *Pediatr Res* 2000;47:36-42

Quinn D, Cooper B, Clyman RI. Factors associated with permanent closure of the ductus arteriosus: a role for prolonged indomethacin therapy. *Pediatrics* 2002;110:e10

Tammela O, Ojala R, Iivainen T, et al. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. *J Pediatr* 1999;134:552-7

van Overmeire B. Patent ductus arteriosus: how aggressive should we be? *Neonatology* 2007;91:318

van Overmeire B, van de Broek H, van Laer P, et al. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 2001;138:205-11

van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;343:674-81

van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F179-84

Evidence Level: I

Does the feeding regime need to be altered when the patient is on indometacin?

Early enteral nutrition has been supposed to be associated with an increased risk for necrotising enterocolitis (NEC) in preterm infants. The only study to investigate this in conjunction with indometacin treatment, however, has found no such association (Bellander, 2003). 32 infants given indometacin were matched with 32 controls; feeding volumes were the same in both groups. Two infants developed NEC in the treatment group, and two in the control group.

Bellander M, Ley D, Polberger S, et al. Tolerance to early human milk feeding is not compromised by indomethacin in preterm infants with persistent ductus arteriosus. *Acta Paediatr* 2003;92:1074-8

Evidence Level: IV

Does ibuprofen have advantages over indometacin?

Four randomised trials (Lago, 2002; Supapannachart, 2002; Van Overmeire, 2000; Van Overmeire, 1997) have found ibuprofen to be equivalent to indometacin in the treatment of PDA. No differences were observed in efficacy, mortality, NEC, or progression of intracranial haemorrhage. The infants receiving ibuprofen experienced a smaller rise in serum creatinine and were less likely to develop oliguria (NNT = 6) than those receiving indometacin.

Three RCTs in a total of 221 infants (Patel, 2000; van Overmeire, 2000; van Overmeire, 1997) have found ibuprofen to be as effective as indometacin in closing PDA, whilst causing significantly fewer side-effects.

A systematic review on the use of ibuprofen in PDA (Aranda, 2006) advises that, as ibuprofen does not reduce the incidence of intraventricular haemorrhage (IVH), indometacin should be used on the first day of life if IVH prophylaxis is needed.

Ibuprofen should then be used on the second and subsequent days of life.

A Cochrane systematic review of 11 trials in a total of 620 patients (Ohlsson, 2005) found no statistically significant difference between the effectiveness of indometacin and ibuprofen for PDA closure and concluded that indometacin should remain the drug of choice.

As neither medical nor surgical interventions have been shown to influence mortality rates in PDA, it has been suggested (Cordero, 2007; van Overmeire, 2007;

Vanhaesebrouck 2007) that a “wait and see” approach may result in more spontaneous closures and avoid potential adverse effects of treatment.

Aranda JV, Ronald T. Systematic review: intravenous ibuprofen in preterm newborns. *Semin Perinatol* 2006;30:114-20

Cordero L, Nankervis CA, Delooze D, et al. Indomethacin prophylaxis or expectant treatment of patent ductus arteriosus in extremely low birth weight infants? *J Perinatol* 2007;27:158-63

Lago P, Bettiol T, Salvadori S, et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. *Eur J Pediatr* 2002;161:202-7

Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003481

Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. *J Med Assoc Thai* 2002;85(Suppl 4):S1252-8

Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;343:674-81

Van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F179-84

Van Overmeire B. Patent ductus arteriosus: how aggressive should we be? *Neonatology* 2007;91:318

Vanhaesebrouck S, Zonnenberg I, Vandervoort P, et al. Conservative treatment of patent ductus arteriosus in the preterm. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F244-7

Evidence Level: I

If a duct fails to close after the first course of indometacin, are further courses indicated?

A study in 32 infants (Keller, 2003) showed that recurrent PDA rarely responds to further courses of indometacin if there is persistent Doppler evidence of ductus flow after completion of the initial course. All 9 of the infants in this category failed the second course of indometacin.

A prospective study in 41 infants (Kumar, 1997) Found that an initial course of indometacin therapy was successful in 90% of cases. The recurrence rate after the first course was 3%. The success rate of therapy increased to 95% following a second course of indometacin.

Keller RL, Clyman RI. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. *Pediatrics* 2003;112:583-7

Kumar RK, Yu VY. Prolonged low-dose indomethacin therapy for patent ductus arteriosus in very low birthweight infants. *J Paediatr Child Health* 1997;33:38-41

Evidence Level: IV

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