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 0.5% reopened. The mean cumulative dose of indometacin was 0.35 mg/kg.

A multicentre, randomised controlled trial in 105 infants (Jegatheesan, 2008) found that increasing indometacin concentrations above the levels achieved with a conventional dosing regimen had little effect on the rate of PDA closure and was associated with higher rates of retinopathy of prematurity and renal compromise.

A Cochrane review of 19 trials in 2872 infants (Fowlie, 2010) found the incidence of symptomatic PDA [RR 0.44, 95% CI 0.38 to 0.50] and PDA surgical ligation (RR 0.51, 95% CI 0.37,0.71) was significantly lower in infants treated with prophylactic indometacin.

Prophylactic indomethacin also significantly reduced the incidence of severe intraventricular haemorrhage (RR 0.66, 95% CI 0.53 to 0.82). Meta-analyses found no evidence of an effect on mortality (RR 0.96, 95% CI 0.81 to 1.12) or on a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months old (RR 1.02, 95% CI 0.90, 1.15).
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.


Evidence Level: IV

Does ibuprofen have advantages over indometacin?

A number of randomised trials (Su, 2008; Fakhraee, 2007; Lago, 2002; Supapannachart, 2002; Patel, 2000; van Overmeire, 2000; van Overmeire, 1997) have found ibuprofen to be as effective as indomethacin 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.

An updated Cochrane systematic review of 20 trials (Ohlsson, 2010) concluded that “Ibuprofen is as effective as indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency. Given the reduction in NEC noted in this update, ibuprofen currently appears to be the drug of choice.”

As neither medical nor surgical interventions have been shown to influence mortality rates in PDA, it has been suggested (Nemerofsky, 2008; Bose, 2007; 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.


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


Evidence Level: I

If a duct fails to close after the first course of indomethacin, are further courses indicated?
A study in 32 infants (Keller, 2003) showed that recurrent PDA rarely responds to further courses of indomethacin 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 indomethacin.

A prospective study in 41 infants (Kumar, 1997) Found that an initial course of indomethacin 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 indomethacin.

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


Evidence Level: IV

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