

## ORIGINAL ARTICLE

## Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis

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**Background:** Rates of long term morbidity remain unacceptably high in infants surviving after preterm birth. Prophylactic indomethacin has been shown to effectively reduce the rate of intraventricular haemorrhage in this group but there is the potential for unwanted side effects because of reduced organ perfusion.

**Objective:** To examine the effect of prophylactic indomethacin on mortality and short and long term morbidity of preterm infants.

**Data sources:** Medline (1966–2002), the Cochrane Controlled Trials Register and abstracts of the Society for Pediatric Research and the European Society for Pediatric Research were searched independently by both authors.

**Review methods:** Trials were included if they used a randomised design, enrolled preterm infants given intravenous indomethacin within 24 hours of birth, and reported any of the prespecified outcome measures. Each author extracted data and assessed trial quality independently, according to the methods of the Cochrane Collaboration. Data were combined in a meta-analysis where appropriate.

**Results:** Nineteen trials fulfilling the inclusion criteria were identified, of which four reported long term outcomes. Short term benefits of indomethacin were identified, including a reduction in the rate of severe intraventricular haemorrhage (relative risk (RR) 0.66 (95% confidence interval (CI) 0.53 to 0.82)) and the need for surgical ligation of a patent ductus arteriosus (RR 0.51 (95% CI 0.37 to 0.71)). No evidence of short term gastrointestinal or renal adverse effects was detected. There was no significant difference between indomethacin and control groups with respect to the important long term outcome of death or severe neurosensory impairment (RR 1.02 (95% CI 0.90 to 1.15)).

**Conclusions:** Prophylactic indomethacin has a number of short term benefits for the preterm infant but there is no evidence to suggest that it results in an improvement in the rate of survival free of disability.

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The improvement in rates of survival of very low birthweight infants is one of the more remarkable achievements in modern medicine. However, preterm birth is associated with increased risk of neurodevelopmental disability, specifically developmental delay, cerebral palsy, blindness, and deafness. The combined rates of disability range between 20% and 40% for very low birthweight infants born in the 1990s. The preterm infant is susceptible to a unique form of brain injury resulting from intraventricular haemorrhage (IVH). IVH, particularly when it involves the parenchyma of the brain, is strongly associated with poor neurodevelopmental outcome.

Indomethacin is a prostaglandin inhibitor which has long been used to treat patent ductus arteriosus (PDA) in preterm infants. More recently it has been used prophylactically in attempts to reduce the rate of IVH in high risk groups, with the aim of reducing mortality and long term morbidity.

Previous meta-analysis<sup>1,2</sup> has suggested that prophylactic indomethacin leads to an improvement in short term outcomes including reduced rates of IVH, but recent publication of new studies and follow up data from previous studies allow a better evaluation of the benefits and risks of this promising treatment.

We conducted a meta-analysis using the methods and software of the Cochrane Collaboration to determine whether prophylactic indomethacin improves the outcome of preterm infants.

## METHODS

## Search strategy

PubMed Medline (1966–2002) was searched using the terms indomethacin and infant and (prophylactic or prophylaxis or

prevention) and the Cochrane Controlled Trials Register using indomethacin and infant. Abstracts of the Society for Pediatric Research and the European Society for Paediatric Research were searched from 1996–2001, and full text articles sought using Medline searches of the authors' names. Previous reviews were cross referenced, and personal files searched for additional references. No language restrictions were applied.

## Inclusion criteria

Both authors assessed all published articles and abstracts identified as potentially relevant by the literature search for inclusion in the review. In order to be included, trials had to meet all four of the following criteria:

- Study design: randomised controlled trials
- Participants: preterm infants
- Intervention: intravenous indomethacin given within 24 hours of birth
- Outcome measures: included any of the following—death, IVH, PDA, or long term neurodevelopmental outcome

## Quality assessment and data abstraction

Both authors assessed each article according to the following criteria: blinding of randomisation, blinding of intervention, completeness of follow up, and blinding of outcome

**Abbreviations:** IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; RR, relative risk; CI, confidence interval

assessment. Both authors extracted the data from each trial independently, then compared results and resolved differences.

### Data analysis

Data measuring similar outcomes were combined in a meta-analysis where appropriate. For categorical outcomes, treatment effect was analysed using relative risk (RR), risk difference, and number needed to treat with their 95% confidence intervals (CI). A fixed effects model was used. Evaluation of heterogeneity of results was performed for all outcomes, and  $p < 0.05$  on  $\chi^2$  test was considered to represent significant heterogeneity.

## RESULTS

### Quality assessment

Nineteen randomised trials comprising 2872 infants fulfilled the inclusion criteria. Four of these reported long term outcomes (1862 infants). The exact method of randomisation was specified in 12 of the studies.<sup>3-14</sup> Methods included telephone randomisation, sealed envelopes, and coded drug vials. In the remaining seven trials it was not possible to determine how well the process of randomisation was blinded.<sup>15-21</sup> In three studies it was not possible to determine whether the caregivers and those assessing the outcomes of interest were blinded to the intervention group.<sup>17 19 20</sup> In the remainder there was adequate description of methods used to ensure blinding including description of the placebo.

Follow up rates for short term outcomes were adequate—that is, > 90%—for all included studies. Long term follow up rates were less complete, ranging from 75% to 100%.

### Trial characteristics

Table 1 shows clinical details of included studies. Some clinical practices changed over time—for example, surfactant was given either as prophylaxis or rescue therapy in seven trials.<sup>4 10-14 16</sup>

### Quantitative data synthesis

Table 2 shows the pooled results of the trials. There was no difference in mortality to latest follow up between the treatment and placebo groups (RR 0.96 (95% CI 0.81 to 1.12)). The reduction in cranial ultrasound abnormalities (all

IVH (RR 0.88 (95% CI 0.80 to 0.96)) and severe (grades 3 and 4) IVH (RR 0.66 (95% CI 0.53 to 0.82)) seen in the treatment group did not translate into improved long term outcomes. Rates of mortality and severe neurosensory impairment (blindness, deafness, cerebral palsy, or developmental quotient more than two standard deviations below the mean) were high in this group of infants and were not decreased by prophylactic indomethacin (RR 1.02 (95% CI 0.90 to 1.15)).

There were some short term advantages observed in infants given indomethacin. The rate of PDA (RR 0.44 (95% CI 0.38 to 0.50)) and particularly the rate of surgical ligation for this condition (RR 0.51 (95% CI 0.37 to 0.71)) were reduced in the treatment group. Twenty infants would need to be treated with prophylactic indomethacin to prevent one surgical ligation. There were no differences in other short term outcomes including necrotising enterocolitis and bronchopulmonary dysplasia. Although oliguria was more often observed in infants receiving indomethacin, there were no differences in proportions of babies developing high serum creatinine levels.

Heterogeneity of results was found only for the outcome “all IVH” ( $p = 0.011$ ). The remaining pooled outcomes had  $p$  values > 0.2 for heterogeneity, indicating that variability between studies may be explained by chance alone.

## DISCUSSION

There is now a substantial body of literature available to evaluate the role of prophylactic indomethacin in preterm infants. The quality of trials included in this systematic review is good but there is variation in enrolment criteria, indomethacin dosage regimens, and some of the outcome definitions.

This review confirms the usefulness of prophylactic indomethacin in the prevention of symptomatic PDA. Some clinicians would find the reduction in the need for surgical ligation of the ductus, combined with the lack of evidence for short or long term harm, justification for providing this treatment. Other factors influencing such a decision would be the background rate of ligations and the availability of cardiology and cardiac surgery services.

In the past, the presence of a PDA was thought to increase the risk of developing both pulmonary haemorrhage and bronchopulmonary dysplasia. Reduction in the rate of PDA

**Table 1** Clinical details of included studies

Study (year)	n	Participants	Dose*	Long term follow up
Bada (1989)	141	BW <1500 g	3 doses starting at 6 hours	No
Bandstra (1988)	199	BW <1300 g	3 doses starting at <12 hours	Between 6 and 24 months: Bayley MDI and PDI
Couser (1996)	93	BW 600–1250 g	6 doses starting <24 hours	No
Domenico (1994)	100	BW <1250 g	3 doses starting <12 hours	No
Gutierrez (1987)	59	GA <34 weeks and BW <1751 g	3 doses starting <24 hours	No
Hanigan (1988)	111	BW <1500 g	3 doses starting <12 hours	No
Krueger (1987)	32	BW 750–1500 g	Single dose at 24 hours	No
Mahony (1985)	110	BW 700–1300 g	3 doses starting at 12–18 hours	No
Ment (1985)	48	BW 600–1250 g	5 doses starting at 6 hours	No
Ment (1988)	36	BW 600–1250 g	3 doses starting at 6–12 hours	No
Ment (1994a)	61	BW 600–1250 g	3 doses starting at 6–12 hours	No
Ment (1994b)	431	BW 600–1250 g	3 doses starting at 6–12 hours	At 36 and 54 months: Stanford Binet Intelligence Scale Peabody Picture Vocabulary Test (R), CP, blindness, deafness
Morales-Suarez (1994)	80	GA 28–36 weeks	3 doses starting <12 hours	No
Puckett (1985)	32	BW <1400 g	3 doses starting at <24 hours	No
Rennie (1986)	50	BW <1750 g	3 doses starting <24 hours	No
Supannachart (1999)	30	BW <1250 g	3 doses starting <24 hours	No
Schmidt (2001)	1202	BW 500–999 g	3 doses starting <6 hours	At 18 months: Bayley MDI, blindness, deafness, CP
Vincer (1987)	30	BW <1500 g	3 doses starting at 12 hours	At 24 months: CP
Yaseen (1997)	27	BW <1750 g	3 doses starting at 12 hours	No

\*Doses were either 0.1 or 0.2 mg/kg and dosing interval 12 or 24 hours.

BW, Birth weight; GA, gestational age; MDI, mental developmental index; PDI, physical developmental index; CP, cerebral palsy.

**Table 2** Results of the trials

Outcome	No of studies	Indomethacin	Control	Relative risk	Risk difference	NNT
Death at latest follow up	18	231/1372	245/1397	0.96 (0.81 to 1.12)	-0.01 (-0.04 to 0.02)	
All IVH	14	422/1258	482/1274	0.88 (0.80 to 0.96)	-0.04 (-0.08 to -0.01)	25
Severe IVH	14	115/1285	177/1303	0.66 (0.53 to 0.82)	-0.05 (-0.07 to -0.02)	20
Symptomatic PDA	14	204/1093	471/1100	0.44 (0.38 to 0.50)	-0.24 (-0.28 to -0.21)	4
PDA ligation	8	49/891	97/900	0.51 (0.37 to 0.71)	-0.05 (-0.08 to -0.03)	20
Pulmonary haemorrhage	4	104/795	123/796	0.84 (0.66 to 1.06)	-0.02 (-0.06 to 0.01)	
BPD (in oxygen at 28 days)	9	188/500	183/522	1.08 (0.92 to 1.26)	0.03 (-0.03 to 0.08)	
Necrotising enterocolitis	12	84/1187	77/1214	1.09 (0.82 to 1.46)	0.01 (-0.01 to 0.03)	
Gastrointestinal perforation	1	36/601	32/601	1.12 (0.71 to 1.79)	0.01 (-0.02 to 0.03)	
Diminished urine output	8	131/1045	70/1070	1.90 (1.45 to 2.47)	0.06 (0.04 to 0.08)	16‡
Raised creatinine	4	10/298	10/320	1.09 (0.47 to 2.51)	0.00 (-0.03 to 0.03)	
Excessive bleeding	5	16/880	23/896	0.74 (0.40 to 1.38)	-0.01 (-0.02 to 0.01)	
Severe developmental delay*†	3	143/641	151/645	0.96 (0.79 to 1.17)	-0.01 (-0.05 to 0.04)	
Cerebral palsy*	4	78/678	77/694	1.04 (0.77 to 1.40)	0.00 (-0.03 to 0.04)	
Blindness*	2	10/635	8/639	1.26 (0.50 to 3.18)	0.00 (-0.01 to 0.02)	
Deafness*	2	11/626	11/633	1.02 (0.45 to 2.33)	0.00 (-0.01 to 0.01)	
Severe neurosensory impairment*	3	164/682	173/706	0.98 (0.81 to 1.18)	0.00 (-0.05 to 0.04)	
Death or severe neurosensory impairment*	3	304/743	299/748	1.02 (0.90 to 1.15)	0.01 (-0.04 to 0.06)	

\*In survivors examined.

†Either Bayley mental developmental index (MDI <68 or Wechsler preschool and primary scale of intelligence-revised (WPPSI-R) <70)

‡Number needed to harm.

NNT, Number needed to treat (calculated where significant result obtained); IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

without a significant change in rates of bronchopulmonary dysplasia or pulmonary haemorrhage challenges traditional assumptions about the pathophysiology of these conditions.

This review confirms the significant reduction in rates of severe intraventricular haemorrhage in infants given indomethacin. This result is not accompanied by any of the adverse outcomes that were possible given the vasoconstrictive nature of the drug—that is, important renal side effects, gastrointestinal perforation, and necrotising enterocolitis. However, the improvement in rates of IVH did not translate to improvement in rates of neurosensory impairment. One clear message of this systematic review is that traditional surrogate outcomes used in evaluating interventions in preterm infants may not be sufficient to guide changes in treatment. Put another way, when new interventions are considered in this population, particularly when they are being given prophylactically (and therefore to some infants who are not expected to benefit from them), long term outcomes should be assessed.

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