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

P W Fowle, P G Davis

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.

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
assessments. 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 χ² 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.³⁻¹⁴ 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.¹⁵⁻²¹ In three studies it was not possible to determine whether the caregivers and those assessing the outcomes of treatment and placebo groups (RR 0.96 (95% CI 0.81 to 1.12)). The reduction in cranial ultrasound abnormalities (all difference in mortality to latest follow up between the treatment and placebo groups (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>
<thead>
<tr>
<th>Study (year)</th>
<th>n Participants</th>
<th>Dose*</th>
<th>Long term follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bada (1989)</td>
<td>141 BW &lt;1500 g</td>
<td>3 doses starting at 6 hours</td>
<td>No</td>
</tr>
<tr>
<td>Bandara (1988)</td>
<td>199 BW &lt;1300 g</td>
<td>3 doses starting at 12 hours</td>
<td>Between 6 and 24 months: Bayley MDI and PDI</td>
</tr>
<tr>
<td>Cooser (1996)</td>
<td>93 BW 600–1250 g</td>
<td>6 doses starting &lt;24 hours</td>
<td>No</td>
</tr>
<tr>
<td>Domenico (1994)</td>
<td>100 BW &lt;1250 g</td>
<td>3 doses starting at 12 hours</td>
<td>No</td>
</tr>
<tr>
<td>Gutierrez (1987)</td>
<td>59 GA &lt;34 weeks and BW &lt;1751 g</td>
<td>3 doses starting &lt;24 hours</td>
<td>No</td>
</tr>
<tr>
<td>Hanigan (1988)</td>
<td>111 BW &lt;1500 g</td>
<td>3 doses starting &lt;12 hours</td>
<td>No</td>
</tr>
<tr>
<td>Krueger (1987)</td>
<td>32 BW 750–1300 g</td>
<td>Single dose at 24 hours</td>
<td>No</td>
</tr>
<tr>
<td>Mahony (1985)</td>
<td>48 BW 700–1250 g</td>
<td>3 doses starting at 12–18 hours</td>
<td>No</td>
</tr>
<tr>
<td>Ment (1985)</td>
<td>36 BW 600–1250 g</td>
<td>5 doses starting at 6 hours</td>
<td>No</td>
</tr>
<tr>
<td>Ment (1994a)</td>
<td>61 BW 600–1250 g</td>
<td>3 doses starting at 6–12 hours</td>
<td>No</td>
</tr>
<tr>
<td>Ment (1994b)</td>
<td>431 BW 600–1250 g</td>
<td>3 doses starting at 6–12 hours</td>
<td>At 36 and 54 months: Stanford Binet Intelligence Scale Peabody Picture Vocabulary Test (R), CP, blindness, deafness</td>
</tr>
<tr>
<td>Morales-Suarez (1994)</td>
<td>80 GA 28–36 weeks</td>
<td>3 doses starting &lt;12 hours</td>
<td>No</td>
</tr>
<tr>
<td>Puckett (1985)</td>
<td>32 BW &lt;1400 g</td>
<td>3 doses starting &lt;24 hours</td>
<td>No</td>
</tr>
<tr>
<td>Reenie (1986)</td>
<td>50 BW &lt;1750 g</td>
<td>3 doses starting &lt;24 hours</td>
<td>No</td>
</tr>
<tr>
<td>Supapanachart (1999)</td>
<td>30 BW &lt;1250 g</td>
<td>3 doses starting &lt;24 hours</td>
<td>No</td>
</tr>
<tr>
<td>Schmidt (2001)</td>
<td>1202 BW 500–999 g</td>
<td>3 doses starting &lt;6 hours</td>
<td>At 18 months: Bayley MDI, blindness, deafness, CP</td>
</tr>
<tr>
<td>Vincer (1987)</td>
<td>30 BW &lt;1500 g</td>
<td>3 doses starting at 12 hours</td>
<td>At 24 months: CP</td>
</tr>
<tr>
<td>Yaseen (1997)</td>
<td>27 BW &lt;1750 g</td>
<td>3 doses starting at 12 hours</td>
<td>No</td>
</tr>
</tbody>
</table>

*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.
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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**REFERENCES**


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