

Indomethacin and long-term outcome for tiny babies

Trial: Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; 344: 1966-1972.

Question

Does indomethacin given prophylactically after birth improve long-term outcome for babies with extremely low birth weight?

Trial details

Design: Randomised, double-blind, controlled trial.

Setting: 32 intensive care nurseries in Australia, Canada, Hong Kong, New Zealand and the United States.

Participants: 1202 babies of 500–999 g birthweight; groups were similar in demographic and perinatal characteristics. Exclusions included major anomalies and inability to give indomethacin before 6 hours of life.

Interventions: Indomethacin (0.1 mg/kg, intravenously) once daily for 3 days, or equivalent volume of saline placebo.

Main outcome measures: Composite outcome of mortality, cerebral palsy, developmental delay, deafness or blindness at 18 months of age, corrected for prematurity.

Main results: There was no substantial difference in the primary composite outcome between the indomethacin (47% [261/574]) and placebo (46% [261/569]) groups (odds ratio [OR], 1.1; 95% CI, 0.8–1.4; $P=0.61$). However, the indomethacin group had a lower rate of patent ductus arteriosus (PDA), including cases requiring medical or surgical treatment, and severe (grade 3 or 4) cerebroventricular haemorrhage (CVH).

Conclusion: In infants with extremely low birthweight, prophylaxis with indomethacin does not improve the rate of survival without neurosensory impairment at 18 months, despite reducing the frequency of PDA and severe CVH.

Commentary

Rationale for the trial

Persistent patent ductus arteriosus (PDA) is a problem after birth for very tiny or preterm infants, many of whom require either medical or surgical intervention to close the ductus in the newborn period. Indomethacin is often successful in closing the ductus when used therapeutically, but is associated with many short-term side effects. Before this trial, prophylactic use of indomethacin was known to reduce the frequency of symptomatic PDA and severe cerebroventricular haemorrhage (CVH) in these babies.¹ Reducing severe CVH might be expected to improve long-term neurological outcome. However, the mechanism for reducing severe CVH may be diminishing cerebral blood flow, which in turn may cause long-term neurological problems. Therefore, whether prophylaxis with indomethacin confers any long-term benefits that outweigh the risks of drug-induced reductions in cerebral blood flow, as well as reduced blood flow to other organs, is not certain.

Trial methods

Infants were stratified by birthweight (< 750 g or \geq 750 g) and individual study centre. This stratification was sensible, as the rate of the major adverse outcomes in the study was much higher in those of < 750 g birthweight (62% [298/481]) than in those of birthweight \geq 750 g (35% [234/662]), and was bound to differ between individual centres (although individual centre data were not reported).

Most infants (86%) received their allocated treatment within 6 hours of birth, and most (81%) received all three doses; there were no differences in drug administration (compliance) between the treatment groups. Other aspects of care followed an individual unit's protocol.

Blinding was achieved by having a placebo that looked identical to the indomethacin. Although unblinding was theoretically possible through observing urine output, only 7% in the indomethacin group and 4% in the placebo group had treatment withdrawn because of oliguria.

Significantly more babies in the placebo group (46%) subsequently received open-label indomethacin to treat a PDA than did babies in the treated group (17%). The follow-up rates to 18 months corrected age were very high (95%) in each group, which is important methodologically, as babies who are difficult to follow-up have more adverse outcomes than those who are followed up more easily.² All analyses were by intention to treat.

New information

In infants of extremely low birthweight, prophylaxis with indomethacin did not improve the rate of survival without neurosensory impairment at 18 months, despite the fact that it reduces the frequency of PDA and severe CVH. Before this study, it would have been assumed that because prophylactic indomethacin reduces severe CVH, it should improve long-term outcome. This study highlights the problem of relying on changes in surrogate (or intermediate) endpoints, or in risk factors, to determine the effectiveness of therapies. For any therapy to be introduced into clinical practice, the endpoints in trials must be clinically meaningful.



Implications for clinical practice

The types of babies included in this study are typically found in intensive care nurseries in the developed world, and hence the results of the study are widely applicable to infants of birthweight < 1000 g, including those cared for in Australian intensive care nurseries.

The study has been incorporated into an update of the Cochrane review of prophylactic indomethacin.³ There are now 19 trials with a total of 2872 babies enrolled. The study by Schmidt et al⁴ is the largest in the review, with 42% of the

total babies enrolled. Its results dominate the review, especially those for long-term neurosensory outcomes, where the study contributes more than two-thirds of all babies in the review. The Cochrane review confirms that prophylactic indomethacin confers no important long-term benefit (or harm) on survival free of neurosensory impairment, despite significantly reducing the rate of severe CVH (relative risk [RR], 0.66; 95% CI, 0.53–0.82). However, the duration of follow-up in most studies is short, and important long-term neurological effects may not be manifest until school-age or later. Hence, it is still not certain that indomethacin imparts no long-term harm.

Prophylactic indomethacin reduces the incidence of symptomatic PDA (RR, 0.44; 95% CI, 0.38–0.50), and the need for ductal ligation (RR, 0.51; 95% CI, 0.37–0.71). The absolute reduction in the rate of surgical ligation is 5%, which means that prophylaxis would need to be given to 20 babies to prevent one surgical ligation. For neonatal units where surgical ligation is not an option and where the need for surgical ligation is relatively frequent, giving 20 babies indomethacin to prevent one operation might be a reasonable option. However, this should be undertaken in the full knowledge that indomethacin prophylaxis does not impart any other important short-term benefits, such as a reduction in oxygen requirements, and that there remains the unknown issue of potential longer-term harm. There is no evidence of substantial differences in rates of necrotising

enterocolitis, gut perforation, excessive clinical bleeding, or sepsis.

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Competing interests

None identified.

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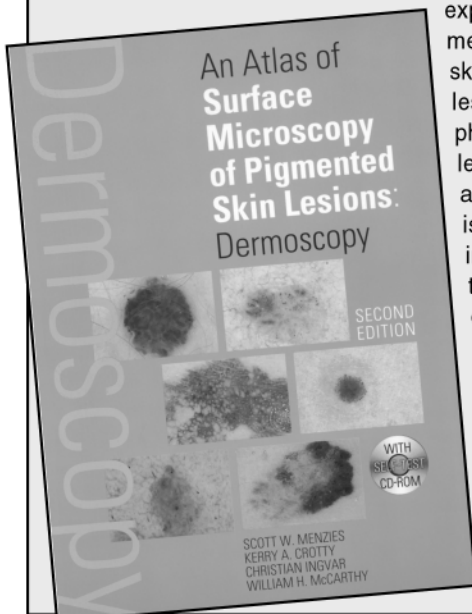
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