

**Systematic review and network meta-analysis of
intravenous ibuprofen vs. intravenous indomethacin vs.
placebo in the management of clinically and/or
echocardiographically important patent ductus arteriosus
in preterm infants at greater than 24 hours of life.**

Lisa Jane Jones

BNurs, Grad Cert Paed Crit Care, Grad Dip Clin Epid

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Statement of Originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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I hereby certify that the work embodied in this thesis contains a published paper of which I am a joint author. I have included as part of the thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publication.

Other acknowledgements

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Dedication

To my husband Stephen and son Matthew for their support and endless patience during the writing of this thesis.

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Objectives

To evaluate the effects of indomethacin or ibuprofen compared with placebo on closure, morbidity and mortality in preterm infants <37 weeks' gestation with echocardiographically and/or clinically important patent ductus arteriosus (PDA) at >24 h of life.

Data sources

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, Cochrane Library, clinicaltrials.gov, controlled-trials.com, American Pediatric and European Paediatric Research Societies and Effective Care of the Newborn Infant.

Review methods

Systematic review with network meta-analysis of randomised studies comparing intravenous indomethacin, ibuprofen or placebo for PDA in preterm infants at >24 h of life.

Results

Ten trials compared intravenous indomethacin versus intravenous ibuprofen, nine compared intravenous indomethacin versus placebo and one intravenous ibuprofen versus placebo. Both intravenous indomethacin [pooled RR 2.39 (95% CI 2.05 to 2.78)] and intravenous ibuprofen [RR 2.40 (95% CI 2.03 to 2.84)] closed a PDA more effectively than placebo. Intravenous ibuprofen was associated with approximately 30% greater risk of chronic lung disease than intravenous indomethacin [RR 1.28 (95% CI 1.03 to 1.60)] or placebo [RR 1.29 (95% CI 0.99 to 1.70)]. Differences in risk or benefit were not significant between any combination of intravenous indomethacin, intravenous ibuprofen or placebo groups for intraventricular haemorrhage, necrotising enterocolitis and death. Reporting on neurological outcomes was insufficient for pooling. Sensitivity analyses indicate a gestational and post-natal age dependent effect on PDA closure and the risk of CLD. The majority of trials comparing intravenous indomethacin with placebo administered non-randomised rescue treatment to > 20% of the placebo group. Sample size estimations for intravenous indomethacin suggest large numbers are needed to provide adequate power to detect a difference in the risk of outcomes other than PDA closure. Smaller numbers are required for intravenous ibuprofen with a minimum of 131 per group for the outcome of CLD.

Conclusions

Intravenous indomethacin or ibuprofen administered to preterm infants for PDA at >24 h of life promoted ductal closure, but other short-term benefits were not seen. Data from randomized trials concerning the effect of treatment with indomethacin or ibuprofen for PDA closure on IVH, CLD, NEC, survival and longer-term neurodevelopmental outcomes is presently insufficient to guide current practice. There is a need for well-designed good quality modern randomized controlled trials comparing intravenous ibuprofen and intravenous indomethacin administered for echo-targeted PDA and PDA detected by clinical signs in preterm infants at greater than 24 hours of life. Such trials should be multi-centre and incorporate improved methods of handling the administration of rescue treatment in the placebo group in order to improve the chance of detecting a benefit or risk. Data on longer-term respiratory and neurological outcomes are also urgently needed. Suggested trial methods include comparing early targeted at <24 hours with placebo randomised to either echo-targeted or symptomatic PDA as rescue at > 24 hours of life. Comparisons can then be made between the risk of outcomes in preterm infants with PDA receiving rescue treatment based on echo alone compared to those randomised to symptomatic rescue treatment but remaining untreated.