Meta-analyses of the effectiveness of intravenous immune globulin for prevention and treatment of neonatal sepsis

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Authors' objectives
To determine the effectiveness of intravenous immune globulin (IVIG) in the prevention and treatment of neonatal sepsis.

Searching
MEDLINE (no dates given) was searched for English language papers plus identification of studies by "personal knowledge".

Study selection
Study designs of evaluations included in the review
Peer-reviewed, prospective randomised trials including a concurrent control group receiving either placebo or no IVIG treatment were eligible for inclusion. IVIG administration had to be given shortly after birth for prophylaxis, or on clinical diagnosis of sepsis for treatment.

Specific interventions included in the review
IVIG given either prophylactically to prevent neonatal sepsis or therapeutically to treat documented neonatal sepsis.

Participants included in the review
Newborns who were given IVIG prophylactically or as a treatment for sepsis. All studies included preterm low birth weight infants. The median upper age limits ranged between 23-34 weeks and median upper weight limits around 1500g. Excluded were infants with severe congenital malformation, intrauterine infection, hemolytic disease, metabolic disease and infants who died within 24 to 72 hours of birth or who were suspected or proven to be infected at the time prophylactic IVIG was given.

Outcomes assessed in the review
Prevention of neonatal sepsis was analysed on the basis of the outcome of a positive blood culture associated with clinical signs of systemic infection. Treatment of early onset neonatal sepsis was analysed on the basis of case fatality associated with sepsis.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The studies were assessed according to the quality of study design and the rigour of scientific investigation. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The data were extracted into two by two contingency tables to determine the relationship between IVIG administration and outcome. The number of authors involved is not stated.

Methods of synthesis
How were the studies combined?
Odds ratios and 95% confidence intervals (CIs) were calculated and, where appropriate, summary measures across studies were estimated as a Mantel-Haenszel common odds ratio.

How were differences between studies investigated?
Heterogeneity was investigated using the Breslow and Day homogeneity test chi-squared statistic (see Publications of Related Interest no.1).

Results of the review
Twelve prospective randomised studies for the effectiveness of IVIG prophylaxis were included. There were 7 placebo-controlled, double-blind trials (total neonates = 4,933) and 3 prospective randomised studies of the effectiveness of IVIG treatment, of which 2 were placebo-controlled, double-blind trials (total neonates = 110).

The 12 studies addressing the prevention of neonatal sepsis were too heterogeneous to justify calculation of a common odds ratio. Instead a stratified analysis was performed and IVIG use was reported to be significantly associated with the rate of sepsis (p=0.019).

Across the three studies that addressed treatment of sepsis a statistically significant relationship was found between IVIG administration and a decreased death rate (OR 0.173, 95% CI: 0.031, 0.735 p<0.007).

Authors' conclusions
The addition of IVIG to standard therapies is of minimal but demonstrable benefit in preventing sepsis when administered prophylactically to premature low birth weight newborns and of unequivocal benefit in preventing death when administered therapeutically for early-onset neonatal sepsis.

CRD commentary
This review evaluates the effectiveness of IVIG in both the prevention and treatment of neonatal sepsis. It is unclear, however, how many relevant studies may have been missed as a result of the limited search. Only one electronic database was searched and neither the years or the search terms were given. As only peer reviewed publications were eligible for inclusion there is a risk of publication bias, arising from the exclusion of grey literature. Also, excluded were non-English language articles. Although the authors state that each study was scrutinised for quality of design and rigour of scientific investigation it is unclear which individual items of methodological quality were actually assessed. Also, no details are provided of how many reviewers were involved in decisions about which studies to include, quality assessment or data extraction. Study details were presented in tables and the methods of analysis were well documented. However, due to the limitations described above the authors conclusions should be treated with some caution.

Implications of the review for practice and research
The authors state that the role of IVIG as prophylaxis for low birth weight premature infants will likely remain controversial. Conversely, the additive benefit of IVIG given to neonates with sepsis in decreasing acute mortality is clearly unequivocal and substantial. The authors address the need for cost-effectiveness analyses to justify the routine prophylactic administration of IVIG given the minimal benefit demonstrated to date.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.