Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn

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CRD summary
This review compared high-dose intravenous immunoglobulin (HDIVIG) plus phototherapy with phototherapy alone. The authors concluded that addition of HDIVIG to phototherapy is an effective treatment for haemolytic disease of the newborn. The review was generally well conducted and the evidence presented supports the conclusions, although it should be noted that the number of included studies and patients was small.

Authors’ objectives
To compare the effectiveness of high-dose intravenous immunoglobulin (HDIVIG) plus phototherapy with phototherapy alone in neonates with proven haemolytic disease due to Rh and/or ABO incompatibility.

Searching
MEDLINE (from 1986 to 2000), EMBASE (from 1984 to 2000) and the Cochrane Controlled Trials Register were searched; the search terms were stated. In addition, handsearches of the Journal of Pediatrics (1985 to 2000), Pediatrics (1990 to 2000) and Archives of Disease in Childhood (1990 to 2000) were conducted, with abstracts of presentations at scientific meetings also being eligible. The reference lists in identified reports were checked and experts were contacted for additional unpublished and published studies. Studies in any language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-randomised trials were eligible for inclusion. All of the included studies were RCTs. Two identified studies were excluded: one was a report of an RCT already included; the other compared two doses of HDIVIG, but there were differences between the treatment groups at baseline and there was no intention-to-treat analysis.

Specific interventions included in the review
Studies that compared HDIVIG plus phototherapy with phototherapy alone were eligible for inclusion. Studies of any dose or duration of HDIVIG were included. The included studies were conducted in Turkey, Germany and Argentina. There were variations in both the type and dose of HDIVIG given (single dose of 0.5 to 1 g/kg, or 0.8 g/kg per day for 3 days). In all studies, HDIVIG treatment was reported to have been started as soon as possible after diagnosis and randomisation.

Participants included in the review
Studies of infants with proven Rh and/or ABO incompatibility were eligible for inclusion. Studies of neonates were included regardless of their birth weight, gestational age, severity of haemolytic disease, or whether the infants or their mothers had received antenatal treatment. The studies varied in their inclusion criteria for the infants: one study excluded infants with prenatal treatment, while another definitely included these infants.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported at least one of the following outcomes: the number of exchange transfusions, the length of phototherapy, or the length of hospital stay. The review also assessed the proportion of infants requiring multiple transfusions and adverse effects. The studies used different criteria for initiating exchange transfusion and phototherapy.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
Validity was assessed using the Jadad scale, which considers randomisation, blinding and withdrawals (see Other Publications of Related Interest). The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The following information was tabulated: ABO/Rh status of the infants; the gestational age and birth weight of the infants in each treatment group; sample size; dose of HDIVIG; criteria used for exchange transfusion; and outcomes reported. Where necessary, authors were contacted for missing data.

Methods of synthesis
How were the studies combined?
The pooled relative risk (RR) and risk difference were calculated, along with 95% confidence intervals (CIs), for dichotomous data using a fixed-effect model. The pooled weighted mean differences (WMD) and 95% CIs were estimated for continuous data. The number-needed-to-treat (NNT) and 95% CI were estimated for significant findings.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the chi-squared statistic and forest plots were presented. The pooled RR, risk difference and NNT were calculated separately for the number of infants with Rh disease requiring exchange transfusions.

Results of the review
Four RCTs (226 infants) were included.

The Jadad scores for study quality ranged from 1 to 3 out of a possible 5 points. There were several methodological flaws: failing to report intention-to-treat analysis; a lack of reporting when phototherapy treatment was started; and unclear criteria for late transfusion.

When compared with phototherapy alone, HDIVIG plus phototherapy significantly reduced the need for exchange transfusion (3 RCTs, 189 infants); the RR was 0.28 (95% CI: 0.17, 0.47). No significant heterogeneity was detected (P=0.58).

For infants with Rh disease (2 RCTs, 73 infants), HDIVIG treatment significantly reduced the need for exchange transfusion to a greater extent (RR 0.21, 95% CI: 0.10, 0.45). No significant heterogeneity was detected (P=0.77).

HDIVIG treatment plus phototherapy significantly reduced multiple exchange transfusions compared with phototherapy alone (3 RCTs, 198 infants); the RR was 0.22 (95% CI: 0.08, 0.61). No significant heterogeneity was detected (P=0.38).

The addition of HDIVIG treatment to phototherapy significantly reduced the length of hospital stay (2 RCTs, 153 infants); the WMD was -1.06 (95% CI: -1.65, -0.46). Significant heterogeneity was detected (P=0.042). One RCT found that both treatment groups had a longer stay than the other RCT.

The addition of HDIVIG treatment to phototherapy significantly reduced the duration of phototherapy treatment (2 RCTs, 153 infants); the WMD was 0.87 (95% CI: -1.37, -0.37). No significant heterogeneity was detected (P=0.36).

The increase in the number of infants receiving red cell transfusions for late anaemia just reached statistical significance, but the CIs were wide (3 RCTs, 189 infants); the RR was 8.0 (95% CI: 1.03, 62.2). No significant heterogeneity was detected (P=0.7).

The risk difference and NNT were also reported in the review.
In terms of adverse effects, in 3 studies infants were monitored for possible febrile, allergic, haemolytic and volume overload effects of HDIVIG. None of the 3 studies reported any such events. Two studies reported problems in infants in control groups, but no causal link was established; one infant had inspissated bile syndrome; one infant had bacterial sepsis; two infants had hypoglycaemia and hypocalcaemia after exchange transfusions.

Authors' conclusions
The addition of HDIVIG to phototherapy is an effective treatment for infants with haemolytic disease of the newborn.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched, the search terms were stated, no language limitations were applied, and attempts were made to locate unpublished studies. The methods used to select the studies, assess validity and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged. Validity was assessed using validated criteria and some methodological limitations in the included studies were discussed in the text.

Relevant information on the included studies was tabulated. The data were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. Where significant heterogeneity was found, the authors discussed one potential reason for this. The results were clearly presented. The evidence presented appears to support the authors' conclusions, although it must be acknowledged that the evidence came from a small number of studies and patients, and there was some evidence that HDIVIG treatment may increase the need for late transfusion.

Implications of the review for practice and research
Practice: The authors stated that it may be unethical not to use HDIVIG while further research is undertaken.

Research: The authors stated that research is required to determine the optimum treatment dose and frequency of HDIVIG treatment.

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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.