Chapter 6

Cochrane systematic review: Immunoglobulin for alloimmune disease in neonates

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Abstract

Background

Exchange transfusion (ET) and phototherapy have traditionally been used to treat jaundice and avoid the associated neurological complications. Because of the risks and burdens of ET, intravenous immunoglobulin (IVIg) has been suggested as an alternative therapy for alloimmune hemolytic disease of the newborn (HDN) to reduce the need for ET.

Objectives

To assess whether, in newborns with alloimmune HDN, IVIg is effective in reducing the need for ET.

Search methods

Electronic searches were made of PubMed, Embase (OVID version), COCHRANE Library (including CENTRAL), Web of Science, CINAHL (EbscoHost-version), Academic Search Premier and the trial registers clinicaltrials.gov and controlled-trials.com. Reference lists of included and excluded trials and relevant reviews were searched for further relevant studies.

Selection criteria

All randomized and quasi-randomized controlled trials of the use of IVIg in the treatment of alloimmune HDN were considered. Trials must have used predefined criteria for both IVIg and ET therapy to be included.

Data collection and analysis

The standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. Studies were assessed for inclusion and quality and data were extracted by two reviewers working independently. Any differences of opinion were discussed and a consensus reached. Investigators were contacted for additional or missing information. For categorical outcomes, relative risk (RR) and number needed to treat (NNT) were calculated. For continuous variables, mean difference (MD) was calculated.

Results

Fourteen studies fulfilled inclusion criteria and included a total of 942 infants. Term and preterm infants with Rh and/or ABO incompatibility were included. The use of ET decreased significantly in the immunoglobulin treated group (RR 0.40, 95% CI 0.27 to 0.59; NNT 5.4).

Mean number of ETs per infant was also significantly lower in the immunoglobulin treated group (MD -0.31, 95% CI -0.45 to -0.17). However, subgroup analysis of the only two high quality studies showed no difference in the need for or number of ETs. Two studies assessed long-term outcomes and found no cases of kernicterus, deafness or cerebral palsy.

Authors' conclusions

Although overall results show a significant reduction in the need for ET in infants treated with IVIg, the applicability of the results is limited. The only two high quality studies show no benefit of IVIg in reducing the need for and number of ET. Further well designed studies are needed before solid advice can be given about the use of IVIg for the treatment of alloimmune HDN.

Background

Description of the condition

The use of anti-D prophylaxis in Rh D negative women has led to a marked decline in Rh hemolytic disease of the newborn (HDN). However, anti-D immunoglobulin is in short supply world-wide. Sensitization can occur despite immunoprophylaxis, particularly if it is given too late or in insufficient dose. Fetal therapy has led to a reduction in severity of disease in Rh sensitized fetuses, but it does not comprehensively prevent need for neonatal treatment. A proportion of significant HDN is caused by antibodies to antigens other than Rh D and is therefore not preventable with anti-D immunoglobulin. Primary modes of postnatal therapy include phototherapy and exchange transfusion (ET) to reduce risk of mortality and kernicterus. Top-up transfusions are used to treat early and late anemia. In contemporary perinatal centers, 15-40% of neonates admitted for Rh or ABO HDN require at least one ET.[1,2]

The safety of ET has been reported for over 50 years. Published mortality rates vary from 0.53-4.7% per infant.[3-9] ET-related death is more common in sick or premature infants than in healthy term infants.[1,4,6,7] Rates of morbidity and ET-related adverse events as high as 74% have been reported. Risks related to ET include adverse cardio-respiratory events, catheter-related complications, those related to the use of blood products, metabolic derangements and other serious complications such as pulmonary hemorrhage, necrotizing enterocolitis, and bowel perforation.[1,3,6,7,9-12] Because improved perinatal care has reduced the need for ET, the complication rate could increase as clinicians become less experienced with the procedure.[1] However, Steiner et al. reported that over a 21 year period, despite a sharp decline in the number of ETs performed, no increase in morbidity and mortality was observed.[1]

Description of the intervention

Intravenous immunoglobulin (IVIg) is an alternative therapy that may be effective in treating alloimmune HDN. In 1987 the first report of successful treatment of late anemia due to Rh E incompatibility with IVIg was published.[13] Subsequent case reports and case series reported success of IVIg treatment in neonates with both Rh or ABO incompatibility.[14-16] However, Hammerman et al. found a reduced or no response to IVIg treatment in infants with ABO incompatibility who had early and severe hemolysis.[17] In the last two decades several quasi-randomized or randomized controlled trials on the use of IVIg to reduce ET have been published. Timing of administration of IVIg varied from a few hours to several days after birth, single doses varied from 0.5 g/kg to 1 g/kg and total doses from 0.5 g/kg to 2.25 g/kg.

The potential benefits of IVIg over ET include that the treatment is less complicated and less labor intensive. In addition, IVIg could allow safe treatment of some infants in less sophisticated neonatal units, or avoid delaying treatment whilst transferring infants for ET. Comprehensive assessment of IVIg in premature infants, particularly in the treatment of sepsis, has shown that it is safe and well tolerated.[18] It is a well-established therapy for alloimmune thrombocytopenia due to maternal and fetal human platelet antigen (HPA) incompatibility. The risk of transmission of viral infection is extremely low.[19] Hemolysis and acute renal failure have been reported as uncommon complications of IVIg treatment.[20] One study showed an increased incidence of sepsis in premature infants receiving prophylactic IVIg.[21] A recent case-control study showed a higher incidence of necrotizing enterocolitis in near-term infants with Rh HDN treated with IVIg.[22] Other rare serious side effects of IVIg have been described in pediatric and adult cohorts, but not in newborns.[23]

How the intervention might work

IVIg might reduce the rate of hemolysis in alloimmune HDN by non-specific blockade of Fc-receptors. Red blood cells are probably destroyed by an antibody-dependent cytotoxic mechanism mediated by Fc-receptor bearing cells of the neonatal reticuloendothelial system.[24] Ergaz et al. demonstrated a decline in carboxyhemoglobin levels in four of five infants treated with IVIg for alloimmune HDN.[25] Hammerman et al. demonstrated a significant reduction in carboxyhemoglobin levels in 19 of 26 Coombs positive infants treated with IVIg.[26] Carboxyhemoglobin levels are a sensitive index of hemolysis and hence these studies suggest that immunoglobulin could decrease hemolysis.

Why it is important to do this review

This is an update of a Cochrane review first published in 2002. Although results of the previous review showed a significant reduction in the need for ET in infants treated with IVIg, the applicability of the results was limited because none of three included studies was of high quality. Nevertheless, American Academy of Pediatrics (AAP) guidelines recommend the administration of 0.5-1 g/kg IVIg in alloimmune HDN if total serum bilirubin (TSB) is rising despite intensive phototherapy or if TSB level is within 34-51 µmol/L (2-3 mg/dL) of exchange level.[27] As a result of these guidelines, despite the equivocal conclusions of the previous Cochrane review, the use of IVIg in alloimmune HDN has become widespread in many countries. However supplies of IVIg are limited and it does present some hazards. Therefore, use of IVIg should be restricted to treatment of conditions for which it is of proven benefit.

Objectives

To assess the effect of IVIg in newborn infants with alloimmune HDN on the need for and number of ETs. The review also assesses complications of therapy, short-term outcomes such as bilirubin levels, duration of phototherapy and hospitalization, top-up transfusion requirements, and long-term outcomes such as hearing loss, kernicterus and cerebral palsy.

Methods

Criteria for considering studies for this review

Types of studies

All randomized and quasi-randomized controlled trials of IVIg in the treatment of alloimmune HDN.

Types of participants

Neonates with alloimmune HDN due to either Rh or ABO blood group antibodies with or without any other blood group antibodies.

Types of interventions

IVIg given for treatment of alloimmune HDN, versus control (placebo or "standard care"). Early and late IVIg administration have been defined (for this review) as IVIg started within or after the first 12 hours of life, respectively. Studies should include predefined criteria for both IVIg and ET therapy.

Types of outcome measures

Primary outcomes

Efficacy:

- Use of ET (proportion of infants receiving one or more ETs)
- ETs performed per infant

Secondary outcomes

Efficacy:

- Use of top-up transfusion(s) in first week of life (% of infants)
- Number of top-up transfusions performed in first week of life per infant
- Use of top-up transfusion(s) after first week of life (% of infants)
- Number of top-up transfusions performed after first week of life per infant
- Maximum total serum bilirubin (TSB) (µmol/L (mg/dL))

- Duration of phototherapy (days)
- Duration of hospitalization (days)
- Incidence of sensorineural hearing loss (any severity)
- Incidence of kernicterus
- Incidence of cerebral palsy

Safety:

- Neonatal mortality
- Incidence of adverse reactions possibly related to the use of IVIg or ET

Search methods for identification of studies

Electronic searches

We performed a search in PubMed, Embase (OVID version), COCHRANE Library (including CENTRAL), Web of Science, CINAHL (EbscoHost-version), and Academic Search Premier. The subject query was applied in all databases taking into account the terminological differences between these databases. The query consisted of the combination of four subjects: immunoglobulins, alloimmune hemolytic jaundice, newborn infants, and randomized controlled trials. Various synonyms and related terms for all subjects were used. Two search strategies were used: the first strategy was limited to randomized trials and systematic reviews, the second strategy included only the subjects immunoglobulins and alloimmune hemolytic disease (and synonyms and related terms for those subjects). The search was performed on the 22nd of March 2012. The bibliographic databases yielded 1251 references in total of which titles and abstracts were screened. In addition to database searches, searches were made of the trial registers clinicaltrials.gov and controlled-trials.com. No language restrictions were applied.

Searching other resources

We searched the reference lists of all included and excluded trials and relevant reviews for further relevant studies.

Data collection and analysis

The standard method of the Cochrane Collaboration and its Neonatal Review Group was used.

Selection of studies

Two reviewers independently screened all 1251 references for possible inclusion using predefined criteria for inclusion (see below). If a report appeared to meet inclusion criteria

for the review, or if it was not clear based on title and abstract, a full text version of the article was obtained. Any disagreements were resolved through discussion.
The inclusion criteria for this review were:

- Randomized and quasi-randomized controlled trials
- Study compared IVIg with any definition of "standard care" plus placebo, or with any definition of "standard care" without placebo
- Study included patients with alloimmune HDN due to either ABO or Rh blood group antibodies with or without any other blood group antibodies
- Study measured ETs (primary outcome) for each study arm and/or at least one of the secondary outcomes for each study arm
- Study used predefined criteria for both IVIg and ET therapy

Data extraction and management
Two review authors independently extracted data using a data collection form that was pilot tested before use. Any disagreements were resolved through discussion and if necessary with the help of a third reviewer blinded to trial author, institution and journal of publication. One review author contacted authors of studies that did not report all required data or information. Data were entered into Review Manager 5.1 by one review author and checked by at least one review author.

Assessment of risk of bias in included studies
Two review authors independently assessed the risk of bias in included studies using the 'Risk of bias' tool as described in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (Higgins 2011).[28] The following items for risk of bias were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each item was rated as 'Low risk of bias', 'Unclear risk of bias' or 'High risk of bias'. Any differences of opinion were discussed with a third blinded reviewer and a consensus reached. For selective reporting the following criteria were used to rate a study as 'Low risk of bias':

- For studies enrolling neonates with Rh or both Rh and ABO HDN: reporting (in paper or subsequent correspondence) at least one outcome related to each of ET, bilirubin and top-up transfusion, plus adverse effects and hospitalization.
- For studies enrolling only neonates with ABO HDN: reporting (in paper or subsequent correspondence) at least one outcome related to each of ET and bilirubin, plus adverse effects and hospitalization. Top-up transfusion was not considered to be a preferred

outcome measure because anemia requiring treatment is an unusual consequence of ABO alloimmune hemolysis.

- Study protocols or methods section of papers should not describe an intention to report outcomes that were not subsequently reported in the paper.

Measures of treatment effect

For categorical outcomes, such as the incidence of ET, the relative risk (RR) was calculated. For continuous variables, such as the maximum bilirubin level, the mean difference (MD) was calculated. The number needed to treat (NNT) to avoid ET was also calculated.

Dealing with missing data

Investigators were contacted for missing information about study design and/or results.

Assessment of heterogeneity

Clinical heterogeneity was assessed by determining whether clinical characteristics of patients, interventions, outcome measures and timing of outcome measurements were similar for included studies. Statistical heterogeneity was assessed using Chi^2 and I^2 tests. An I^2 test of ≥50% was considered as substantial or considerable heterogeneity according to the Cochrane Handbook.[28]

Assessment of reporting biases

Funnel plots were used to assess publication bias for those outcomes with ≥10 trials. No substantial asymmetry was encountered in the funnel plots.

When selective reporting bias was suspected based on the criteria described under 'Assessment of risk of bias in included studies', investigators were contacted to request the missing outcome data.

If the data remained unavailable and the absence was thought to introduce serious bias, the impact of including such studies was explored in the overall assessment of results by a sensitivity analysis.

Data synthesis

Review Manager 5.1 was used to synthesize the available data. Whether a fixed-effect model or a random-effects model was used, depended on the level of clinical heterogeneity, the results of the Chi^2 test and I^2 statistic for heterogeneity[28] and the number of included studies for an outcome. If substantial heterogeneity was detected and the number of included studies on that outcome was ≥10, a random-effects model was used and the

sources of heterogeneity examined. If no substantial statistical heterogeneity was detected or the number of included studies on an outcome was <10, a fixed-effect model was used.

Subgroup analysis and investigation of heterogeneity
Subgroup analyses were conducted to determine if effects depend on:
Population:
1. Rh incompatibility
2. ABO incompatibility
3. Gestational age at birth (<37 weeks and ≥37 weeks)

Intervention:
1. Early administration of IVIg: start of IVIg ≤12 hours after birth
2. Late administration of IVIg: start of IVIg >12 hours after birth
3. Single versus multiple doses

Quality of studies (see 'Sensitivity analysis')

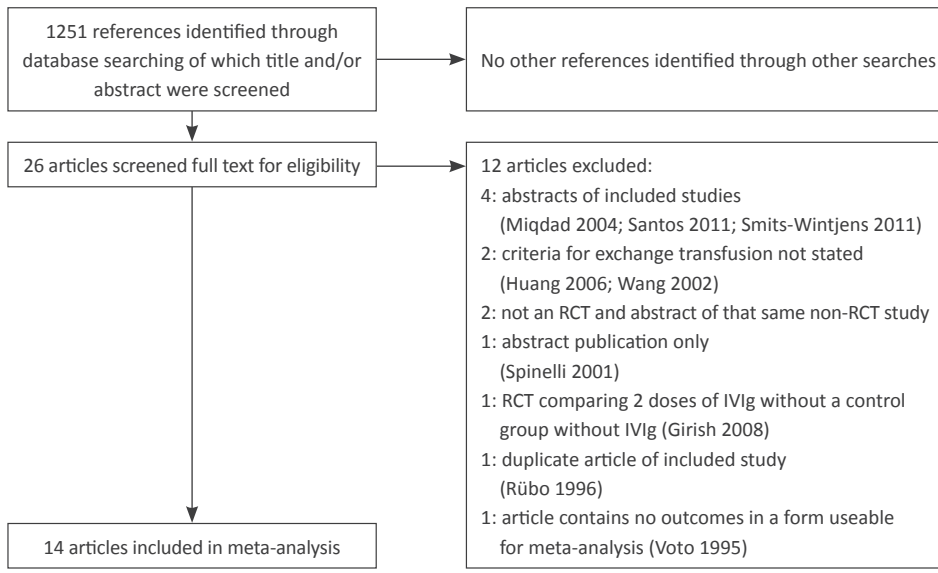
Sensitivity analysis
We conducted a sensitivity analysis based on the quality of included studies. We considered a study to be of high quality if it was rated as low risk of bias for random sequence generation, allocation concealment, blinding (performance and detection bias), incomplete outcome data, selective reporting and other risk of bias (if present).

Results

Description of studies
Detailed information of included and excluded studies is provided in Appendix 1 and 2.

Results of the search
The search conducted up until 22 March 2012 identified a total of 1251 references. After title and abstract screening, the full text of 26 references was screened. After full text screening 14 studies were included in the meta-analysis (Rübo 1992; Dağoğlu 1995; Atici 1996; Rübo 1996; Alpay 1999; Pishva 2000; Tanyer 2001; Garcia 2004; Miqdad 2004; Nasseri 2006; Elalfy 2011; Hematyar 2011; Smits-Wintjens 2011; Santos 2011).[2,29-41] Details of the studies are given in the table of included studies. Two studies have been excluded until further information is available from the authors.[42,43] Three studies have been permanently excluded from this review. Details of these studies are given in appendix 2. Searching reference lists of included and excluded studies and relevant reviews has not resulted in additional studies. A flow diagram of the study selection process is presented in Figure 1.

Figure 1. Flow diagram of the study selection process



Included studies

Fourteen randomized controlled trials published between 1992 and 2011 were included in this review.

Participants

The 14 included studies comprised 942 participants. Six studies included only infants with Rh incompatibility.[2,31-33,37,40] One study included only infants with ABO incompatibility.[35] Four studies enrolled mostly infants with ABO incompatibility but also some with Rh incompatibility and both ABO and Rh incompatibility (Alpay 1999: 93 ABO, 16 Rh, 7 both; Atici 1996: 49 ABO, 23 Rh; Hematyar 2011: 62 ABO, 11 Rh, 7 both; Nasseri 2006: 21 ABO, 13 Rh).[29,30,34,36] Pishva et al. predominantly included infants with Rh incompatibility (n = 37) and only three infants with ABO incompatibility.[38] Rübo et al. (Rübo 1996) stated that they included infants with Rh, Kell and Duffy incompatibility, although the breakdown into these groups is unclear from the paper.[39] Tanyer et al. included 34 infants with ABO incompatibility, 18 with Rh incompatibility, 2 with "subgroup" incompatibility and 7 with "more than one incompatibilities".[41] Only Nasseri et al. reported results for each type of incompatibility separately and Alpay et al. provided this information through correspondence.[29,36] Five studies enrolled only term infants ≥37 weeks of gestation.[29,30,32,36,41] None of the studies only included premature infants <37 weeks of gestation. Three studies did not describe details of the gestational age at birth of enrolled infants.[38-40] Santos et al. and Smits-Wintjens et al. provided outcomes for term and preterm infants separately.[2,37]

Interventions

Nine of 14 studies which met inclusion criteria examined the effect of a single dose of IVIg in combination with phototherapy.[2,29-32,35,37,38,40] Two studies examined multiple doses[33,36] and two studies compared groups treated with a single dose or multiple doses with a control group.[39,41] Tanyer et al. were inconsistent in describing which group received a single dose or multiple doses of IVIg and therefore this study was excluded from the subgroup analysis of single and multiple doses.[41] In the study of Hematyar et al. 15 infants received a single dose of IVIg, also 15 infants received 2 doses and 9 infants received 3 doses of IVIg.[34] Results were not provided separately for subgroups treated with a single dose and multiple doses of IVIg. Three studies used a placebo in addition to phototherapy for the control groups.[2,33,37] The intensity and topography of phototherapy fits the definition of intensive phototherapy in only three studies.[2,32,37] Tanyer et al. used an obsolete model with 3 overhead lights from a single angle and Miqdad et al. did not use a phototherapy blanket beneath the baby.[35,41] The remainder of included studies did not describe the intensity and topography of phototherapy in sufficient detail to allow a conclusion as to whether it is reasonable to describe it as intensive phototherapy. Seven studies started IVIg ≤12 hours after birth[2,31-33,37,39,40] and five studies >12 hours.[29,30,34,36,41] Miqdad et al. started IVIg within 12 hours in 9 patients and >12 hours in 47 patients, but they did not report outcomes for early and late IVIg administration separately.[35]

Outcomes

All included studies reported ET as the primary outcome. In the abstract of Garcia et al. the number of ETs per infant was reported and data on the number of infants who received one or more ETs were provided by the authors.[33] For nine studies mean (or median) number of ETs per infant were reported[2,33,36,38] or could be calculated from reported data.[30-32,40,41] Unpublished data (standard deviation and/or mean) on this outcome were provided by authors of five studies.[2,29,33,35,37] The maximum bilirubin level was reported in five studies.[2,31,37,39,40] Unpublished data on this outcome were provided by the authors of four studies.[29,32-34] Although all studies commented on the duration of phototherapy in their results, the numerical data were reported or subsequently provided in ten studies.[2,29,30,32-37,41] These studies, except for Hematyar et al., all used predefined criteria for commencing phototherapy but not all for ceasing it. Eight studies reported or subsequently provided numerical data on the duration of hospitalization.[2,29,30,32,34-37] and Pishva et al. reported only a comment.[38] Only three studies reported (after correspondence) predefined criteria for hospital discharge.[34,35,37] Seven studies included top-up transfusion as an outcome.[2,29,31,35,36,39,40] Additional data on top-up transfusions were provided by authors of

Garcia 2004; Elalfy 2011; Smits-Wintjens 2011 and Santos 2011.[2,32,33,37] Smits-Wintjens et al. did not report top-up transfusions separately for the first week and after the first week of life, but subsequently provided this information.[2] Elalfy et al. and Garcia et al. had a follow up period of only one week after discharge and until discharge, respectively.[32,33] Predefined criteria for top-up transfusions were reported in only three studies[2,29,36] and were later provided through correspondence by Santos et al.[37] All studies reported on short-term adverse events and Garcia et al.[33] provided additional information after correspondence. None of the included studies reported data on neurodevelopmental outcomes. Additional information on neurodevelopmental outcomes was provided by Miqdad et al. and Santos et al.[35,37]

Excluded studies

In total, six studies were excluded after review by authors. One study had a retrospective design, one study only compared groups with a high or a low dose of IVIg[44], and one study was only reported in abstract form.[45] Two studies did not report pre-defined criteria for the primary outcome ET.[42,43] One study did not report any outcome in a form usable for meta-analysis.[46] Details of excluded studies are given in Appendix 2.

Additional data

We have attempted to contact the authors of all studies (except for the seven studies which were identified for the previous review[29,31,39-41,45,46]) to request both further methodological information and results. We have to date successfully contacted the authors of ten papers (including contact for the previous review).[2,29,32-35,37,39,40,42]

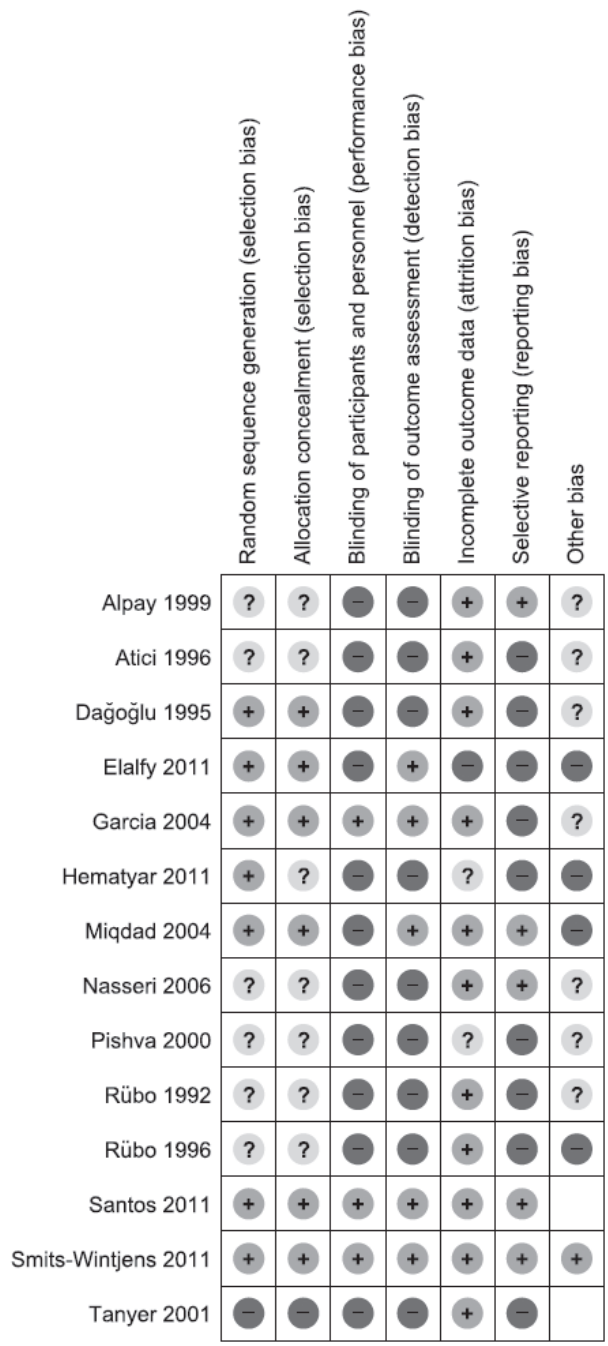
Risk of bias in included studies

For details of risk of bias of included studies, see Appendix 1 and Figure 2.

Allocation (selection bias)

Only seven studies reported an adequate method of randomization and were rated as low risk of bias.[2,31-35,37] Garcia et al., Miqdad et al., Elalfy et al., and Hematyar et al. provided information on randomization method only through correspondence.[32-35] A quasi-RCT allocated participants by order of admission.[41] This study was rated as high risk of bias for both random sequence generation and allocation concealment.

Figure 2. Summary of risk of bias of included studies



Blinding (performance bias and detection bias)

Only three studies used a placebo in the control group and were rated as low risk of bias for performance bias and detection bias.[2,33,37] Miqdad et al. reported through subsequent correspondence that data were kept and entered to their database by personnel who were not involved in the management of the cases and this study was therefore rated as low risk of detection bias.[35] Elalfy et al. replied to correspondence that the person who performed the randomization was different from the one who conducted the study and the one who analyzed the data, so their study was also rated as low risk of detection bias.[32] None of the other studies described any method of blinding of intervention after allocation and were rated as high risk of bias on both items.

Incomplete outcome data (attrition bias)

Reporting of outcome data was rated as low risk of bias in 11 studies.[2,29-31,33,35-37,39-41] For nine of these studies there were no missing data. In the Rübo 1992 trial, the amount of and reasons for missing data were similar between groups and in the study by Garcia et al. the missing data related only to 3 patients who were excluded after randomization because their blood type was Rh negative.[33,40] One study was rated as high risk of bias because of a substantial amount of missing data on bilirubin levels.[32]

Selective reporting (reporting bias)

Reporting bias was suspected in nine studies because important outcomes were either not reported or were not reported in a form that was useable for meta-analysis, or that allowed judgement about local treatment practices (for example if the authors only stated that there was no significant difference between groups).[30-34,38-41]

Other potential sources of bias

Two studies had non-random crossover after randomization,[32,39] one study used an additional criterion for ET in the control group only[35] and in two studies analysis was not performed on an intention to treat basis.[34,39] These four studies were rated as high risk of bias. Dağoğlu et al. used post randomization consent and although follow-up was complete for all infants for whom consent was obtained, two infants randomized to each arm of the study were excluded because consent was withheld.[31] Two infants were also excluded post-randomization in the Rübo 1992 study because of “protocol violations” but no details were given.[40] The latter two studies were rated as unclear risk of bias because the review authors were unable to assess the impact of these withdrawals on overall outcomes. Six other studies were rated as unclear risk of bias or low risk of bias for a potential risk of bias.[2,29,30,33,36,38] For details see “Risk of bias tables” in Appendix 1.

Effects of interventions

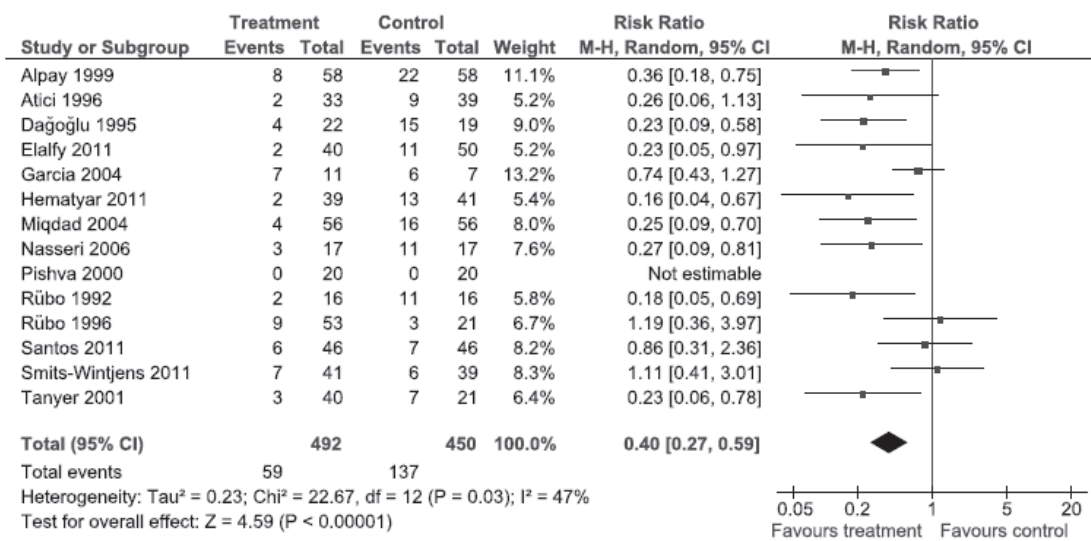
A complete overview of the results of all analyses is provided in Appendix 3.

Primary outcomes

Exchange transfusion

The results of 14 included studies could be entered into the meta-analysis.[2,29-41] Most studies found a statistically significant reduction in the use of ET for IVIg treated infants.[29-32,34-36,40,41] Four studies concluded that the use of (one or more) ETs was not reduced despite using early IVIg in combination with phototherapy.[2,33,37,39] The meta-analysis of all fourteen studies showed that IVIg reduces the need for an ET (RR 0.40, 95% CI 0.27 to 0.59; NNT 5.4) (see Figure 3).

Figure 3. Forest plot of the use of exchange transfusion (one or more)

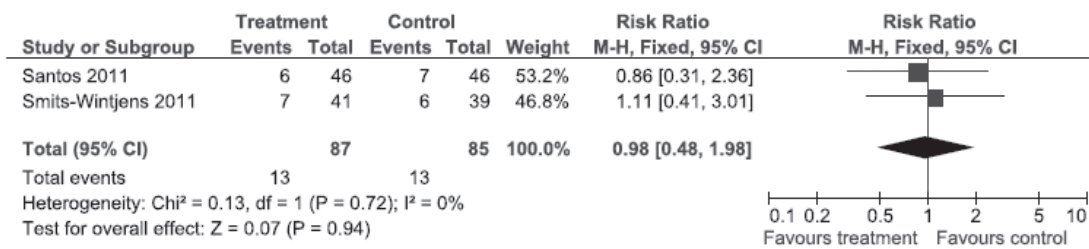


Subgroup analysis of infants with only Rh incompatibility supports a reduction in the use of ET with IVIg treatment (RR 0.42, 95% CI 0.29 to 0.61; NNT 5.7).[2,29,31-33,36-38,40] Analysis of infants with only ABO incompatibility also showed a reduction in the use of ET (RR 0.33, 95% CI 0.18 to 0.60; NNT 4.7).[29,35,36,38] In only those infants born ≥37 weeks of gestation IVIg reduced the use of ETs (RR 0.37, 95% CI 0.24 to 0.57; NNT 5.7).[2,29,30,32,36,37,41] In the subgroup of infants born <37 weeks of gestation IVIg did not reduce the use of ETs (RR 0.77, 95% CI 0.31 to 1.91).[2,37] Reductions in the use of ET were also found in the seven studies in which IVIg was used ≤12 hours after birth[2,31-33,37,39,40] (RR 0.51, 95% CI 0.35 to 0.73; NNT 7.3) and

in the five studies which used IVIg >12 hours after birth[29,30,34,36,41] (RR 0.27, 95% CI 0.17 to 0.44; NNT 3.9). Subgroup analyses of both infants receiving a single dose of IVIg [2,29-32,35,37-40] and those receiving multiples doses of IVIg[33,36,39] support a reduction in the use of ET with IVIg treatment (RR 0.41, 95% CI 0.29, 0.57; NNT 6.3 and RR 0.48, 95% CI 0.27, 0.83, NNT 4.6, respectively).

However, despite these apparently promising results, analysis of the only two high quality studies did not show a reduction in the use of ET (RR 0.98, 95% CI 0.48 to 1.98; NNT 284) (see Figure 4).[2,37]

Figure 4. Forest plot of the use of exchange transfusion (one or more). High quality studies only.



Overall, immunoglobulin treatment also led to a reduction in the mean number of ETs per infant (MD -0.31, 95% CI -0.45 to -0.17). In contrast, analysis of the two high quality studies showed that IVIg did not reduce the number of ETs (MD -0.04, 95% CI -0.18 to 0.10).

Secondary outcomes

Top up transfusions during and after the first week

The results of five studies could be entered in the meta-analysis of the use of top-up transfusions in the first week[2,29,32,33,37] and of 8 studies for the use of top-up transfusions after the first week of life.[2,29,31,35-37,39,40] IVIg did not increase the need for top-up transfusions during the first week (RR 1.05, 95% CI 0.65 to 1.69) or in the period after the first week (RR 1.20, 95% CI 1.00 to 1.45). IVIg also did not increase the need for top-up transfusions in the first week and after the first week of life in the following subgroups: infants with Rh incompatibility only (RR 1.08, 95% CI 0.65 to 1.77 and RR 1.09, 95% CI 0.92 to 1.28); infants with ABO incompatibility only (RR 0.80, 95% CI 0.19 to 3.38 and RR 5.02, 95% CI 0.62 to 40.67); infants born ≥37 weeks of gestation (RR 0.91, 95% CI 0.48 to 1.74 and RR 1.18, 95% CI 0.81 to 1.71); infants born <37 weeks of gestation (RR 1.39, 95% CI 0.70 to 2.73 and RR 1.24, 95% CI 0.93 to 1.67); infants treated with IVIg ≤12 hours after birth (RR 1.18, 95% CI 0.70 to 2.00 and RR 1.10, 95% CI 0.92 to 1.31); and in those infants treated with a single

dose of IVIg (RR 1.05, 95% CI 0.65 to 1.69 and RR 1.19, 95% CI 0.99 to 1.42). Although the need for top-up transfusions during the first week of life was not increased for the subgroup of infants treated with IVIg >12 hours after birth (RR 0.71, 95% CI 0.24 to 2.12), the need for top-up transfusions after the first week of life was increased with IVIg treatment (RR 8.00, 95% CI 1.03 to 62.26). However, the CI is very large and the lower CI limit is nearly one. For infants treated with multiple IVIg doses the use of top-up transfusions after the first week of life was not increased (RR 2.09, 95% CI 0.54 to 8.13) and not estimable for the first week of life. For the subgroup of infants included in high quality studies only[2,37], the need for top-up transfusions in the first week of life and thereafter was also not altered in infants treated with IVIg (RR 1.18, 95% CI 0.70 to 2.00 and RR 1.01, 95% CI 0.80 to 1.27).
Santos et al. and Smits-Wintjens et al. were the only studies included in the analysis of the number of top-up transfusions per infant.[2,37] In the first week of life and thereafter, the number of top-up transfusions was not altered in IVIg treated infants (MD 0.05, 95% CI -0.07 to 0.17 and MD -0.00, 95% CI -0.12 to 0.12, respectively).

Maximum serum bilirubin

Results for this outcome were available for nine studies.[2,29,31-34,37,39,40] The meta-analysis of all 9 studies showed that the mean maximum serum bilirubin decreased by 17.52 µmol/L in those receiving IVIg (MD -17.52, 95% CI -25.20 to -9.84). Furthermore, subgroup analyses showed that IVIg decreased maximum bilirubin levels in infants with both Rh and ABO incompatibility, those of >37 weeks of gestation, those treated early or late and those treated with a single dose of IVIg. However, subgroup analyses of the only two high quality studies[2,37], of infants born <37 weeks[2,37] and of infants treated with multiple doses of IVIg[33,39] showed that IVIg did not reduce maximum serum bilirubin (MD 0.92, 95% CI -23.94 to 25.79; MD -18.91, 95% CI -54.49 to 16.68; and MD 22.89, 95% CI -12.00 to 57.78, respectively).

Duration of phototherapy

Results of ten studies could be included in the meta-analysis of the duration of phototherapy.[2,29,30,32-37,41] Although criteria for commencing phototherapy were given in all studies except for the study by Hematyar et al.[34], only five studies described or provided predefined criteria for ceasing phototherapy.[2,29,32,37,41] Analysis of all ten studies showed that duration of phototherapy decreased by 0.87 days with IVIg treatment (MD -0.87, 95% CI -1.24 to -0.50). All subgroup analyses showed a decrease in duration of phototherapy in IVIg treated infants varying from a mean decrease of 0.74 days in those infants treated with IVIg >12 hours after birth (MD -0.74, 95% CI -1.00 to -0.49) to 1.22 days (MD -1.22, 95% CI

-1.42 to - 1.01) in infants treated with IVIg ≤12 hours after birth. However, as for maximum bilirubin levels, analyses of the two high quality studies (MD -0.50 95% CI -1.24 to 0.24) and of infants born <37 weeks of gestation (MD -0.91, 95% CI -1.96 to 0.14) showed no reduction in duration of phototherapy.

Duration of hospitalization

Results of eight studies could be entered in the meta-analysis.[2,29,30,32,34-37] None of these studies described predefined criteria for hospital discharge and only three studies provided them through correspondence.[34,35,37] The analysis showed that IVIg treatment shortens duration of hospitalization by 1.50 days (MD -1.50, 95% CI -1.72 to -1.28). All subgroup analyses showed a shorter duration of hospitalization with IVIg treatment varying from a mean decrease of 0.87 days in the infants with ABO incompatibility (MD -0.87, 95% CI -1.40 to -0.35) to 2.28 days less in infants born <37 weeks of gestation (MD -2.28, 95% CI -3.84 to -0.72).

Incidence of adverse reactions

All studies, except for Hematyar et al.[34], reported or subsequently provided data on adverse reactions. Eleven studies reported that no adverse reactions of IVIg treatment were observed.[2,29,31,32,35-41] In one study five patients developed fever up to 38.5 °C after ET which spontaneously disappeared after 4-6 hours.[30] In the study by Garcia et al., two deaths/adverse events occurred in both groups.[33] Causes of death in the IVIg group were pulmonary arrest and septic shock in babies with severe HDN and in the control group two infants died of hydrops and cardiac arrest also in the setting of severe HDN.[33] In the study by Alpay et al. two control infants receiving ET developed hypoglycemia and hypocalcemia after ET.[29] In the Rübo 1992 study, one control infant who required ET developed sepsis and one control infant who required ET developed inspissated bile syndrome.[40] However, the authors stated that a causal relationship with ET could not be established in either infant. Also in the study by Dağoğlu et al., one control infant developed inspissated bile syndrome.[31] Miqdad et al. described that “no immediate adverse effects related to IVIg were noted, including fever, allergic reactions, volume overload or hemolysis”, however they also stated that “ten of the babies who had ET, from both groups, had to be treated for blood culture-positive or clinical sepsis”.[35] In the study by Smits-Wintjens et al. one infant from the IVIg group developed a Bacillus cereus sepsis with brain abscesses a few days after ET.[2] Sterility tests on the used IVIg batches and cultures of all donor blood products used for IUTs and ET were found to be sterile. The sepsis may have been related to the umbilical venous catheterization and ET. Detailed information on this exceptional case is described in a case report.[47]

Long-term outcomes

Only the studies by Santos et al. and Miqdad et al. had a relatively long follow up period of one year and two years, respectively.[35,37] In both studies no cases of kernicterus, deafness or cerebral palsy were observed.

Discussion

Summary of main results

Overall there is limited evidence that IVIg treatment in neonates with alloimmune HDN reduces the need for ET. Although this review update showed a significant reduction in the need for ET, most of the included studies were not of high quality. In contrast, subgroup analysis of the only two studies which were of high quality showed that IVIg treatment had no effect on the need for ET or the number of ETs per infant. IVIg treatment was also associated with a significant reduction in maximum bilirubin level and duration of phototherapy when all included studies were analyzed as well as for most of the subgroup analyses based on type of alloimmunization, gestational age at birth and timing and number of doses of IVIg. However, as for ET, analysis of the two high quality studies demonstrated no difference in maximum bilirubin level and duration of phototherapy. Duration of hospitalization was significantly reduced when analyzing all studies which reported this outcome and for almost all subgroup analyses, including the subgroup analysis of high quality studies only. Although there is some evidence that IVIg reduces hemolysis and shortens hospital stay, these results should be interpreted with caution because only three studies used predefined criteria for hospital discharge and criteria for stopping phototherapy were not reported in most studies. In addition, over the last two decades guidelines for phototherapy have recommended using it more promptly for infants at risk of hemolysis.[48] In many hospitals, the quality of phototherapy has also improved over the years. Nevertheless, the quality/intensity of phototherapy can still vary today, especially in low-resource settings and if good quality control is not applied. The incidence of late top-up transfusions is an important outcome, especially in areas where follow-up of infants is difficult or where supply of safe blood for transfusion is limited. However, as thresholds for top-up transfusions in neonates vary widely, this outcome is susceptible to bias, particularly in unblinded studies. Eight of fourteen studies were included in the analysis of the incidence of top-up transfusion after the first week of life. However, only five of the eight studies used predefined criteria for top-up transfusions. In addition, those predefined criteria varied between studies, thus conclusions that could be drawn for this outcome are limited. Data on adverse events of IVIg seem to indicate that it can be used safely, although it is unclear

whether IVIg contributed to the two deaths in the IVIg study arm in the study by Garcia et al.[33]

Overall completeness and applicability of evidence

This review included all (quasi-)RCTs on the use of IVIg in alloimmune HDN. Nineteen trials were identified, of which fourteen trials, comprising a total of 942 infants, fulfilled inclusion criteria for the review. The only two included studies that were of high quality comprising a total of 172 infants, enrolled only infants with Rh HDN and the intervention consisted of a single dose of 0.5-0.75 g/kg IVIg administered within 4-6 hours after birth.[2,37] Santos et al. included infants of ≥32 gestational weeks and Smits-Wintjens et al. included infants of ≥35 gestational weeks.[2,37] Criteria for phototherapy and ET were similar in both studies. From subgroup analysis of these two studies, it can be concluded that early administration of IVIg in a single dose of 0.5-0.75 g/kg does not reduce ETs or have other benefits in the treatment of Rh HDN. There is no clear evidence from this review that a higher dose will improve the efficacy. The only randomized controlled trial comparing the effect of two doses of IVIg in Rh HDN showed that 0.5 g/kg and 1 g/kg had a similar effect on the duration of phototherapy, duration of hospitalization and ET requirements.[44] However, this study was not powered to find a difference in the need for ET. Long-term neurodevelopmental outcome was only examined by Santos et al. and Miqdad et al. who found no cases of kernicterus, deafness or cerebral palsy in a follow up period of one year and two years, respectively.[35,37]

Subgroup analysis of infants with ABO HDN showed a reduction in ET, maximum serum bilirubin level and duration of phototherapy and hospitalization. However, none of the four studies was of high quality and results may be limited in applicability.[29,35,36,38]

American Academy of Pediatrics guidelines of 2004 recommend the administration of 0.5-1 g/kg IVIg in alloimmune HDN if TSB is rising despite intensive phototherapy or if TSB level is within 34-51 µmol/l (2-3 mg/dL) of exchange level.[27] Based on the results of this review and because IVIg administration is not completely without risks[20-22] and supplies of IVIg are limited, we do not recommend routine use of IVIg. However, since there is some evidence that it reduces hemolysis and it appears safe in infants with alloimmune HDN, it might be reasonable to consider using it in special circumstances, such as during transfer of an infant to a location that can perform an ET, or where the risk of ET is considered to be much higher than usual, such as in very or extremely low birth weight infants.

Quality of the evidence

The quality of included studies ranged from fulfilling none of the 'risk of bias' criteria to fulfilling all criteria. Six of fourteen studies used adequate methods for random sequence generation and allocation concealment. Given the nature of the intervention, it was possible to blind patients by using an infusion fluid. However, only three of fourteen studies were placebo-controlled. The lack of blinding could have influenced the decision to perform an ET or top-up transfusion. None of the studies that were not placebo-controlled described any another method to blind outcome assessors except for Miqdad 2004 and Elalfy 2011.[32,35] Attrition was rated as high risk of bias in only one study (on the basis of both extent and reasons for attrition) and two studies were rated as unclear risk of bias because the available information was too limited to make a judgement. Selective reporting was suspected in nine studies because they did not report on duration of hospitalization and/or top-up transfusions, which could cause over- or underestimation of the overall benefits of IVIg. In addition, since ETs and top-up transfusions are related in Rh HDN, both outcome measures should be described.[49] Finally, risk of other biases was suspected in four trials which used different ET criteria for the IVIg and control groups, did not perform analysis on an intention to treat basis, or had significant non-random crossover between study groups. In conclusion, only two of fourteen trials fulfilled all criteria to be rated as high quality studies.

Potential biases in the review process

We tried to minimize bias by working with two reviewers who independently assessed eligibility for inclusion of trials, extracted data and assessed risk of bias. However, we were aware that these parts of the review process were based on personal judgement because reviewing research is influenced by prior beliefs. In addition, one included trial was performed by three of the four review authors. Nevertheless, we attempted to review all studies in a similar way. In addition, we were unable to contact authors of all potentially eligible studies and therefore we could not include all available data. While the translator of the Turkish included study was a medical doctor from Turkish parents, he may have missed some details regarding the risk of bias of that study.

Agreements and disagreements with other studies or reviews

The overall findings of this review are consistent with previous systematic reviews. Gottstein et al. included 3 studies that were also included in our review (Rübo 1992; Dağoğlu 1995; Alpay 1999) and one study that was excluded from our review (Voto 1995).[50] They concluded that with IVIg treatment significantly fewer infants required ET. Duration of

hospitalization and phototherapy were also significantly reduced in their review.[50] However, based on our judgement, none of their included studies was of high quality. Two Chinese systematic reviews also found a reduction in ET requirements, duration of phototherapy and hospitalization but concluded that well-designed trials with a larger sample size were required for further evaluation of the efficacy and safety of IVIg.[51,52] Until the date we conducted our search, our review is the most recent, extensive and up-to-date review of all randomized and quasi-randomized trials on the effect of IVIg in alloimmune HDN.

Authors' conclusions

Implications for practice

Routine use of IVIg for the treatment of alloimmune HDN should be discouraged. Results of the only two high quality studies show no reduction in the use of ET. In addition, IVIg is not without risks and supplies are limited. However, since there is some evidence that IVIg reduces hemolysis and appears safe in neonates with alloimmune HDN, it may have a limited role in special circumstances, such as where ET is impossible, or is considered particularly high risk. Nevertheless, undertaking preparations for ET, including ensuring birth at or transfer to a center that can perform ET, would seem to be strongly indicated in high risk infants, and should not be abandoned in the expectation that IVIg will be efficacious.

Implications for research

Future research into the role of IVIg in the early treatment of alloimmune HDN may be warranted, particularly in infants for whom ET is considered to be high risk. Such a trial should examine the safety and efficacy of IVIg by recording both short-term outcomes such as the need for transfusion therapy and the incidence of adverse events and also long-term neurodevelopmental outcomes. Both ETs and (late) top-up transfusions should be recorded because reduction of ETs can increase the number of top-up transfusions.[49] Consideration should also be given to including additional measures to assess the severity of hemolysis such as carboxyhemoglobin or end tidal carbon monoxide. Based on evidence from the two high quality trials, the conclusion of the review authors is that IVIg is of very limited usefulness in Rh HDN. However, neither of these high quality studies enrolled infants with severe established jaundice due to ABO incompatibility. In contrast to Rh incompatibility, ABO incompatibility mainly results in hyperbilirubinemia without significant anemia. This is primarily due to the relatively few group A and B antigenic sites on neonatal red blood cells.[53] Furthermore, infants with ABO-mediated hemolysis often present for neonatal care when they already have severe jaundice. Due to these differences between Rh and ABO

incompatibility it is conceivable that IVIg has a greater role in ABO-mediated jaundice. If it is efficacious in ABO HDN, it could, for example, be used during transfer to a hospital that can provide intensive phototherapy and perform ET. However, due to the relative rarity of severe jaundice, unresponsive to phototherapy in ABO incompatibility, exploring the use of IVIg to treat established jaundice would require a multicenter randomized controlled trial. Such a trial should either use a placebo or an alternative method for blinding of treatment and outcome assessment. Future trials should be well planned and give priority to establishing guidelines for the "conventional" management of alloimmune HDN, focusing on the criteria for performing both top-up and ETs and on the role of intensive phototherapy.

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Appendix 1: Details of included studies

Alpay 1999[29]

Methods	RCT
Participants	116 newborn term infants. ABO and/or Rh incompatibility. TSB >204 µmol/L (12 mg/dL), positive direct Coombs test and reticulocyte count ≥10%.
Interventions	Treatment group: Single dose of IVIg 1 g/kg (ISIVEN) plus phototherapy, started at 51.53 ± 3.5 h (mean ± SD) after birth. (n = 58) Contol group: Phototherapy only, started 54.33 ± 4.0 h (mean ± SD) after birth. (n = 58)
Outcomes	ETs, maximum TSB*, duration of phototherapy, duration of hospitalization, top-up transfusions*, and adverse events. Criteria for ET: TSB >290 µmol/L (17 mg/dL) and increased by >17 µmol/L/hour (1 mg/dL/hour). Criteria for phototherapy: started and continued as long as TSB levels were above the levels for starting phototherapy.[55] Details of phototherapy: 5 special blue lights (Philips F20 T12/BB) placed 30 cm above the patient; body position was changed periodically; no phototherapy blanket. Criteria for top-up transfusions: after 15-21 days red blood cell transfusions were given because hemoglobin levels were ≤87 g/L . * = (part of the) outcome available through correspondence
Notes	Unpublished data and information supplied.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated. Method of randomization unclear despite correspondence with author.
Allocation concealment (selection bias)	Unclear risk	Only stated: "The attending neonatologists who made the decision regarding the choice of treatment were different from those conducting the study."
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.

Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	Low risk	Although adverse events of IVIg were not reported explicitly, assumed that there were no adverse events of IVIg because authors described that 2 patients had hypoglycemia and hypocalcemia after ET.
Other bias	Unclear risk	Average bilirubin levels at study entry were already above bilirubin thresholds to invoke outcome event ET. Possible sources of bias include: 1) dilution effect of IVIg could have affected bilirubin after infusion, 2) rate of rise of bilirubin might have been measured over different intervals, 3) decision to prepare for ET might easily have been influenced by treatment group allocation, because of the urgency.

Atici 1996[30]

Methods	RCT
Participants	116 newborn term infants. ABO and/or Rh incompatibility. TSB >204 µmol/L (12 mg/dL), positive direct Coombs test and reticulocyte count ≥10%.
Interventions	Treatment group: Single dose of IVIg 1 g/kg (ISIVEN) plus phototherapy, started at 51.53 ± 3.5 h (mean ± SD) after birth. (n = 58) Contol group: Phototherapy only, started 54.33 ± 4.0 h (mean ± SD) after birth. (n = 58)
Outcomes	ETs, maximum TSB*, duration of phototherapy, duration of hospitalization and adverse events. Criteria for ET: TSB level 86 µmol/L (5 mg/dL) above the limit in Oski 1982.[56] Criteria for phototherapy: TSB level beneath the level for ET. Details phototherapy: blue light 420-470 nm. * = not presented in a form usable for meta-analysis
Notes	Not stated whether any ethics approval or if parental consent was given.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated "block randomization".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Low risk	3 patients appear to be missing in Table 3 of outcome data (n = 36 for control group), but this is probably a typing mistake since percentages correspond with inclusion of all patients (n = 39) in control group.
Selective reporting (reporting bias)	High risk	Top-up transfusions not reported.
Other bias	Unclear risk	Absence of strict criteria for enrolment. In addition, a positive direct antiglobulin test was not a criterion for enrolment and only present in 63% and 59% of infants in IVIg and control group, respectively. Unclear if block randomization included stratification for Rh versus ABO HDN.

Dağoğlu 1995[31]

Methods	RCT
Participants	45 term and preterm infants with Rh incompatibility randomized. Four infants withdrawn post-randomization because parental consent was not provided. Rh positive infant, Rh negative mother and positive direct Coombs test.
Interventions	Treatment group: Single dose of IVIg 0.5 g/kg (Sandoglobulin) as soon as possible after birth (usually within 2 hours) plus phototherapy. (n = 22) Control group: Only phototherapy. (n = 19)

Outcomes	ETs, maximum TSB, duration of phototherapy*, top-up transfusions and adverse events. Criteria for ET: TSB increase by >17 µmol/L/hour (1 mg/dL/hour) or TSB >342 µmol/L (20 mg/dL) in term infants or if TSB >308 µmol/L (18 mg/dL) in infants weighing >2000g. Criteria for phototherapy: started when bilirubin levels exceeded the relevant curves of Oski and Naiman (Oski 1982).[56] Details phototherapy: blue lights 420-460 nm. Criteria for top-up transfusion: not stated. * = not presented in a form usable for meta-analysis
Notes	45 infants eligible. Post-randomization consent used. All infants received at least one IUT.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated "random numbers".
Allocation concealment (selection bias)	Low risk	Stated "sealed envelopes".
Blinding of participants and personnel (performance bias)	High risk	Stated "not blinded because an appropriate placebo for IVIg could not be found".
Blinding of outcome assessment (detection bias)	High risk	Not stated. Contact with authors unsuccessful. Assumed that blinding was not performed.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	High risk	Duration of hospitalization not reported.
Other bias	Unclear risk	Consent after randomization and 2 infants from each group withdrawn post-randomization because consent not provided. Reasons for parental refusal are not stated. Some differences in IVIg and control groups despite randomization: higher M:F ratio in IVIg group (72%) than control group (47%) although most other characteristics don't differ. High rate of ET in control group (79%) for patients who all had IUT. ET criteria inconsistently described in Methods and Discussion.

Elalfy 2011[32]

Methods	RCT
Participants	90 term neonates (>38 weeks of gestation) born to Rh negative mothers who had not received anti-D after previous deliveries with: 1) isoimmune HDN "proven by": Rh incompatibility between blood group of the mother and baby, a positive direct antiglobulin test and a high reticulocyte count and 2) significant hyperbilirubinemia requiring phototherapy in the first 12 hours of life and/or rising by 8.6 µmol/L/hour (0.5 mg/dL/hour) while TSB is still below the ET criteria on admission according to the AAP management guidelines for hyperbilirubinemia.[27]
Interventions	Treatment group 1: Single dose of IVIg 0.5 g/kg administered at 12 hours after birth plus phototherapy. (n = 25) (Number randomized n = 23, however 3 moved to control group and 5 gained from high dose IVIg group.) Treatment group 2: Single dose of IVIg 1 g/kg administered at 12 hours after birth plus phototherapy. (n = 15) (Number randomized n = 22, however 2 moved to control group and 5 to low dose IVIg group.) Control group: phototherapy only. (n = 50) (Number randomized n = 45, however 5 gained from IVIg groups)
Outcomes	ETs, duration of phototherapy, top-up transfusions*, duration of hospitalization and adverse events. Criteria for ET: "When bilirubin increased by 17 µmol/L/hour (1 mg/dL/hour), the neonate will require ET according to the guidelines of the AAP".[27] Criteria for phototherapy: "Initiation and discontinuation of phototherapy was according to the serum bilirubin levels as provided by the AAP guidelines".[27] Phototherapy details: 5 special blue lights, of which one fiberoptic blanket and 4 overhead lights. Criteria top-up transfusion: not stated. * = information on this outcome through correspondence.
Notes	Unpublished data and information supplied. Follow up until one week after discharge.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From correspondence: randomization by using sealed envelopes which were kept in a big box and shuffled. A neonatologist picked one envelop out of the box to randomize a participant.
Allocation concealment (selection bias)	Low risk	See above.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	Low risk	No placebo or other method of blinding described. An e-mail reply to correspondence stated that the study was blinded and there was no detection bias, but does not state what methods were used. The authors explained that they meant by "the study was blinded" that the person who performed the randomization was different from the one who conducted the study and the one who analyzed the data.
Incomplete outcome data (attrition bias)	High risk	Substantial amount of missing data for bilirubin levels after 48 hours (figure 2 in article).
Selective reporting (reporting bias)	High risk	Top-up transfusions were not reported in the paper, but data on the number of top-up transfusions in the first week and thereafter were provided through correspondence. However, duration of follow-up was only until one week after discharge from the hospital, therefore top-up transfusions after the first week are still missing.
Other bias	High risk	Significant non-random crossover between study groups after randomization, quote: "...five parents in the intervention group did not consent using IVIg, so they were treated eventually by the conventional method. Of the 40 infants finally in the intervention group, five babies assigned to the higher IVIg dose... their parents chose the lower dose...". Authors explained through correspondence that when parents signed the informed consent form, they had the right to change the treatment without knowing in which arm their child was randomized. It happened to be that all parents who changed the treatment were initially randomized to the low dose arm.

Garcia 2004[33]

Methods	Double blind, placebo controlled RCT (pilot study)
Participants	18 neonates with jaundice due to Rh incompatibility and who required phototherapy.
Interventions	Treatment group: IVIg 0.75 g/kg/day (15 ml/kg/day) for 3 days started 2 h (mean) after birth plus phototherapy. (n = 11) Control group: An equal amount (15 ml/kg/day) of saline started 2 h (mean) after birth with the same frequency plus phototherapy. (n = 7)
Outcomes	ETs, maximum TSB*, duration of phototherapy, top-up transfusions*, adverse events* and mortality* Criteria for ET: based on a local protocol ("Instituto Nacional de Perinatologia. Incompatibilidad al Antigeno Rh. Normas y procedimientos de Neonatologica 1998.") which was based on the guidelines from the AAP. Criteria for phototherapy: started when infants were enrolled and based on local protocol (see above). Details phototherapy: Blue lights were used, one light for each patient. Criteria for top-up transfusion: not stated. * = information on this outcome through correspondence.
Notes	Unpublished data and information supplied. Ethics approval and parental consent was given. Follow up until discharge.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	From correspondence: By a random number table.
Allocation concealment (selection bias)	Low risk	From correspondence: The random number table was managed by a secretary from the unit and each time a Rh negative woman was in the operating room for a caesarean section she informed the pharmacy which delivered the study medication labeled only with "Group 1" or "Group 2".
Blinding of participants and personnel (performance bias)	Low risk	A placebo was used and study medication only labeled with "Group 1" or "Group 2".

Blinding of outcome assessment (detection bias)	Low risk	A placebo was used and study medication only labeled with “Group 1” or “Group 2”.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes in abstract or after correspondence.
Selective reporting (reporting bias)	High risk	Duration of hospitalization not measured.
Other bias	Unclear risk	Three infants were withdrawn post-randomization because their blood type was Rh negative. Very small numbers of patients in each group. Because only one light was used per patient, phototherapy seems unlikely to have been intensive.

Hematyar 2011[34]

Methods	RCT
Participants	80 newborns of >32 weeks of gestation and birth weight >2500 gram who developed jaundice on the first postnatal day due to ABO or Rh HDN with evidence of hemolysis (positive Coombs’ test, reticulocytes >10%, Hb or Ht decline) without other causes of jaundice. Exclusion criteria were: a serious condition such as hemodynamic instability and asphyxia, indication of ET at birth, fetal hydrops, congestive cardiac dysfunction and occurrence of serious IVIg complications.
Interventions	Treatment group: 0.5 g/kg IVIg up to a maximum of 3 doses, if it was required, plus phototherapy. The first dose was administered after 12 hours after birth in all infants. (n = 39) Control group: phototherapy only. (n = 41)
Outcomes	ETs*, maximum TSB*, duration of phototherapy*, and duration of hospitalization*. Criteria for phototherapy: not provided (additional information has been requested). Criteria for ET: according to the AAP guidelines.[27] Criteria for hospital discharge: “When TSB levels did not significantly increased 24 hours after terminating phototherapy.” * = information on this outcome through correspondence.
Notes	Follow up until discharge. The study was approved by an ethical committee and all parents gave informed consent.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From correspondence: "By a random number."
Allocation concealment (selection bias)	Unclear risk	Not enough information provided to make a judgement. Additional information has been requested.
Blinding of participants and personnel (performance bias)	High risk	Not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Not enough information to make a judgement. Additional information has been requested.
Selective reporting (reporting bias)	High risk	Top-up transfusions, adverse events and number of ETs per infant not reported.
Other bias	High risk	Occurence of serious IVIg complications was an exclusion criterion and analyses were not performed on an intention to treat basis.

Miqdad 2004[35]

Methods	RCT
Participants	112 neonates with "significant hyperbilirubinemia due to ABO HDN confirmed by a positive Coombs' test".
Interventions	Treatment group: single dose of IVIg 0.5 g/kg plus phototherapy. (Nine patients received IVIg <12 h and 47 patients >12 h after birth). (n = 56) Control group: phototherapy only. (n = 56)

Outcomes	ETs, duration of phototherapy, duration of hospitalization*, top-up transfusions, and adverse events. Criteria for phototherapy: TSB rising by 8.5 µmol/L/hour (0.5 mg/dL/hour) or TSB >170 µmol/L (10 mg/dL) at <12 hours after birth, TSB >204 µmol/L (12 mg/dL) at <18 hours after birth or TSB >238 µmol/L (14 mg/dL) at 24 hours after birth. Phototherapy was discontinued when TSB was <205 µmol/L (12 mg/dL). Details of phototherapy: Blue fluorescent lights were used (Ameda, Switzerland and Airshields, USA). Each unit had 4 lights at wavelength 460 nm. During the study they used one unit to denote single phototherapy, two units to denote double phototherapy and three units for triple phototherapy. These were placed 35-40 cm above the infant. They did not use phototherapy blankets. Criteria for ET: if at any time TSB ≥340 µmol/L (20 mg/dL), in any of the two groups, or if it was rising by ≥8.5 µmol/L/hour (0.5 mg/dL/hour) in the neonates in the control group. Criteria for top-up transfusions: Stated that no transfusions were performed because hemoglobin levels remained >100 g/L. Criteria for hospital discharge: TSB levels not increasing 24 hours after terminating phototherapy, no feeding problems and nursing staff and parents satisfied with discharge. * = measure of variance through correspondence
Notes	Study was approved by their hospital research committee. However, it was not clear from correspondence whether parental consent was given for this study. Additional correspondence: At the time they conducted the trial in Saudi Arabia there was resistance of parents and patients to consent to research in general because of misconception that patients would not receive appropriate treatment if they were included in research projects. However, “now that there is a body governing medical practice things are changing and research now requires approval by the institute and consent of the patient or guardian.”

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From correspondence: Randomization was done by simple sampling randomization. The first 10 participants who were numbered 1,4,7 and 10 were assigned to the IVIg group and those numbered 2,3,5,6,8 and 9 were assigned to the control group. The second group of 10 participants who were numbered 1,4,7 and 10 were assigned to the control group and those numbered 2,3,5,6,8 and 9 to the IVIg group. This sequence continued alternating between the groups until they reached 110 participants and the final 2 participants were assigned to the IVIg group so that each group consisted of 56 patients.
Allocation concealment (selection bias)	Low risk	From correspondence: Random number table was kept by the head nurse and none of the treating physicians were involved in the randomization process.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	Low risk	All data were kept and entered to their database by personnel who were not involved in the management of the cases and that data was given to the outcome assessors.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	High risk	Control group has an additional criterion to perform ET which could have resulted in more ETs in the control group. Very high rate of ET for ABO HDN in both study groups, especially control group. Very high rate of clinical or culture positive sepsis in neonates who had ET. Not clear whether neonates in each group were enrolled at similar post-natal age. Unsubstantiated claim in conclusions that IVIg works even when given up to 72 hours of age. No data presented to support whether late vs early administration influenced efficacy.

Nasseri 2006[36]

Methods	RCT (although in Methods stated that it was a prospective case control study).
Participants	34 neonates with: 1) gestational age of ≥37 weeks; 2) a positive direct Coombs' test due to Rh or ABO incompatibility; 3) significant hyperbilirubinemia as defined by bilirubin rising by ≥0.5 mg/dL/hour (8.5 µmol/L/hour); 4) bilirubin below ET criterion on admission; and 5) "no other risk factors such as sepsis, G6PD deficiency".
Interventions	Treatment group: 3 doses of 0.5 g/kg IVIg 12 hours apart within 2-4 hours of admission (average age at admission about 20 hours) plus phototherapy. (n = 17) Control group: Only phototherapy. (n = 17)
Outcomes	ETs, duration of phototherapy, duration of hospitalization, top-up transfusions, and incidence of adverse events. Criteria for phototherapy: "Phototherapy was started once the baby was admitted to the NICU". Details phototherapy: "double surface blue light phototherapy". Criteria for ET: Bilirubin ≥342 µmol/L (20 mg/dL) or rising by 17 µmol/L/hour (1 mg/dL/hour). Criteria for top-up transfusions: hemoglobin level <70 g/L.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Unclear risk	Treatment group with multiple doses received a relatively large dose of IVIg (1.5 g/kg in the first 26-28 hours of life). This might cause a dilutional effect on bilirubin levels and therefore influence the decision for ET.

Pishva 2000[38]

Methods	RCT
Participants	40 neonates with Rh or ABO incompatibility. Inclusion criteria: a) Rh positive neonates, b) History of Rh positive sibling(s), c) maternal blood group O, d) Positive direct Coombs' test, both A and B in Rh negative mothers.
Interventions	Treatment group: single dose of IVIg 0.5 g/kg (Sandoglobulin) in the first 24 hours of life plus phototherapy. (n = 20) Control group: phototherapy only. (n = 20)
Outcomes	ETs, maximum TSB*, duration of phototherapy*, duration of hospitalization*, and adverse events. Criteria for phototherapy and ET: based on postnatal age (hours), birth weight and the level of bilirubin according to Faranoff et al.[57] * = not presented in a form usable for meta-analysis
Notes	Not stated whether any ethics approval was given.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Unclear risk	Not stated whether any attrition from study.
Selective reporting (reporting bias)	High risk	Top-up transfusions not reported.
Other bias	Unclear risk	Seems likely to have been only a mildly affected group of infants - using conservative criteria for phototherapy and ET, rates of these treatments were very low even in the control group.

Rübo 1992[40]

Methods	RCT
Participants	34 newborn infants. Rh incompatibility. Rh positive infant, Rh negative mother and positive direct Coombs' test.
Interventions	Treatment group: Single dose of IVIg 0.5 g/kg (Polyglobin N) as soon as Rh status confirmed, plus phototherapy. (n = 17) Control group: Phototherapy only. (n = 17)
Outcomes	ETs, maximum TSB, duration of phototherapy*, top-up transfusions and adverse events. Criteria for ET: TSB 34 µmol/L (2 mg/dL) > modified curve of Polácek.[58-59] Criteria for phototherapy: TSB 68 µmol/L (4 mg/dL) < modified curve of Polácek.[58-59] Details phototherapy: performed with "quartz lamps or blue light". Criteria for top-up transfusion: not stated. * = not presented in a form usable for meta-analysis
Notes	Two infants were excluded post randomization because of unspecified "protocol violations". Authors contacted. No further information available.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Low risk	Not stated, but probably data complete for all 32 infants who could be analyzed.
Selective reporting (reporting bias)	High risk	Duration of hospitalization not reported.

Other bias	Unclear risk	Two post-randomization withdrawals (one from each group) because of protocol violations. Insufficient data to determine that the 2 groups were similar at enrolment (e.g. with respect to post-natal age, gender, gestation, serum bilirubin). Described that two infants in IVIg group who needed an ET were treated suboptimally. Different treatment in this unblinded study?

Rübo 1996[39]

Methods	Multicenter RCT
Participants	74 neonates with HDN due to Rh, Kell or Duffy incompatibility proven by a positive direct Coombs' test.
Interventions	Treatment group 1: single dose of IVIg 0.5 g/kg (Polyglobin N) immediately started after Coombs' test was known to be positive plus phototherapy. (n = 28) Treatment group 2: as group 1 but with a second dose of IVIg administered after 48 hours after the first dose. (n = 25) Control group: phototherapy only. (n = 21)
Outcomes	ETs, maximum TSB, duration of phototherapy, top-up transfusions and adverse events. Criteria for phototherapy: phototherapy was given when bilirubin levels were 68 µmol/L (4 mg/dL) or less below predefined levels of ET. Criteria for ET: if bilirubin levels were ≥34 µmol/L (2 mg/dL) above the modified curves from Polácek (reference 7 and 8 of article). Criteria for top-up transfusion: not stated.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	High risk	Duration of hospitalization not reported and for duration of phototherapy only mentioned that it was not significantly different between the 3 groups without providing the data.
Other bias	High risk	Protocol violations led to 2 post-randomization withdrawals (unclear from what group(s)) and 4 control group infants being treated with IVIg and subsequently included in analysis (not intention to treat analysis). Stated that the treatment was conducted in accordance to guidelines of the individual hospitals. Risk of bias possible if participating hospitals did not provide the same number of patients to each study group. At admission, the control group had a significantly higher bilirubin level than the two IVIg groups.

Santos 2011[37,60]

Methods	Double blind, placebo controlled RCT
Participants	92 neonates: 1) born to Rh D negative woman with anti-Rh D antibodies; 2) of gestational age ≥32 weeks; 3) with Rh D positive blood type; and 4) with positive direct Coombs' test.
Interventions	Treatment group: single dose of IVIg 0.5 g/kg (Immunglobulin®) in the first 6 hours of life plus phototherapy. (n = 46) Control group: Saline in corresponding volume as IVIg (10 ml/kg) plus phototherapy. (n = 46)

Outcomes	ETs, maximum TSB*, top-up transfusions*, duration of phototherapy, duration of hospitalization, sensorineural hearing loss*, kernicterus*, mortality*, and adverse events. Criteria for phototherapy: Started in the first hours of life and discontinued when bilirubin level fell below 10 mg/dL after 2 days of life. Phototherapy details: high intensity phototherapy (irradiance >30 IW/cm²/nm) with special blue fluorescent light (Bili-berço, model 006/FB, FANEM, São Paulo, Brazil), halogen lamp (Bilispot, model 006/BP, FANEM); irradiance level checked prior to initiation of phototherapy using a FANEM radiometer, model 2620. Criteria for ET: bilirubin level ≥340 µmol/L (20 mg/dL) or rising by ≥8.5 µmol/L/hour (0.5 mg/dL/hour). Criteria for top-up transfusions: hemotocrit <25% with positive direct or indirect Coombs' test; hematocrit <21% with negative Coombs' test and reticulocytes <1%; hematocrit <30% with clinical signs of severe anemia (lethargy, dyspnea, feeding problems, need for oxygen, failure to thrive). Criteria for hospital discharge: gestational age >34 weeks, absence of clinical signs of anemia, bilirubin level <10 mg/dL and decreasing, ability to suck without tiring. * = information available through correspondence and from paper published after our search on 22 March 2012.[60]
Notes	Unpublished data and information supplied.

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomization in blocks of 4 with a 1:1 allocation was performed by a statistician.
Allocation concealment (selection bias)	Low risk	Statistician was responsible for concealment and opaque envelopes were used.
Blinding of participants and personnel (performance bias)	Low risk	The medication was prepared by the pharmacist and applied such that the parents, nurses and pediatricians were blinded to its identity (IVIg versus placebo).
Blinding of outcome assessment (detection bias)	Low risk	Intervention blinded as described above and investigators and treating clinicians were different groups.

Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	Low risk	Data on top-up transfusions were provided after correspondence but reason for not including data (journal advised to remove that information) in the report was reasonable and therefore classified as low risk of bias.

Smits-Wintjens 2011[2]

Methods	Double blind, placebo controlled RCT
Participants	80 neonates of ≥35 weeks of gestation. Rh HDN with positive direct Coombs' test caused by anti-D or -c antibodies of Rh D negative or Rh c negative mother. Maternal antibody-dependent cellular cytotoxicity test >50% (comparable with titer 1:64)
Interventions	Treatment group: Single dose of IVIg 0.75 g/kg (Nanogam, Sanquin, The Netherlands) within first 4 hours after birth, plus intensive phototherapy. (n = 41) (Also stratified for treatment with intrauterine transfusion.) Control group: Placebo 5% glucose infusion plus phototherapy. (n = 39)
Outcomes	ETs, maximum TSB, duration of phototherapy, duration of hospitalization, top-up transfusions* and adverse events. Criteria for ET: according to AAP 2004 guidelines[27] TSB > threshold or rate of rise of TSB >8.5 µmol/L/hour (0.5 mg/dL/hour) despite intensive phototherapy, or clinical symptoms of acute bilirubin encephalopathy. Criteria for phototherapy: started when infants were admitted and continued according to AAP 2004 guidelines.[27] Phototherapy details: intensive phototherapy using white light with an intensity of 10-20 µW/cm/nm given by Air Shield and Ohmeda lamps, in combination with a phototherapy blanket providing blue light 30 µW/cm/nm. During phototherapy extra fluids (10 ml/kg) were administered. Criteria for top-up transfusion: Hemoglobilin level <8 g/dL or <9.6 g/dL in the presence of clinical symptoms of anemia (such as lethargy, feeding problems, need for oxygen, or failure to thrive). * = not presented in a form usable for meta-analysis
Notes	Unpublished data and information supplied.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated, sequence code kept by chief pharmacist.
Allocation concealment (selection bias)	Low risk	Pharmacy controlled block randomization.
Blinding of participants and personnel (performance bias)	Low risk	Identical coded drug boxes and vials. One infant's treatment unblinded due to serious adverse event. Unblinding unlikely to have affected study outcomes.
Blinding of outcome assessment (detection bias)	Low risk	Sequence code broken after three months follow-up period of last included patient.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	Low risk	Some outcomes are not completely reported as described in the published protocol. In protocol described that changes in bilirubin in the first 24 and 48 hours (%) will be measured. The paper only describes bilirubin levels at birth and maximum bilirubin during admission. In protocol described that top-up transfusions would be measured in the first week of life and after the first week until three months of life. The paper describes top-up transfusions for the whole period until three months after birth. However, data on changes in bilirubin levels are available and data on the top-up transfusion were provided for the first week and thereafter separately, therefore rated as low risk of bias.
Other bias	Low risk	One set of twins randomized to same treatment (done to avoid discrepant treatment for infants of same family). Re-analysis unlikely to change overall results.

Tanyer 2001[41]

Methods	Quasi-randomized trial
Participants	61 neonates with a positive direct Coombs' test; ABO or Rh or subgroup incompatibility, without "contributing risk factors (such as sepsis, drug use by mothers) that could raise bilirubin levels", not prematurely born and with bilirubin levels below ET criterion on admission.
Interventions	Treatment group 1: Single dose of IVIg 0.5 g/kg within 2-4 hours of admission (mean age of admission 2.3 days) plus phototherapy. (n = 20) Treatment group 2: IVIg 0.5 g/kg/day for 3 days within 2-4 hours of admission (mean age of admission 2 days) plus phototherapy. (n = 20) Control group: Phototherapy only (mean age of admission 2.8 days). (n = 21)
Outcomes	ETs, duration of phototherapy, and adverse events. Criteria for phototherapy: phototherapy was started once patient was admitted to the clinic and stopped when bilirubin level "decreased to the safe limit". Details phototherapy: performed using a white quartz halogen lamp (Air Shields Microlite Phototherapy system) with a distance between the infant and light source of 41 cm. Criteria for ET: performed when bilirubin levels exceeded the accepted limits which are shown in Table 1 or paper with reference to a study by Bryla et al.[61]

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	By order of admission. Given the distribution of bilirubin levels at admission, some infants may have been at ET thresholds on admission. This could have influenced treatment allocation.
Allocation concealment (selection bias)	High risk	Not concealed.
Blinding of participants and personnel (performance bias)	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias)	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias)	Low risk	Complete data for all pre-defined outcomes.
Selective reporting (reporting bias)	High risk	Duration of hospitalization and top-up transfusions not reported.

Appendix 2: Details of excluded studies and studies awaiting assessment

Excluded studies

Girish 2008[44]

Reason for exclusion	This randomized controlled trial compared two doses of IVIg and had no placebo or "standard care" control group.

Spinelli 2001[45]

Reason for exclusion	This abstract only selectively reports outcome for enrolled infants who had moderate-severe hemolysis. Criteria for severity were not stated although stratification into mild, moderate and severe was pre-defined. Correspondence with authors seems unlikely to yield further information given interval since report, abstract only (no paper) and previous unsuccessful attempt.

Voto 1995[46]

Reason for exclusion	This randomized controlled trial compared a single dose of IVIg with control. However, none of the outcomes were reported in a form usable for the meta-analysis. Top-up transfusions and ET were not separately reported, bilirubin levels were presented as graphs rather than tables, and although the means of duration of phototherapy and hospitalization were presented in a table, the measure of variance was not clear. Correspondence with authors seems unlikely to yield further information given interval since report and previous unsuccessful attempt.

Studies awaiting assessment

Huang 2006[42]

Methods	Quasi-randomized trial. Randomization "by date of birth".
Participants	74 neonates who "tested positive for ABO HDN" and had "high bilirubin levels".
Interventions	Treatment group: IVIg 0.4-0.6 g/kg/day for 1-2 days plus albumin 1-2 g/kg/day for 2-3 days plus phototherapy. (n = 36) Control group: Phototherapy plus albumin 1-2 g/kg/day for 2-3 days. (n = 38)
Outcomes	ETs and duration of phototherapy.
Notes	Authors provided additional information, however it was still not clear what criteria for ET were used and consequently this study could not be included yet. Further information has been requested.

Wang 2002

Methods	RCT
Participants	121 neonates with: 1) blood type A or B of mothers with type O, 2) mothers with a Anti-A or Anti-B IgG >1:128, 3) a positive DAT or free-antibody test or antibody-release test, 4) methemoglobin reduction rate >75%, and 5) "clinical characteristics: hemolysis, jaundice, anemia and the like".
Interventions	Treatment group: IVIg 0.4 g/kg/day for 3 days (although in conclusion section 2-3 days) plus phototherapy and albumin 1 g/kg/day for 1-3 days and correcting acidosis, supplement of fluid and calories. (Mean (± SD) time of admission 41 ± 20 h). (n = 61) Control group: phototherapy and albumin 1 g/kg/day for 1-3 days and correcting acidosis, supplement of fluid and calories. (n = 51)
Outcomes	ETs, duration of phototherapy (not in form useable for meta-analysis), kernicterus, and adverse events.
Notes	Not stated whether any ethics approval or parental consent was given. Criteria for ET: not stated. Criteria for initiating phototherapy: not stated, (stopping criteria: transcutaneous bilirubin level <110mmol/L). Further information has been requested.

Appendix 3: Results of analyses

1. IVIg plus phototherapy versus phototherapy

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Use of exchange transfusion (one or more)	14	942	RR (M-H, Random, 95% CI)	0.40 [0.27, 0.59]
1.2 Exchange transfusions per infant	12	788	MD (IV, Random, 95% CI)	-0.31 [-0.45, -0.17]
1.3 Use of top-up transfusion in 1st week	5	396	RR (M-H, Fixed, 95% CI)	1.05 [0.65, 1.69]
1.4 Top-up transfusions in 1st week per infant	4	280	MD (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
1.5 Use of top-up transfusion after 1st week	8	581	RR (M-H, Fixed, 95% CI)	1.20 [1.00, 1.45]
1.6 Top-up transfusions after 1st week per infant	4	316	MD (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]

1.7 Maximum serum bilirubin (µmol/L)	9	623	MD (IV, Fixed, 95% CI)	-17.52 [-25.20, -9.84]
1.8 Duration of phototherapy (days)	10	755	MD (IV, Random, 95% CI)	-0.87 [-1.24, -0.50]
1.9 Duration of hospitalization (days)	8	676	MD (IV, Fixed, 95% CI)	-1.50 [-1.72, -1.28]
1.10 Incidence of adverse reaction	13	837	RR (M-H, Fixed, 95% CI)	0.83 [0.43, 1.58]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

2. IVIg plus phototherapy versus phototherapy. Rh incompatibility only

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Use of exchange transfusion (one or more)	9	426	RR (M-H, Fixed, 95% CI)	0.42 [0.29, 0.61]
2.2 Exchange transfusions per infant	9	426	MD (IV, Fixed, 95% CI)	-0.25 [-0.34, -0.16]
2.3 Use of top-up transfusion in 1st week	5	303	RR (M-H, Fixed, 95% CI)	1.08 [0.65, 1.77]
2.4 Top-up transfusions in 1st week per infant	4	280	MD (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
2.5 Use of top-up transfusion after 1st week	6	281	RR (M-H, Fixed, 95% CI)	1.09 [0.92, 1.28]
2.6 Top-up transfusions after 1st week per infant	3	204	MD (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
2.7 Maximum serum bilirubin (µmol/L)	7	376	MD (IV, Fixed, 95% CI)	-21.40 [-30.43, -12.37]
2.8 Duration of phototherapy (days)	6	316	MD (IV, Fixed, 95% CI)	-1.21 [-1.40, -1.01]
2.9 Duration of hospitalization (days)	5	298	MD (IV, Fixed, 95% CI)	-1.47 [-1.75, -1.19]
2.10 Incidence of adverse reaction	8	403	RR (M-H, Fixed, 95% CI)	0.79 [0.22, 2.87]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

3. IVIg plus phototherapy versus phototherapy. ABO incompatibility only

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Use of exchange transfusion (one or more)	4	229	RR (M-H, Fixed, 95% CI)	0.33 [0.18, 0.60]
3.2 Exchange transfusions per infant	4	229	MD (IV, Fixed, 95% CI)	-0.21 [-0.32, -0.10]
3.3 Use of top-up transfusion in 1st week	1	93	RR (M-H, Fixed, 95% CI)	0.80 [0.19, 3.38]
3.4 Use of top-up transfusion after 1st week	3	226	RR (M-H, Fixed, 95% CI)	5.02 [0.62, 40.67]
3.5 Maximum serum bilirubin (µmol/L)	1	93	MD (IV, Fixed, 95% CI)	-60.60 [-83.24, -37.96]
3.6 Duration of phototherapy (days)	3	249	MD (IV, Fixed, 95% CI)	-0.76 [-1.12, -0.41]
3.7 Duration of hospitalization (days)	3	249	MD (IV, Fixed, 95% CI)	-0.87 [-1.40, -0.35]
3.8 Incidence of adverse reaction	3	136	RR (M-H, Fixed, 95% CI)	1.00 [0.45, 2.21]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

4. IVIg plus phototherapy versus phototherapy. Gestational age ≥37 weeks

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Use of exchange transfusion (one or more)	7	463	RR (M-H, Fixed, 95% CI)	0.37 [0.24, 0.57]
4.2 Exchange transfusions per infant	7	463	MD (IV, Fixed, 95% CI)	-0.18 [-0.25, -0.10]
4.3 Use of top-up transfusion in 1st week	4	296	RR (M-H, Fixed, 95% CI)	0.91 [0.48, 1.74]
4.4 Top-up transfusions in 1st week per infant	3	180	MD (IV, Fixed, 95% CI)	-0.01 [-0.35, 0.33]
4.5 Use of top-up transfusion after 1st week	4	240	RR (M-H, Fixed, 95% CI)	1.18 [0.81, 1.71]
4.6 Top-up transfusions after 1st week per infant	2	90	MD (IV, Fixed, 95% CI)	-0.03 [-0.20, 0.13]

4.7 Maximum serum bilirubin (µmol/L)	4	296	MD (IV, Fixed, 95% CI)	-26.81 [-35.97, -17.65]
4.8 Duration of phototherapy (days)	7	463	MD (IV, Fixed, 95% CI)	-1.01 [-1.17, -0.84]
4.9 Duration of hospitalization (days)	6	402	MD (IV, Fixed, 95% CI)	-1.20 [-1.45, -0.96]
4.10 Incidence of adverse reaction	7	463	RR (M-H, Fixed, 95% CI)	0.59 [0.09, 3.70]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

5. IVIg plus phototherapy versus phototherapy. Gestational age <37 weeks

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Use of exchange transfusion (one or more)	2	82	RR (M-H, Fixed, 95% CI)	0.77 [0.31, 1.91]
5.2 Exchange transfusions per infant	2	82	MD (IV, Fixed, 95% CI)	-0.10 [-0.32, 0.12]
5.3 Use of top-up transfusion in 1st week	2	82	RR (M-H, Fixed, 95% CI)	1.39 [0.70, 2.73]
5.4 Top-up transfusions in 1st week per infant	2	82	MD (IV, Fixed, 95% CI)	0.08 [-0.12, 0.27]
5.5 Use of top-up transfusion after 1st week	2	82	RR (M-H, Fixed, 95% CI)	1.24 [0.93, 1.67]
5.6 Top-up transfusions after 1st week per infant	2	82	MD (IV, Fixed, 95% CI)	0.04 [-0.13, 0.20]
5.7 Maximum serum bilirubin (µmol/L)	2	82	MD (IV, Fixed, 95% CI)	-18.91 [-54.49, 16.68]
5.8 Duration of phototherapy (days)	2	82	MD (IV, Fixed, 95% CI)	-0.91 [-1.96, 0.14]
5.9 Duration of hospitalization (days)	2	82	MD (IV, Fixed, 95% CI)	-2.28 [-3.84, -0.72]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

6. IVIg plus phototherapy versus phototherapy. IVIg administration ≤12 hours after birth

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Use of exchange transfusion (one or more)	7	427	RR (M-H, Fixed, 95% CI)	0.51 [0.35, 0.73]
6.2 Exchange transfusions per infant	6	353	MD (IV, Fixed, 95% CI)	-0.19 [-0.28, -0.10]
6.3 Use of top-up transfusion in 1st week	4	280	RR (M-H, Fixed, 95% CI)	1.18 [0.70, 2.00]
6.4 Top-up transfusions in 1st week per infant	4	280	MD (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
6.5 Use of top-up transfusion after 1st week	5	319	RR (M-H, Fixed, 95% CI)	1.10 [0.92, 1.31]
6.6 Top-up transfusions after 1st week per infant	3	204	MD (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
6.7 Maximum serum bilirubin (µmol/L)	7	427	MD (IV, Fixed, 95% CI)	-16.99 [-25.86, -8.11]
6.8 Duration of phototherapy (days)	4	280	MD (IV, Fixed, 95% CI)	-1.22 [-1.42, -1.01]
6.9 Duration of hospitalization (days)	3	262	MD (IV, Fixed, 95% CI)	-1.46 [-1.76, -1.17]
6.10 Incidence of adverse reaction	7	427	RR (M-H, Fixed, 95% CI)	0.79 [0.22, 2.87]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

7. IVIg plus phototherapy versus phototherapy. IVIg administration >12 hours after birth

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Use of exchange transfusion (one or more)	5	363	RR (M-H, Fixed, 95% CI)	0.27 [0.17, 0.44]
7.2 Exchange transfusions per infant	4	283	MD (IV, Fixed, 95% CI)	-0.29 [-0.41, -0.17]
7.3 Use of top-up transfusion in 1st week	1	116	RR (M-H, Fixed, 95% CI)	0.71 [0.24, 2.12]
7.4 Use of top-up transfusion after 1st week	2	150	RR (M-H, Fixed, 95% CI)	8.00 [1.03, 62.26]

7.5 Maximum serum bilirubin (µmol/L)	2	196	MD (IV, Fixed, 95% CI)	-19.10 [-34.41, -3.79]
7.6 Duration of phototherapy (days)	5	363	MD (IV, Fixed, 95% CI)	-0.74 [-1.00, -0.49]
7.7 Duration of hospitalization (days)	4	302	MD (IV, Fixed, 95% CI)	-1.60 [-1.93, -1.26]
7.8 Incidence of adverse reaction	4	283	RR (M-H, Fixed, 95% CI)	0.20 [0.01, 4.08]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

8. IVIg plus phototherapy versus phototherapy. Single dose of IVIg

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Use of exchange transfusion (one or more)	10	724	RR (M-H, Fixed, 95% CI)	0.41 [0.29, 0.57]
8.2 Exchange transfusions per infant	9	675	MD (IV, Fixed, 95% CI)	-0.21 [-0.27, -0.14]
8.3 Use of top-up transfusion in 1st week	4	378	RR (M-H, Fixed, 95% CI)	1.05 [0.65, 1.69]
8.4 Top-up transfusions in 1st week per infant	3	262	MD (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
8.5 Use of top-up transfusion after 1st week	7	522	RR (M-H, Fixed, 95% CI)	1.19 [0.99, 1.42]
8.6 Top-up transfusions after 1st week per infant	4	316	MD (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
8.7 Maximum serum bilirubin (µmol/L)	7	500	MD (IV, Fixed, 95% CI)	-22.68 [-31.17, -14.19]
8.8 Duration of phototherapy (days)	6	562	MD (IV, Fixed, 95% CI)	-0.95 [-1.12, -0.79]
8.9 Duration of hospitalization (days)	6	562	MD (IV, Fixed, 95% CI)	-1.21 [-1.46, -0.96]
8.10 Incidence of adverse reaction	10	724	RR (M-H, Fixed, 95% CI)	0.86 [0.43, 1.73]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

9. IVIg plus phototherapy versus phototherapy. Multiple doses of IVIg

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 Use of exchange transfusion (one or more)	3	98	RR (M-H, Fixed, 95% CI)	0.48 [0.27, 0.83]
9.2 Exchange transfusions per infant	2	52	MD (IV, Fixed, 95% CI)	-0.83 [-1.28, -0.38]
9.3 Use of top-up transfusion in 1st week	1	18	RR (M-H, Fixed, 95% CI)	Not estimable
9.4 Top-up transfusions in 1st week per infant	1	18	MD (IV, Fixed, 95% CI)	Not estimable
9.5 Use of top-up transfusion after 1st week	2	80	RR (M-H, Fixed, 95% CI)	2.09 [0.54, 8.13]
9.6 Maximum serum bilirubin (µmol/L)	2	64	MD (IV, Fixed, 95% CI)	22.89 [-12.00, 57.78]
9.7 Duration of phototherapy (days)	2	52	MD (IV, Fixed, 95% CI)	-1.00 [-1.90, -0.10]
9.8 Duration of hospitalization (days)	1	34	MD (IV, Fixed, 95% CI)	-1.41 [-2.51, -0.31]
9.9 Incidence of adverse reaction	3	98	RR (M-H, Fixed, 95% CI)	0.64 [0.11, 3.54]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance

10. IVIg plus phototherapy versus phototherapy. High quality studies only.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
10.1 Use of exchange transfusion (one or more)	2	172	RR (M-H, Fixed, 95% CI)	0.98 [0.48, 1.98]
10.2 Exchange transfusions per infant	2	172	MD (IV, Fixed, 95% CI)	-0.04 [-0.18, 0.10]
10.3 Use of top-up transfusion in 1st week	2	172	RR (M-H, Fixed, 95% CI)	1.18 [0.70, 2.00]
10.4 Top-up transfusions in 1st week per infant	2	172	MD (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
10.5 Use of top-up transfusion after 1st week	2	172	RR (M-H, Fixed, 95% CI)	1.01 [0.80, 1.27]

10.6 Top-up transfusions after 1st week per infant	2	172	MD (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
10.7 Maximum serum bilirubin (µmol/L)	2	172	MD (IV, Fixed, 95% CI)	0.92 [-23.94, 25.79]
10.8 Duration of phototherapy (days)	2	172	MD (IV, Fixed, 95% CI)	-0.50 [-1.24, 0.24]
10.9 Duration of hospitalization (days)	2	172	MD (IV, Fixed, 95% CI)	-1.38 [-2.55, -0.20]
10.10 Incidence of adverse reaction	2	172	RR (M-H, Fixed, 95% CI)	2.86 [0.12, 68.10]

RR = Risk Ratio, M-H = Mantel-Haenszel, CI = Confidence Interval, MD = Mean Difference, IV = Inverse Variance